ESSENTIAL

ENDOCRINOLOGY AND DIABETES

RICHARD I.G. HOLT | NEIL A. HANLEY SEVENTH EDITION



Table of Contents

Cover
<u>Title Page</u>
<u>Copyright Page</u>
<u>Preface</u>
<u>List of abbreviations</u>
Part 1: Foundations of Endocrinology
CHAPTER 1: Overview of endocrinology
A brief history of endocrinology and diabetes
The role of hormones
<u>Classification of hormones</u>
Control systems regulating hormone production
Endocrine disorders
CHAPTER 2: Basic cell biology and hormone
<u>synthesis</u>
Chromosomes, mitosis and meiosis
Synthesizing a peptide or protein hormone
Synthesizing a hormone derived from amino
acids or cholesterol
<u>Hormone transport</u>
CHAPTER 3: Molecular basis of hormone action
<u>Cell-surface receptors</u>
Nuclear receptors
CHAPTER 4: Investigations in endocrinology and
<u>diabetes</u>
Pre-analytical requirements for accurate
<u>endocrine testing</u>

<u>Laboratory assay piatiorms</u>
Reference ranges
Static and dynamic testing
Cell and molecular biology as diagnostic tools
<u>Imaging in endocrinology</u>
Part 2: Endocrinology - Biology to Clinical Practice
CHAPTER 5: The hypothalamus and pituitary gland
Embryology and anatomy
<u>Pituitary tumours</u>
<u>The hypothalamus</u>
The hypothalamic-anterior pituitary hormone
<u>axes</u>
The anterior pituitary hormones
<u>Hypopituitarism</u>
Hormones of the posterior pituitary
CHAPTER 6: The adrenal gland
The adrenal cortex
The adrenal medulla
CHAPTER 7: Reproductive endocrinology
Embryology of the reproductive organs
The male reproductive system
The female reproductive system
<u>Pubertal disorders</u>
<u>Subfertility</u>
CHAPTER 8: The thyroid gland
<u>Embryology</u>
Anatomy and vasculature
Thyroid hormone biosynthesis

<u>Circulating thyroid hormones</u>
Function of thyroid hormones
Thyroid function tests
<u>Clinical disorders</u>
CHAPTER 9: Calcium and metabolic bone disorders
<u>Calcium</u>
Hormones that regulate calcium
Clinical disorders of calcium homeostasis
Bone health and metabolic bone disease
Clinical conditions of bone metabolism
Vitamin D deficiency, osteomalacia and rickets
CHAPTER 10: Pancreatic and gastrointestinal
endocrinology and endocrine neoplasia
Pancreatic endocrinology
Gastrointestinal endocrinology and associated clinical conditions
Endocrine tumour predisposition syndromes
Tumours with ectopic hormone production
<u>Hormone-sensitive tumours</u>
Other tumours relevant to endocrinology
Part 3: Diabetes and Obesity
CHAPTER 11: Overview of diabetes
A brief history of diabetes and its classification
<u>Classification of diabetes</u>
<u>Diagnosis of diabetes</u>
<u>Insulin</u>
<u>Glucagon</u>
CHAPTER 12: Type 1 diabetes
What is type 1 diabetes?

<u>Epidemiology</u>
<u>Pathogenesis</u>
<u>Aetiology</u>
<u>Clinical features</u>
<u>Diagnosis</u>
Management of type 1 diabetes
Acute metabolic emergencies
CHAPTER 13: Type 2 diabetes
<u>Epidemiology</u>
<u>Pathophysiology</u>
<u>Prognosis</u>
<u>Clinical features</u>
<u>Prevention of diabetes</u>
Screening for diabetes
Management of type 2 diabetes
CHAPTER 14: Complications of diabetes
Introduction
<u>Microvascular complications</u>
Pathology of microvascular complications
Pathogenesis of microvascular complications
Clinical features of microvascular complications
<u>Diabetes-related kidney disease</u>
<u>Neuropathy</u>
The diabetic foot
Genitourinary and sexual problems of diabetes
Atherosclerotic cardiovascular disease
<u>Heart failure</u>
<u>Cancer</u>

Non-alcoholic fatty liver disease

Gastro-intestinal tract

Bone and Joint

Skin disorders

<u>Psychological and psychiatric sequelae of</u> diabetes

<u>Diabetes and pregnancy</u>

Social sequelae of diabetes

Organization of diabetes care

CHAPTER 15: Obesity

Introduction

What is obesity?

