ESSENTIALS

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ENDOCRINOLOGY AND DIABETES

RICHARD I.G. HOLT | NEIL A. HANLEY

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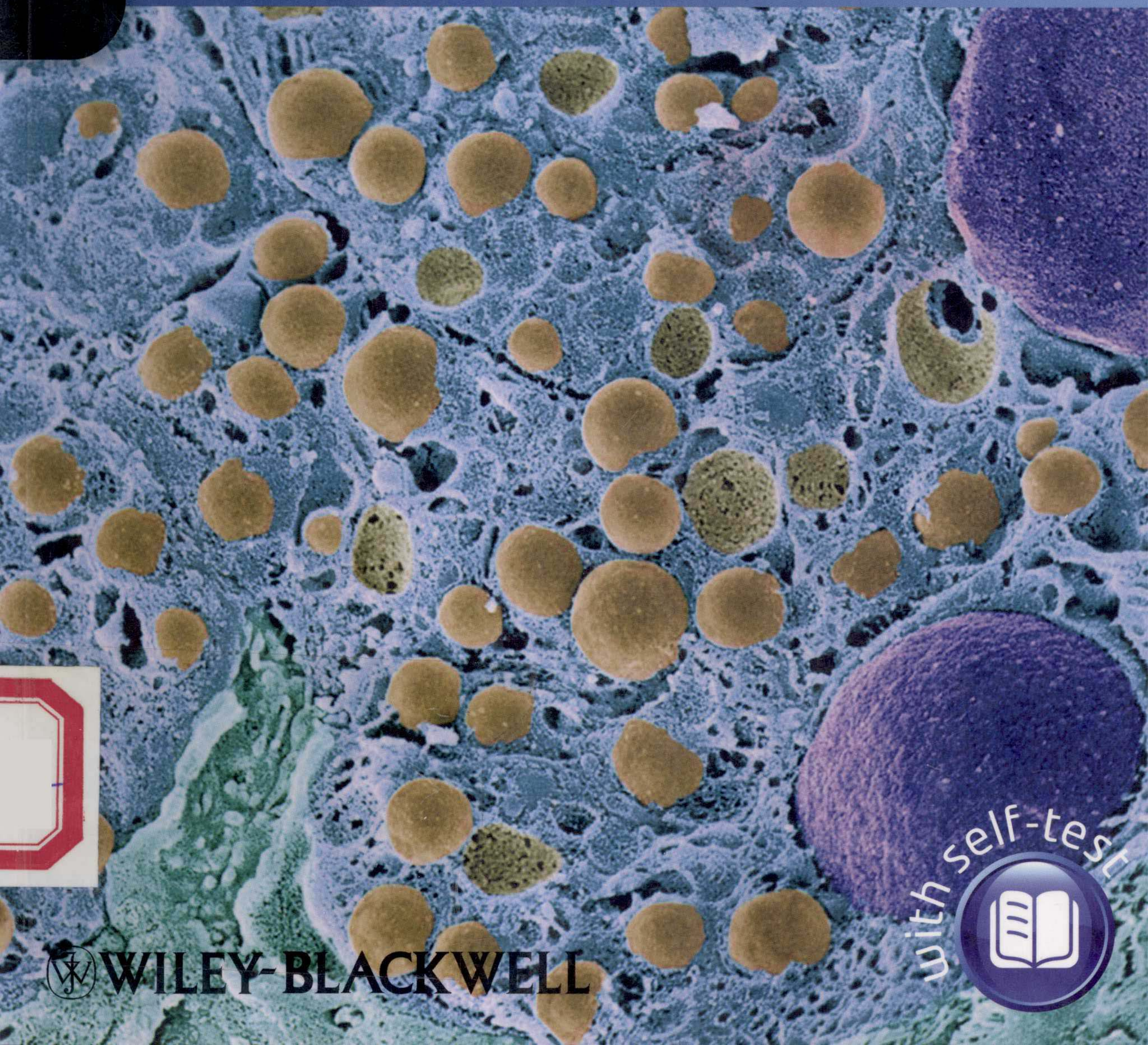

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Essential Endocrinology and Diabetes

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Sixth edition

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Preface

There have been significant advances and developments in the 4 years since we wrote the last edition. Consequently, many areas of the book have required substantial updating and extensive re-writing. Nevertheless, the structure of the book has remained similar to the last edition, which seemed popular around the world.