The health and social consequences of overweight and obesity

Regulation of body weight

The causes of obesity

Genetic factors

Environmental changes

Prevention of obesity

Management of the individual with obesity

Conclusions

Index

End User License Agreement

List of Tables

Chapter 1

<u>Table 1.1 Nobel prizewinners in endocrinology and diabetes or those whose dis...</u>

<u>Table 1.2 The endocrine organs and their</u> hormones*

Chapter 2

Table 2.1 Definition and classification of enzymes

Chapter 3

Table 3.1 Use of different G-protein α-subunits by various hormone signalling...

<u>Table 3.2 Examples of modifications to hormones,</u> their precursors or metaboli...

Table 3.3 Defects in nuclear hormone signalling

<u>Table 3.4 Examples of important transcription</u> <u>factors required for the develo...</u>

Chapter 4

Table 4.1 Endocrine reference ranges

Chapter 5

<u>Table 5.1 Summary of anatomy and function of the hypothalamic nuclei</u>

<u>Table 5.2 Hormone-secreting cell types of the anterior pituitary</u>

Table 5.3 Cranial nerves in the cavernous sinus

<u>Table 5.4 Dynamic tests of growth hormone (GH)</u> <u>status</u>

Table 5.5 Treatments of acromegaly

<u>Table 5.6 Investigation and management of diabetes insipidus (DI).</u>

Chapter 6

<u>Table 6.1 Alternative names in common usage for steroidogenic enzymes</u>

Table 6.2 Dexamethasone suppression tests
Table 6.3 The effects of catecholamines
Table 6.4 Genes and associated PPGL syndromes
Chapter 7
Table 7.1 Advantages and disadvantages for different routes of administration
Table 7.2 Gynaecomastia
<u>Table 7.3 Different phases of ovarian function and their effects</u>
<u>Table 7.4 Approaching amenorrhoea with absent</u> <u>oestrogen</u>
Table 7.5 Approach to amenorrhoea with endogenous oestrogen production
Table 7.6 Treatment of PCOS
Table 7.7 Precocious puberty
Table 7.8 An approach to subfertility
Chapter 8
Table 8.1 Interpretation of thyroid function tests
Table 8.2 Symptoms, signs and examination of thyroid eye disease
Table 8.3 Thyroid malignancy
Chapter 9
Table 9.1 Comparative actions of vitamin D, parathyroid hormone (PTH) and cal
Table 9.2 Diagnostic criteria for osteoporosis on DEXA
Table 9.3 Drugs used to prevent bone demineralisation and to treat osteoporos

Chapter 10

<u>Table 10.1 Pancreatic and gastrointestinal</u> <u>hormones</u>

Table 10.2 Distribution of carcinoid tumours

<u>Table 10.3 Categories of endocrine tumour</u> <u>predisposition syndromes</u>

Table 10.4 Features of multiple endocrine neoplasia

<u>Table 10.5 Examples of ectopic hormone secretion</u>

Chapter 11

<u>Table 11.1 Prevalence of diabetes in people aged</u> <u>20–79 years in 2019 and proj...</u>

<u>Table 11.2 Genetic mutations in maturity-onset</u> <u>diabetes of the young (MODY)</u>

<u>Table 11.3 The WHO criteria for diagnosing</u> <u>diabetes with plasma glucose</u>

Table 11.4 Factors regulating insulin release from the β -cells of the pancrea...

<u>Table 11.5 Insulin actions on carbohydrate</u> metabolism

Table 11.6 Insulin actions on fatty acid metabolism

Chapter 12

Table 12.1 Islet cell autoantibodies involved in the pathogenesis of type 1 d...

<u>Table 12.2 Risk of developing type 1 diabetes for relatives of people with ty...</u>

<u>Table 12.3 The main putative environmental</u> <u>triggers of type 1 diabetes</u>

<u>Table 12.4 Comparison of presenting features of type 1 diabetes, type 2 diabe...</u>

<u>Table 12.5 Pharmacokinetics of meal and basal</u> insulins

<u>Table 12.6 Advantages and disadvantages of twice daily and basal-bolus regime...</u>

Table 12.7 Recommendations for time-in-target for people with diabetes using ...