The first part strives to create a knowledgeable reader prepared for the clinical sections. Recognizing that many students now come to medicine from non-scientific backgrounds, we have tried to limit assumptions on prior knowledge. For instance, the concept of negative feedback regulation, covered in Chapter 1, is mandatory for understanding almost all endocrine physiology and is vital for the interpretation of many clinical tests. Similarly, molecular diagnostics has advanced far beyond the historical development of immunoassays. New modalities, such as molecular genetics, mass spectrometry and sophisticated imaging, are already standard practice and it is important that aspiring clinicians, as well as scientists, appreciate their methodology, application and limitations. The second part retains a largely organ-based approach. The introductory basic science in these chapters aims to be concise yet sufficient to understand, diagnose and manage the associated clinical disorders. The chapter on endocrine neoplasia, including hormone-secreting tumours of the gut, has been expanded in recognition of the increasing array of hormones discovered from the pancreas and gastrointestinal tract. In previous editions these hormones have lacked attention. However, many of them are now emerging as key regulators that are exploited in new therapies. For instance, augmentation of glucagon-like peptide 1 signalling is an effective treatment for diabetes. The third part on diabetes and obesity was entirely new in the last edition and these chapters have undergone the greatest change here. Over the last 4 years we have seen significant advances in the treatment of type 2 diabetes such as the new incretin-based therapies and the withdrawal of other treatments due to safety concerns. Clinical algorithms have also changed and these have been updated.

The textbook aims to bridge the gap from basic science training, through clinical training, to the knowledge required for the early postgraduate years and specialist training. The text goes beyond core undergraduate medical education. Learning objectives, boxes, and concluding 'key points' aim to emphasize the major topics. There is hopefully useful detail for more advanced clinicians who, like the authors, enjoy trying to interpret clinical medicine scientifically, but for whom memory occasionally fails. Although the structure of the book is largely unchanged from the previous edition, readers of the old edition will recognize welcome developments. For the first time, the book is in full colour, which has allowed us to include colour photographs in the relevant chapter. We have introduced recap and cross-reference guides at the beginning of each of the clinical chapters to help the reader find important information in other parts of the book more easily. The case histories that were introduced in the last edition proved to be a success and these have been expanded to provide greater opportunity to put theory into practice.

We have brought our clinical and research experiences together to create this book. While it has been a truly collaborative venture and the book is designed to read as a whole, inevitably one of us has taken a lead with each chapter depending on our own interests. As such, NAH was responsible for writing Part 1 and Part 2, while RIGH was responsible for Part 3.

Finally, we must thank a number of people without whom this book would not have come to fruition. We are grateful for the skilled help of Wiley-Blackwell Publishing and remain indebted to our predecessors up to and including the 4th edition, Charles Brook and Nicholas Marshall, for their excellent starting point. We are also grateful to our families without whose support this book would not have been possible and to whom we dedicate this edition.

R.I.G. Holt
University of Southampton
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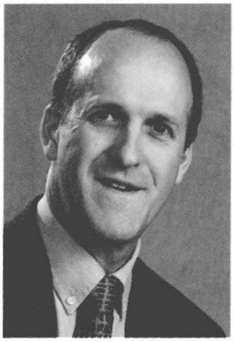
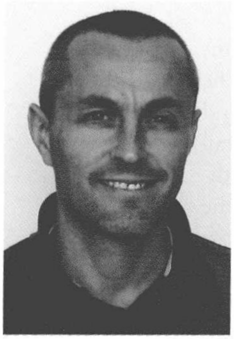
The authors



Richard Holt is Professor in Diabetes and Endocrinology at the University of Southampton School of Medicine and Honorary Consultant in Endocrinology at Southampton University Hospitals NHS Trust. His research interests are broadly focused around clinical diabetes with particular interests in diabetes in pregnancy and young adults, and the relation between diabetes and mental illness. He also has a long-standing interest in growth hormone.



Neil Hanley is Professor of Medicine and Wellcome Trust Senior Fellow in Clinical Science at the University of Manchester. He is Honorary Consultant in Endocrinology at the Central Manchester University Hospitals NHS Foundation Trust where he provides tertiary referral endocrine care. His main research interests are human developmental endocrinology and stem cell biology.

Both authors play a keen role in the teaching of undergraduate medical students and doctors. RIGH is a Fellow of the Higher Education Academy. NAH is Director of the Academy for Training & Education at the Manchester Biomedical Research Centre.

Further reading

The following major international textbooks make an excellent source of secondary reading:

Melmed S, Polonsky KS, Reed Larsen P, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 12th edn. Saunders, 2011.

Holt RIG, Cockram C, Flyvbjerg A, Goldstein BJ. *Textbook of Diabetes*, 4th edn. Wiley-Blackwell, 2010.

In addition, the following textbooks cover topics, relevant to some chapters, in greater detail:

Delves PJ, Martin SJ, Burton DR, Roitt IM. *Roitt's Essential Immunology*, 12th edn. Wiley-Blackwell, 2011.

Johnson M. *Essential Reproduction*, 6th edn. Wiley-Blackwell, 2007.

Nelson DL, Cox MM. *Lehninger Principles of Biochemistry*, 5th edn. W.H. Freeman, 2008.

List of abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptophan
αMSH	α-melanocyte stimulating hormone
ACTH	adrenocorticotrophic hormone
ADH	vasopressin/antidiuretic hormone
AFP	α-fetoprotein
AGE	advanced glycation end-product
AGRP	Agouti-related protein
AI	angiotensin I
AII	angiotensin II
ALS	acid labile subunit
AMH	anti-Müllerian hormone
AR	androgen receptor
APS-1	type 1 autoimmune polyglandular syndrome
APS-2	type 2 autoimmune polyglandular syndrome
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
CBG	cortisol binding globulin
cGMP	guanosine monophosphate
CRE	cAMP response element
CREB	cAMP response element-binding protein
CNS	central nervous system
CRH	corticotrophin-releasing hormone
CSF	cerebrospinal fluid
CT	computed tomography
CVD	cardiovascular disease
DAG	diacylglycerol
DEXA	dual energy X-ray absorptiometry
DHEA	dehydroepiandrosterone
DHT	5α-dihydrotestosterone
DI	diabetes insipidus
EGF	epidermal growth factor
EPO	erythropoietin
ER	oestrogen receptor
FFA	free fatty acid
FGF	fibroblast growth factor
FIA	fluoroimmunoassay
FISH	fluorescence *in situ* hybridization
FSH	follicle-stimulating hormone
fT_3	free tri-iodothyronine
fT_4	free thyroxine
GC	gas chromatography
GDM	gestational diabetes
GFR	glomerular filtration rate
GH	growth hormone (somatotrophin)
GHR	GH receptor
GHRH	growth hormone-releasing hormone
GI	glycaemic index
GIP	glucose-dependent insulinotrophic peptide (gastric inhibitory peptide)
GLUT	glucose transporter
GnRH	gonadotrophin-releasing hormone
GPCR	guanine-protein coupled receptor
GR	glucocorticoid receptor
Grb2	type 2 growth factor receptor-bound protein
hCG	human chorionic gonadotrophin
hMG	human menopausal gonadotrophin
HMGCoA	hydroxymethylglutaryl coenzyme A
HNF	hepatocyte nuclear factor
HPLC	high performance liquid chromatography
HRE	hormone response element
HRT	hormone replacement therapy
ICSI	intracytoplasmic sperm injection
IDDM	insulin-dependent diabetes mellitus
IFG	impaired fasting glycaemia
IFMA	immunofluorometric assay
IGF	insulin-like growth factor
IGFBP	IGF-binding protein
IGT	impaired glucose tolerance
IP	inositol phosphate
IPF	insulin promoter factor
IR	insulin receptor
IRMA	intraretinal microvascular abnormalities (Chapter 14)
IRMA	immunoradiometric assay (Chapter 4)
IRS	insulin receptor substrate
IVF	*in vitro* fertilization
JAK	Janus-associated kinase
LDL	low-density lipoprotein
LH	luteinizing hormone
MAO	monoamine oxidase
MAPK	mitogen-activated protein kinase