Table 12.9 Symptoms and signs of hypoglycaemia

<u>Table 12.10 A management regimen for diabetic ketoacidosis</u>

Chapter 13

<u>Table 13.1 Why is type 2 diabetes increasing?</u>

Table 13.2 Risk factors for type 2 diabetes

Table 13.3 Risk of developing type 2 diabetes for relatives of people with ty...

<u>Table 13.4 Examples of gene polymorphisms linked</u> with the development of type...

Table 13.5 Possible mechanisms of β-cell decline and dysfunction

<u>Table 13.6 Mortality rates in people with diabetes</u> after adjustment for poten...

<u>Table 13.7 Features of commonly used oral</u> <u>antidiabetes agents</u>

<u>Table 13.8 Properties of different sulfonylureas</u>

<u>Table 13.9 Properties of different GLP-1 receptor agonists</u>

Chapter 14

<u>Table 14.1 Five stages of classical diabetic</u> <u>nephropathy</u>

Table 14.2 Do's and Don'ts of foot care

<u>Table 14.3 Features to differentiate acute Charcot from cellulitis</u>

<u>Table 14.4 Cancers that occur more frequently in people with diabetes with re...</u>

<u>Table 14.5 Psychological and psychiatric conditions</u> that are consequences of,...

<u>Table 14.6 Comparison of IADPSG/WHO and NICE diagnostic criteria for gestatio...</u>

Chapter 15

<u>Table 15.1 The World Health Organization</u> <u>assessment of sex-specific waist cir...</u>

<u>Table 15.2 Physical health risks associated with obesity</u>

<u>Table 15.3 Genetic causes of and associations with obesity</u>

<u>Table 15.4 Examples of how the size of commercially available portions has in...</u>

<u>Table 15.5 Examples of light, moderate & vigorous physical activity</u>

Table 15.6 Examples of public health policies to prevent weight gain in the p...

<u>Table 15.7 Health benefits associated with 10% weight loss</u>

<u>Table 15.8 Choice of treatment modality for obesity according to body mass in...</u>

<u>Table 15.9 Clinical assessment of a person with obesity</u>

Table 15.10 Pharmacotherapy for obesity

List of Illustrations

Chapter 1

Figure 1.1 Chemical signalling in the endocrine and neural systems. (a) In e...

<u>Figure 1.2 The sites of the principal endocrine</u> <u>glands. While the stomach, k...</u>

<u>Figure 1.3 The structures of vasopressin and oxytocin are remarkably similar...</u>

<u>Figure 1.4 Control systems regulating hormone</u> <u>production and circulating lev...</u>

Chapter 2

<u>Figure 2.1 Cell division. Prior to mitosis and meiosis, the cell undergoes a...</u>

<u>Figure 2.2 Schematic representation of a gene, transcription and translation...</u>

<u>Figure 2.3 (a) Peptide hormone-synthesizing and (b) steroid hormone-synthesi...</u>

<u>Figure 2.4 Potential post-translational modifications</u> <u>of peptide hormones. F...</u>

<u>Figure 2.5 Synthesis of cholesterol. Step ① is catalyzed by the enzyme thiol...</u>

<u>Figure 2.6 Overview of the major steroidogenic pathways. Yellow shading indi...</u>

Chapter 3

Figure 3.1 The different classes of hormone receptor. Some cell-surface rece...

Figure 3.2 Basic components of a membranespanning cell-surface receptor. Th...

<u>Figure 3.3 Hormone-receptor systems are</u> <u>saturable. Increasing amounts of lab...</u>

<u>Figure 3.4 Hormone-receptor interactions are</u> reversible. Constant amounts of...

<u>Figure 3.5 Intracellular signalling via</u> <u>phosphorylation. (a) Amino acids ser...</u>

Figure 3.6 The insulin receptor and a simplified view of its signalling path...

<u>Figure 3.7 Growth hormone (GH) signalling and its antagonism. GH binds to it...</u>

<u>Figure 3.8 Growth hormone (GH) receptor and its signalling pathways. The rec...</u>

<u>Figure 3.9 Laron syndrome showing truncal obesity.</u>
<u>This boy presented aged 1...</u>

<u>Figure 3.10 G-protein-coupled receptors. The extracellular domain is ligand-...</u>

<u>Figure 3.11 Second messengers that mediate G-protein-coupled receptor signal...</u>

<u>Figure 3.12 Hormonal activation of G-protein-coupled receptors can link to d...</u>

<u>Figure 3.13 Familial male precocious puberty</u> ('testotoxicosis'). This 2-year...

<u>Figure 3.14 McCune-Albright syndrome. At 6 years of age, this girl presented...</u>

<u>Figure 3.15 The activation of protein kinase A, a cAMP-dependent protein kin...</u>

<u>Figure 3.16 Hormonal stimulation of intracellular phospholipid turnover and ...</u>

<u>Figure 3.17 Eicosanoid signalling. Arachidonic acid,</u> released by phospholipa...

Figure 3.18 Simplified schematic of nuclear hormone action. (a) Free hormone...

<u>Figure 3.19 The nuclear hormone receptor superfamily. The receptors, named a...</u>

Figure 3.20 Nuclear hormone receptor-DNA interactions. (a) Steroid hormone r...

Chapter 4

<u>Figure 4.1 The basics of immunoassay are shown</u> <u>for growth hormone (GH; see t...</u>

<u>Figure 4.2 The basics of an immunometric assay for growth hormone (GH; also ...</u>

<u>Figure 4.3 The basics of an immunoassay for thyroxine (T4; also see text). A...</u>

Figure 4.4 Fluorescent *in situ* hybridization in a patient with congenital hy...

<u>Figure 4.5 The basic principles of the polymerase chain reaction (PCR). PCR ...</u>

Figure 4.6 Ultrasound of a polycystic ovary. The presence of multiple small ...

<u>Figure 4.7 Abdominal computed tomography (CT)</u> with contrast. This patient pr...

<u>Figure 4.8 Magnetic resonance imaging of a pituitary tumour. (a) T1-weighted...</u>

<u>Figure 4.9 mIBG uptake by a phaeochromocytoma.</u> A whole-body I¹²³ mIBG scan w...

Chapter 5

Figure 5.1 The human pituitary gland forms at ~8 weeks of development. The b...

<u>Figure 5.2 Highly simplified structure of the hypothalamus and its neural an...</u>

<u>Figure 5.3 Visual field assessment. There is a bitemporal loss of the lower ...</u>

<u>Figure 5.4 Endocrine feedback circuits. The diagram shows interactions betwe...</u>

<u>Figure 5.5 Summary of the regulation and effects of growth hormone (GH). Som...</u>

<u>Figure 5.6 A 24-h profile of serum growth hormone</u> (GH) in a normal 7-year-ol...

<u>Figure 5.7 Dynamic tests of growth hormone (GH)</u> <u>status. (a) In an oral gluco...</u>

Figure 5.8 Two patients with acromegaly. (a) Patient 1. Note the large facia...

<u>Figure 5.9 Short stature due to growth hormone</u> (GH) deficiency and the effec...

<u>Figure 5.10 Summary of the regulation and effects of prolactin. For the infl...</u>

<u>Figure 5.11 The cleavage of pro-opiomelanocortin</u> (POMC). Adrenocorticotrophi...

Chapter 6

<u>Figure 6.1 Development of the adrenal gland. The cortex is derived in part f...</u>

Figure 6.2 Section through the adrenal cortex. (a) The blood vessels run fro...

<u>Figure 6.3 Biosynthesis of adrenocortical steroid</u> <u>hormones. HSD3B activity i...</u>

<u>Figure 6.4 The hypothalamic-anterior pituitary-adrenal axis. Higher brain fu...</u>

Figure 6.5 Typical diurnal variations in serum cortisol. Levels peak in the ...

<u>Figure 6.6 The renin-angiotensin-aldosterone axis.</u> A fall in extracellular f...

<u>Figure 6.7 The structure of a nephron and the juxtaglomerular apparatus. (a)...</u>

<u>Figure 6.8 The effects of glucocorticoid excess in Cushing disease and the b...</u>

Figure 6.9 Cushing syndrome due to an adrenocortical adenoma secreting corti...

<u>Figure 6.10 Ambiguous genitalia of a 46,XX infant with congenital adrenal hy...</u>

<u>Figure 6.11 The synthesis, storage and release of</u> catecholamines from the ch...