MEN	multiple endocrine neoplasia
MIS	Müllerian inhibiting substance
MODY	maturity-onset diabetes of the young
MR	mineralocorticoid receptor
MRI	magnetic resonance imaging
MS	mass spectrometry
MSH	melanocyte-stimulating hormone
NEFA	non-esterified fatty acid
NICTH	non-islet cell tumour hypoglycaemia
NIDDM	non–insulin-dependent diabetes mellitus
NPY	neuropeptide Y
NVD	new vessels at the disc
NVE	new vessels elsewhere
OGTT	oral glucose tolerance test
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PDE	phosphodiesterase
PGE2	prostaglandin E_2
PI	phosphatidylinositol
PIT1	pituitary-specific transcription factor 1
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PNMT	phenylethanolamine *N*-methyl transferase
POMC	pro-opiomelanocortin
PPAR	peroxisome proliferator-activated receptor
PRL	prolactin
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTU	propylthiouracil
RANK	receptor activator of nuclear factor-kappa B
RER	rough endoplasmic reticulum
RIA	radioimmunoassay
rT_3	reverse tri-iodothyronine
RXR	retinoid X receptor
SERM	selective ER modulator
SHBG	sex hormone-binding globulin
SIADH	syndrome of inappropriate antidiuretic hormone
SoS	son of sevenless protein
SRE	serum response element
SS	somatostatin
StAR	steroid acute regulatory protein
STAT	signal transduction and activation of transcription protein
T1DM	type 1 diabetes
T2DM	type 2 diabetes
$t_{1/2}$	half-life
T_3	tri-iodothyronine
T_4	thyroxine
TGFβ	transforming growth factor β
TK	tyrosine kinase
TPO	thyroid peroxidase
TR	thyroid hormone receptor
TRE	thyroid hormone response element
TRH	thyrotrophin-releasing hormone
TSH	thyroid-stimulating hormone
UFC	urinary free cortisol
V	vasopressin/antidiuretic hormone (previously also known as arginine vasopressin)
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal peptide

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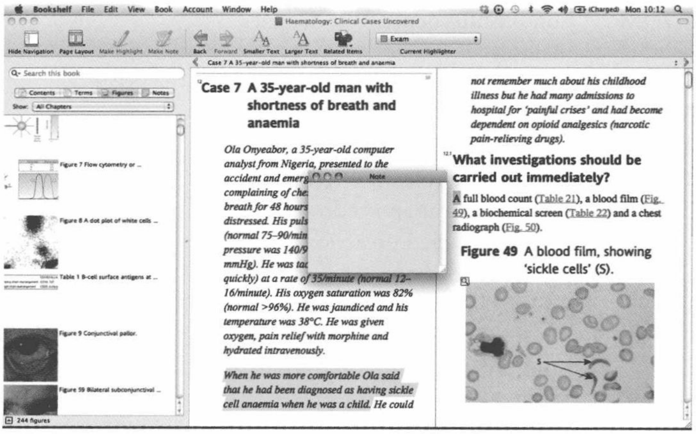

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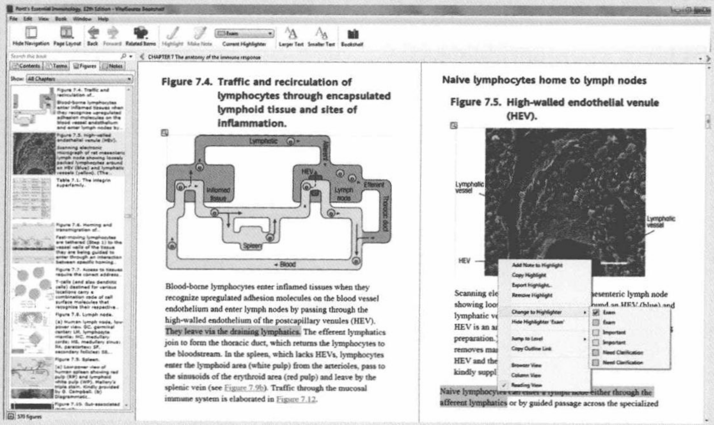

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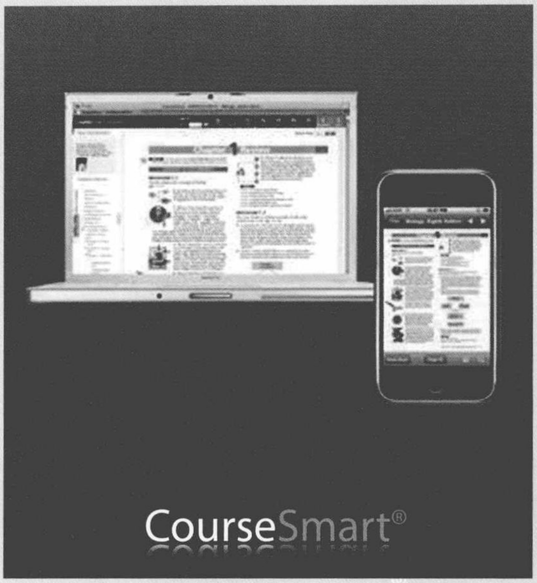

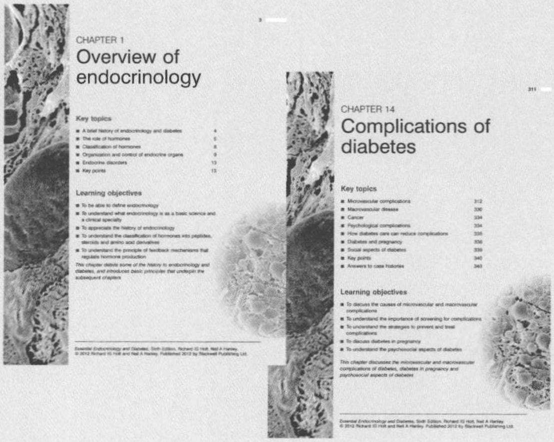

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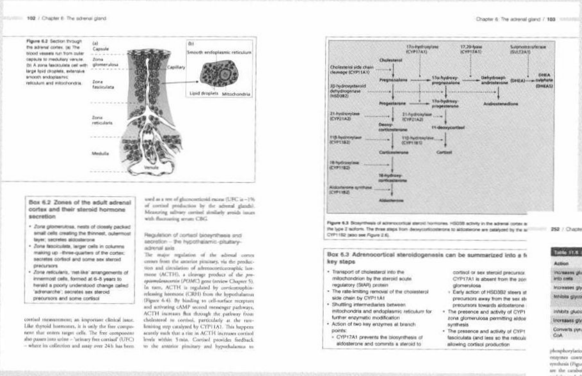

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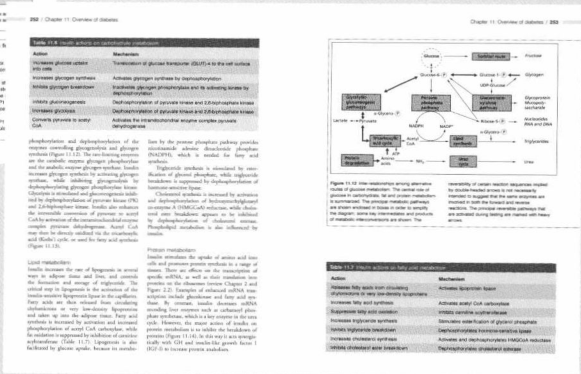