<u>Figure 6.12 The synthesis (upper half) and degradation (lower half) of catec...</u>

Chapter 7

<u>Figure 7.1 Sex determination and sex differentiation. (a) Cross-section of a...</u>

Figure 7.2 **D**ifferentiation of the internal genitalia. (a) The bipotential sta...

<u>Figure 7.3 Development of the external genitalia.</u> <u>DHT, 5α-dihydrotestosteron...</u>

<u>Figure 7.4 Genitalia of a 2-year old with a 46,XY difference in sex developm...</u>

Figure 7.5 A testis in cross-section. (a) The testis is organized into lobul...

<u>Figure 7.6 The structure of the seminiferous tubule.</u> <u>Sertoli cells span the ...</u>

<u>Figure 7.7 The biosynthesis of androgens in Leydig</u> cells. Earlier steps can ...

<u>Figure 7.8 The hypothalamic-anterior pituitary-testicular axis. Negative fee...</u>

<u>Figure 7.9 The stages of pubertal development in</u> males and females as define...

Figure 7.10 Follicle growth, maturation and ovulation. The entire process ta...

<u>Figure 7.11 The 28-day menstrual cycle. The start of menstruation is day 1 o...</u>

Figure 7.12 The two-cell biosynthesis of oestrogens. Luteinizing hormone (LH...

<u>Figure 7.13 The hypothalamic-anterior pituitary-ovarian axis. Note the varia...</u>

Figure 7.14 Changes in the uterine endometrium during the menstrual cycle. (...

<u>Figure 7.15 The role of human chorionic</u> gonadotrophin (hCG) in postponing me...

<u>Figure 7.16 Steroid production in the feto-placental unit.</u>

Chapter 8

<u>Figure 8.1 The thyroid gland and its downward migration. The point of origin...</u>

<u>Figure 8.2 Histology of the human thyroid gland.</u>
(a) <u>Euthyroid follicles are...</u>

Figure 8.3 The structures of active and inactive thyroid hormones and their ...

Figure 8.4 Thyroid hormone biosynthesis within the follicular cell. Active i...

<u>Figure 8.5 A large goitre caused by iodine deficiency in rural Africa. Note ...</u>

<u>Figure 8.6 The hypothalamic-anterior pituitary-thyroid axis. The more active...</u>

<u>Figure 8.7 Metabolism of thyroid hormones in the</u> circulation. Four times mor...

<u>Figure 8.8 Hyperthyroidism caused by Graves disease in a young woman. The do...</u>

<u>Figure 8.9 Complications of Graves disease. (a-c)</u> <u>Examples of thyroid eye di...</u>

Chapter 9

<u>Figure 9.1 Calcium homeostasis. In an adult, daily net absorption from the g...</u>

<u>Figure 9.2 The sources and metabolism of vitamin D.</u>

<u>Figure 9.3 Synthesis of calcitriol. (a) UV irradiation opens the B ring of 7...</u>

Figure 9.4 Effects of changing Ca^{2+} and $PO_{\underline{4}}$ ³⁻ on renal hydroxylation ...

<u>Figure 9.5 Section through the fetal pharynx</u> <u>illustrating development of the...</u>

<u>Figure 9.6 Parathyroid hormone (PTH) secretion in response to serum Ca²⁺. (a...</u>

<u>Figure 9.7 Short fourth metacarpals in pseudohypoparathyroidism.</u>

<u>Figure 9.8 Venous sampling for parathyroid</u> <u>hormone (PTH) prior to surgery to...</u>

<u>Figure 9.9 Bone remodelling. Mechanical stress influences bone remodelling w...</u>

Figure 9.10 Changes in bone mass during life in men and women.

<u>Figure 9.11 Rickets. (a) Bowing of the tibiae in a 3-year-old. (b) Radiologi...</u>

Chapter 10

<u>Figure 10.1 A pancreatic islet surrounded by exocrine tissue.</u> β-cells are de...

<u>Figure 10.2 Congenital hyperinsulinism (diffuse form). Immunohistochemistry ...</u>

<u>Figure 10.3 Necrolytic migratory erythema in a man with the glucagonoma synd...</u>

Figure 10.4 Synthesis and degradation of serotonin. *Rate-limiting step: two...