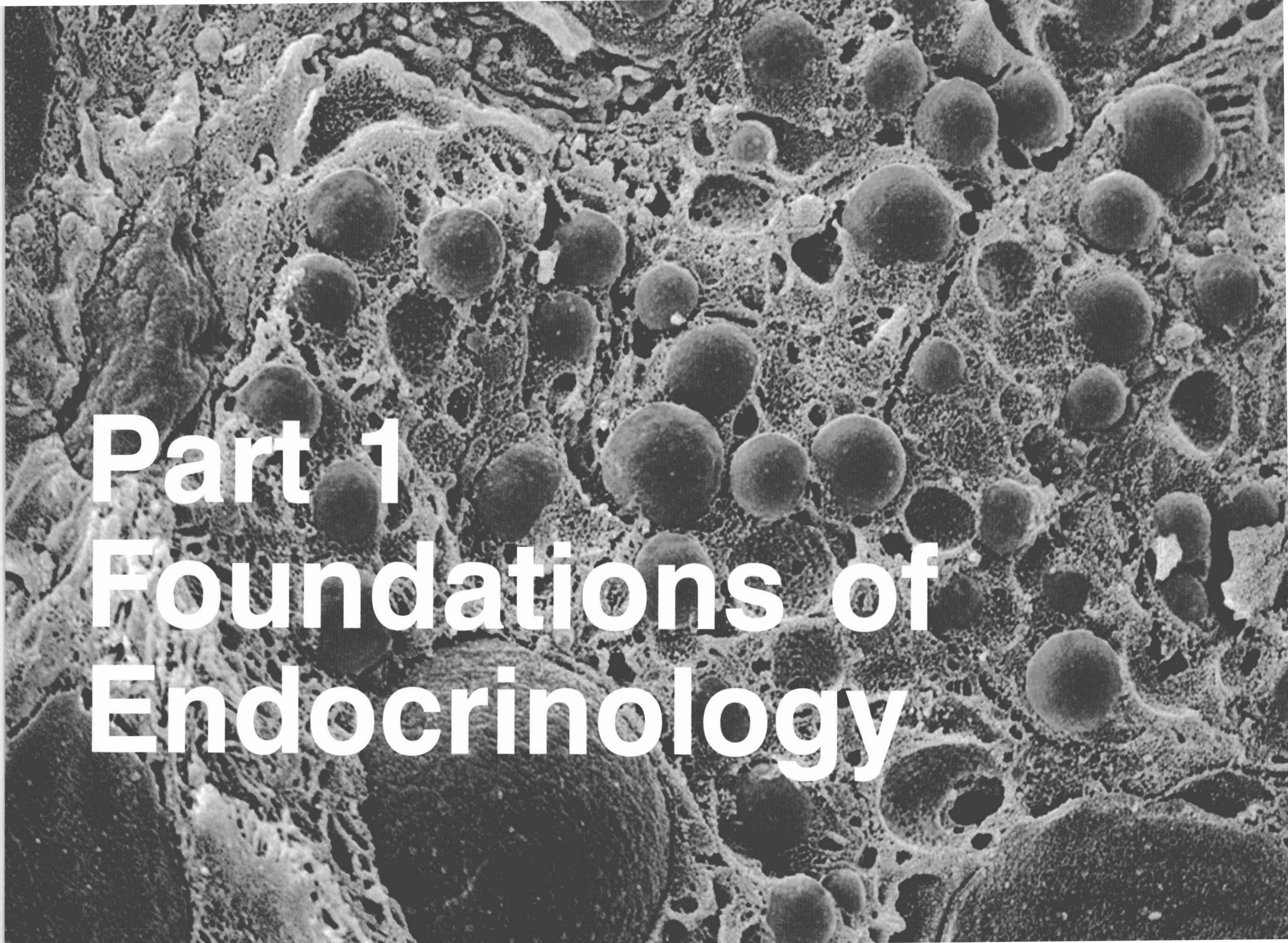
Cross-reference

- The development of the parathyroid and parafollicular C-cells is described alongside the thyroid in Chapter 8
- Tumours of the parathyroid glands are an important component of multiple endocrine neoplasia, covered in Chapter 10
- Other hormones such as cortisol (see Chapter 6) and sex hormones (see Chapter 7) affect mineralization of the bones

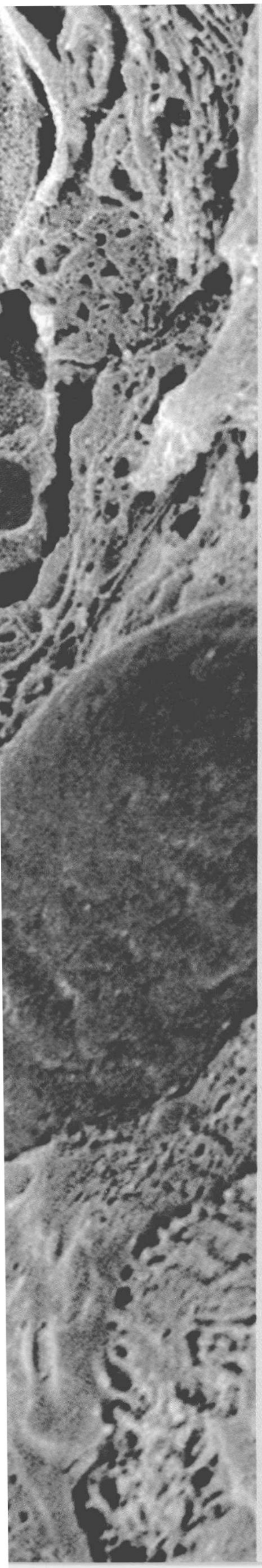
◄ At the beginning of some chapters you will also find cross-references which make it easy to locate related information quickly and efficiently.