<u>Figure 10.5 Two mechanisms for tumour formation.</u>
<u>Mutated or silenced genes a...</u>

Chapter 11

<u>Figure 11.1 Worldwide prevalence of diabetes in 2019 with projected figures ...</u>

<u>Figure 11.2 International Diabetes Federation</u> <u>estimates of the current and p...</u>

Figure 11.3 The Amadori reaction leading to the formation of glycated haemog...

<u>Figure 11.4 Representative distribution of fasting plasma glucose within the...</u>

<u>Figure 11.5 Relationship between plasma glycated</u> <u>haemoglobin and microvascul...</u>

Figure 11.6 Insulin synthesis and secretion from the β cells of pancreatic i...

Figure 11.7 The endocrine pancreas. (a) Small clusters of cells, the islets ...

<u>Figure 11.8 Characteristic biphasic release of insulin.</u>

Figure 11.9 Mechanism of insulin secretion. After uptake, glucose is metabol...

Figure 11.10 Insulin signalling cascade. IRS, insulin receptor substrate; PI...

<u>Figure 11.11 Regulation of blood glucose</u> <u>concentration. Tissue utilization o...</u>

<u>Figure 11.12 Inter-relationships among alternative</u> routes of glucose metabol...

<u>Figure 11.13 Regulation of acetyl co-enzyme A</u> (CoA) carboxylase by allosteri...

<u>Figure 11.14 The synergistic actions of insulin, IGF-I, and GH on protein sy...</u>

Chapter 12

Figure 12.1 Annual number of new cases of type 1 diabetes per 100,000 childr...

<u>Figure 12.2 Life-expectancy and type 1 diabetes in a Scottish cohort. Life-e...</u>

<u>Figure 12.3 The natural history of type 1 diabetes.</u> <u>In stage 1, an autoimmun...</u>

<u>Figure 12.4 Pictures of one of the first people with diabetes to receive ins...</u>

<u>Figure 12.5 Normal insulin secretion throughout a 24-h period. There is a lo...</u>

<u>Figure 12.6 The timeline of the development of insulin. Banting and Best fir...</u>

<u>Figure 12.7 Schematic of the time action of profiles of various insulin prep...</u>

<u>Figure 12.8 Schematic representation of insulin profiles with different regi...</u>

Figure 12.9 Sites for injection.

Figure 12.10 (a) An old insulin needle and syringe. (b) A modern insulin syr...

<u>Figure 12.11 (a) Person with type 1 diabetes</u> wearing a Medtronic Minimed Mio...

<u>Figure 12.12 Freestyle Optium Neo glucose meter.</u>

<u>Figure 12.13 (a) Man wearing Freestyle Libre</u> <u>sensor in the kitchen; (b) Woma...</u>

<u>Figure 12.14 Hypoglycaemia unawareness. The thresholds for activation of hyp...</u>

<u>Figure 12.15 Biochemistry of diabetic ketoacidosis.</u> <u>Hormone-sensitive lipase...</u>

Chapter 13

<u>Figure 13.1 Prevalence of diabetes in selected</u> countries in the age range of...

<u>Figure 13.2 Top ten countries for number of people</u> with diabetes in the age ...

<u>Figure 13.3 Diabetes prevalence in white US men and women by age (2015).</u>

Figure 13.4 Risk of developing diabetes according to body mass index in 114,...

<u>Figure 13.5 The pathophysiology of type 2 diabetes.</u> The cardinal features ar...

<u>Figure 13.6 (a) Endogenous insulin secretion in type 2 diabetes and under no...</u>

<u>Figure 13.7 Natural history of insulin resistance</u> and insulin secretion in t...

Figure 13.8 (a) Under normal physiological conditions, the renal tubule re-a...

<u>Figure 13.9 The imperative for screening for type 2</u> diabetes. It is estimate...

Figure 13.10 Main sites of action for antidiabetes agents. Different antidia...

<u>Figure 13.11 Ligand-activated nuclear hormone</u> <u>receptors (review Chapter 3). ...</u>

<u>Figure 13.12 Thiazolidinediones: mode of action.</u>
<u>After the thiazolidinedione...</u>

Figure 13.13 How thiazolidinediones enhance insulin action and normalize blo...

Figure 13.14 Actions of GLP-1 and mode of action of DPP-4 inhibitors and GLP...

<u>Figure 13.15 Gastrointestinal carbohydrate</u> <u>digestion and site of action of a...</u>

Chapter 14

Figure 14.1 The chronic microvascular and macrovascular complications of dia...

Figure 14.2 Effect of improved glycaemic management on diabetes (DM) related...

Figure 14.3 Molecular mechanisms that may be important in the generation of ...

<u>Figure 14.4 Sorbitol Polyol Pathway. The normal</u> function of aldose reductase...

<u>Figure 14.5 Retinal photographs reproduced with</u> the kind permission of the U...

<u>Figure 14.6 A suggested plan for annual screening</u> <u>for kidney disease in diab...</u>

Figure 14.7 Algorithm for management of painful neuropathy in people with di...

<u>Figure 14.8 Plantar ulcer in a person with diabetes.</u>
<u>Note how dry the skin a...</u>

<u>Figure 14.9 Infected diabetic ulcer on the dorsum</u> of the foot.

Figure 14.10 (a) The combination of infection and vascular disease puts the ...

Figure 14.11 Active Charcot arthropathy.

Figure 14.12 Plantar ulcer in a patient with diabetes whose foot has become ...

Chapter 15

Figure 15.1 The global prevalence of obesity in 2016.

Figure 15.2 All-cause mortality versus BMI for men and women in the range 15...

<u>Figure 15.3 Model of regulation of food intake.</u>
<u>Appetite is stimulated by ne...</u>

<u>Figure 15.4 What is a successful outcome?</u>

Figure 15.5 Rationale of 500 kcal deficit diet.

Figure 15.6 Additive effects of diet and drugs.

Essential Endocrinology and Diabetes

Richard I.G. Holt

Professor in Diabetes and Endocrinology Human Development and Health Faculty of Medicine University of Southampton, Southampton, UK

Neil A. Hanley

Professor of Medicine Faculty of Biology, Medicine and Health University of Manchester, Manchester, UK

Seventh Edition



This edition first published 2021 © 2021 John Wiley & Sons Ltd

Edition History Wiley-Blackwell (6e, 2012)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at http://www.wiley.com/go/permissions.

The right of Richard I.G. Holt and Neil A. Hanley to be identified as the authors of this work has been asserted in accordance with law.

Registered Office(s)

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office

9600 Garsington Road, Oxford, OX4 2DQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-ondemand. Some content that appears in standard print versions of this book may not be available in other formats.

Limit of Liability/Disclaimer of Warranty

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting scientific method, diagnosis, or treatment by physicians for any particular patient. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. While the publisher and authors have used their best efforts in preparing this work, they make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives, written sales materials or promotional statements for this work. The fact that an organization, website, or product is referred to in this work as a citation and/or potential source of further information does not mean that the publisher and authors endorse the information or services the organization, website, or product may provide or recommendations it may make. This work is sold with the understanding that the publisher is not engaged in rendering professional

services. The advice and strategies contained herein may not be suitable for your situation. You should consult with a specialist where appropriate. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this work was written and when it is read. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

Library of Congress Cataloging-in-Publication Data

Names: Holt, Richard I. G., author. | Hanley, Neil A., author.

Title: Essential endocrinology and diabetes / Richard I.G. Holt, Neil A. Hanley.

Other titles: Essentials (Wiley-Blackwell (Firm))

Description: Seventh edition. | Hoboken, NJ: John Wiley & Sons, Inc., 2021. |

Series: Essentials | Includes bibliographical references and index.

Identifiers: LCCN 2020044319 (print) | LCCN 2020044320 (ebook) | ISBN

9781118763964 (paperback) | ISBN 9781118764138 (adobe pdf) | ISBN

9781118764121 (epub)

Subjects: MESH: Endocrine Glands-physiology | Hormones-physiology |

Endocrine System Diseases | Diabetes Mellitus

Classification: LCC RC649 (print) | LCC RC649 (ebook) | NLM WK 100 | DDC

616.4-dc23

LC record available at https://lccn.loc.gov/2020044319

LC ebook record available at https://lccn.loc.gov/2020044320

Cover Design: Wiley

Cover Image: © JOHN BAVOSI/Science Source

Preface

Welcome to the latest edition of Essential Endocrinology & Diabetes. We are delighted that the previous edition was so well received around the world, selling over 5600 copies. The book also had the dubious honour of being the most frequently stolen book from the University of Southampton medical school library suggesting that the medical students, in Southampton at least, found it a useful accompaniment to their endocrinology and diabetes course. However, it is time for an update and a refresh that captures the latest research, clinical guidelines, investigational modalities and therapies. We hope you enjoy the new content.