We hope you enjoy using your new textbook. Good luck with your studies!

Contents



Part 1
Foundations of Endocrinology



CHAPTER 1

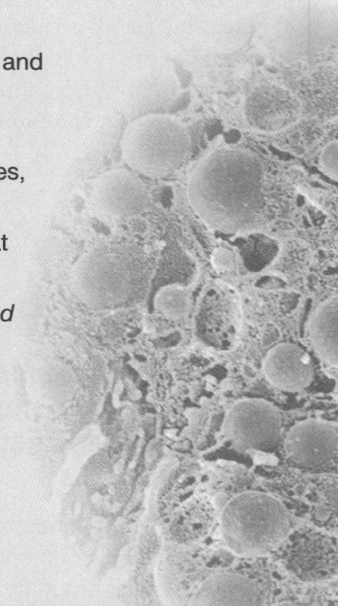
Overview of endocrinology

Key topics

Learning objectives

- To be able to define endocrinology
- To understand what endocrinology is as a basic science and a clinical specialty
- To appreciate the history of endocrinology
- To understand the classification of hormones into peptides, steroids and amino acid derivatives
- To understand the principle of feedback mechanisms that regulate hormone production

This chapter details some of the history to endocrinology and diabetes, and introduces basic principles that underpin the subsequent chapters



Essential Endocrinology and Diabetes, Sixth Edition. Richard IG Holt, Neil A Hanley.

An organism comprised of a single or a few cells analyzes and responds to its external environment with relative ease. No cell is more than a short diffusion distance from the outside world or its neighbours, allowing a constancy of internal environment ('homeostasis'). This simplicity has been lost with the evolution of more complex, larger, multicellular organisms. Simple diffusion has become inadequate in larger animal species where functions localize to specific organs. In humans, there are ~10^{14} cells of 200 or more different types. With this compartmentalized division of purpose comes the need for effective communication to disseminate information throughout the whole organism – only a few cells face the outside world, yet all respond to it. Two communication systems facilitate this: the endocrine and nervous systems (Box 1.1).

The specialized ductless glands and tissues of the endocrine system release chemical messengers – hormones – into the extracellular space, from where they enter the bloodstream. It is this blood-borne transit that defines endocrinology; however, the principles are similar for hormone action on a neighbouring cell ('*para*crinology') or, indeed, itself ('*auto*- or *intra*-crinology') (Figure 1.1).

The nervous and endocrine systems interact. Endocrine glands are under both nervous and hormonal control, while the central nervous system is affected by multiple hormonal stimuli – features reflected by the composite science of neuroendocrinology (Figure 1.1).

Box 1.1 Functions of the endocrine and nervous systems, the two main communication systems

- To monitor internal and external environments
- To allow appropriate adaptive changes
- To communicate via chemical messengers

} maintain homeostasis

A brief history of endocrinology and diabetes

The term 'hormone', derived from the Greek word 'hormaein' meaning 'to arouse' or 'to excite', was first used in 1905 by Sir Ernest Starling in his Croonian Lecture to the Royal College of Physicians;

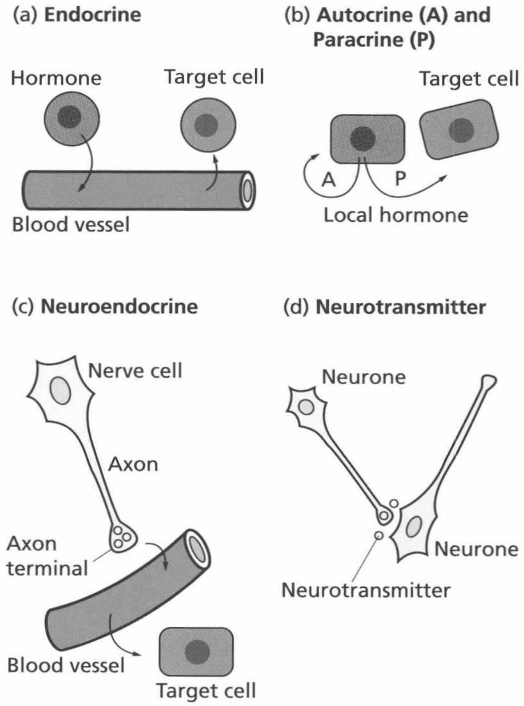


Figure 1.1 Cells that secrete regulatory substances to communicate with their target cells and organs. (a) Endocrine. Cells secrete hormone into the blood vessel, where it is carried, potentially over large distances, to its target cell. (b) Autocrine (A): hormones such as insulin-like growth factors can act on the cell that produces them, representing autocrine control. Paracrine (P): cells secrete hormone that acts on nearby cells (e.g. glucagon and somatostatin act on adjacent β-cells within the pancreatic islet to influence insulin secretion). (c) Stimulated neuroendocrine cells secrete hormone (e.g. the hypothalamic hormones that regulate the anterior pituitary) from axonic terminals into the bloodstream. (d) Neurotransmitter cells secrete substances from axonic terminals to activate adjacent neurones.

however, the specialty is built on foundations that are far older. Aristotle described the pituitary, while the associated condition, gigantism, due to excess growth hormone (GH), was referred to in the Old Testament, two millennia or so before the 19th century recognition of the gland's anterior and posterior components by Rathke, and Pierre Marie's connection of GH-secreting pituitary tumours to acromegaly.

Diabetes was recognized by the ancient Egyptians. Areteus later described the disorder in the second century AD as 'a melting down of flesh and limbs into urine' – diabetes comes from the Greek word meaning siphon. The pancreas was only implicated relatively recently when Minkowski realized in 1889 that the organ's removal in dogs mimicked diabetes in humans.

The roots of reproductive endocrinology are equally long. The Bible refers to eunuchs and Hippocrates recognized that mumps could result in sterility. Oophorectomy in sows and camels was used to increase strength and growth in ancient Egypt. The association with technology is also longstanding. For instance, it took the microscope in the 17th century for Leeuwenhoek to visualize spermatozoa and later, in the 19th century, for the mammalian ovum to be discovered in the Graafian follicle.

During the last 500 years, other endocrine organs and axes have been identified and characterized. In 1564, Bartolommeo Eustacio noted the presence of the adrenal glands. Almost 300 years later (1855), Thomas Addison, one of the forefathers of clinical endocrinology, described the consequences of their inadequacy. Catecholamines were identified at the turn of the 19th century, in parallel with Oliver and Schaffer's discovery that these adrenomedullary substances raise blood pressure. This followed shortly after the clinical features of myxoedema were linked to the thyroid gland, when, in 1891, physicians in Newcastle treated hypothyroidism with sheep thyroid extract. This was an important landmark, but long after the ancient Chinese recognized that seaweed, as a source of iodine, held valuable properties in treating 'goitre', swelling of the thyroid gland.

Early clinical endocrinology and diabetes tended to recognize and describe the features of the endocrine syndromes. Since then, our understanding has advanced through:

- Successful quantification of circulating hormones
- Pathophysiological identification of endocrine dysfunction
- Molecular genetic diagnoses
- Molecular unravelling of complex hormone action.

Some of the landmarks from the last 100 years are shown in Box 1.2, and those researchers who have been awarded the Nobel Prize for Medicine, Physiology or Chemistry for discoveries that have advanced endocrinology and diabetes are listed in Table 1.1.

Traditionally, endocrinology has centred on specialized hormone-secreting organs (Figure 1.2), largely built on the 'endocrine postulates' of Edward Doisy (Box 1.3). While the focus of this textbook remains with these organs, many tissues display appreciable degrees of hormone biosynthesis, and, equally relevant, modulate hormone action. All aspects are important for a complete appreciation of endocrinology and its significance.

The role of hormones

Hormones are synthesized by specialized cells (Table 1.2), which may exist as distinct endocrine glands or be located as single cells within other organs, such as the gastrointestinal tract. The chapters in Part 2 are largely organized on this anatomical basis.

Endocrinology is defined by the secretion of hormones into the bloodstream; however, autocrine or paracrine actions are also important, often modulating the hormone-secreting cell type. Hormones act by binding to specific receptors, either on the surface of or inside the target cell, to initiate a cascade of intracellular reactions, which frequently amplifies the original stimulus and generates a final response. These responses are altered in hormone deficiency and excess: for instance, GH deficiency leads to short stature in children, while excess causes over-growth (either gigantism or acromegaly; Chapter 5).