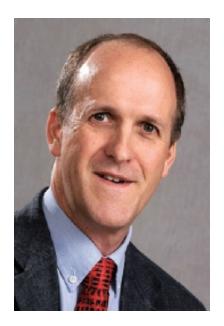
The textbook aims to be valued by different groups of reader. Its core purpose is still to provide a foundation from understanding the science to clinical training in undergraduate medicine. In addition, the content here should also be invaluable for postgraduate clinicians training in the speciality of endocrinology and diabetes. Written 'exit' examinations have become increasingly common during the later stages of clinical speciality training and we hope our textbook provides complementary study material alongside larger reference textbooks and published clinical guidelines. From feedback, we realise that our book has been valued by biomedical undergraduate and masters students and by those pursuing clinical biochemistry. We hope the new content increases this reach across different audiences. Learning objectives, recap points, cross-referencing guides, boxes, and concluding key points help orientate the reader and emphasize the major topics.

Based on the success of previous editions, the book is still structured in much the same way. The first part is designed to create a knowledgeable reader, well prepared for the clinical sections or for more specific scientific study. To assist the many students coming from non-scientific backgrounds we limit assumptions on prior knowledge. <u>Chapter 1</u> still covers the core principle of feedback regulation which underlies nearly all endocrine physiology and is vital for the correct interpretation of many clinical tests. Chapter 3 has advanced to encompass the latest research made possible from next-generation sequencing technology. The latter has already started to impact significantly on clinical investigation and diagnostics in endocrinology and diabetes. This is covered in Chapter 4, which also includes positron emission tomography (PET) imaging. It is important that aspiring clinicians, as well as scientists, appreciate these new approaches, their application and their challenges. The second part of the book still follows its organ or system-based approach. We have retained the more specific scientific knowledge at the start of these chapters to underpin understanding, diagnosing and managing the relevant clinical disorders. The third part on diabetes and obesity has seen the greatest change from the previous edition. Over the last 8 years, there have been significant advances in the treatment of both type 2 diabetes, such as an expansion of the indications for incretin-based therapies and the introduction of the SGLT2 inhibitors, and type 1 diabetes with the development of better insulins and the use of technology to support self-management. Clinical algorithms have also changed and these have been updated.

As previously, the book is founded on our collective clinical and research experience and has been a truly collaborative venture. The book is designed to read as a whole, however, inevitably one of us has taken a lead with each chapter

according to our own particular expertise. When we wrote the 5th edition, NAH took the responsibility for Part 1 and Part 2, while RIGH was responsible for Part 3. Now on our third edition, we have each taken the opportunity to bring our experience to each of the chapters. Finally, we must thank a number of people. We are grateful for the skilled help of the team at Wiley. It is still important to recognise the excellent contribution of Charles Brook and Nicholas Marshall who authored the book up to and including the 4th edition. We are also very grateful to our scientific and clinical colleagues who have been the recipients of frequent questions and from whom we have sought valued opinions. The final thank you is to our families whose support and tolerance made this book possible. Particular thanks go to Tristan Holt, now a medical student, for his helpful comments in making the book as relevant as possible for our target audience.

The authors



Richard Holt is Professor in Diabetes and Endocrinology at the University of Southampton and Honorary Consultant in Diabetes at University Hospital Southampton NHS Foundation Trust. He is partly supported by the Southampton National Institute for Health Research Biomedical Research Centre. His research interests are broadly focused around clinical diabetes with particular interests in diabetes in pregnancy, cystic fibrosis diabetes and diabetes in 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 at the University of Manchester and Honorary Consultant in Endocrinology at the Manchester University NHS Foundation Trust. His research over three decades has focussed on human development. His wider roles now include all aspects of biomedical and clinical research including the application of data science, and interests in how to triangulate healthcare, academia and the commercial sector to drive improved outcomes including economic growth.

Both authors play a keen role in teaching and training at both undergraduate and postgraduate levels. RIGH is a Fellow of the Higher Education Academy. NAH established an Academy for early career researchers at the University