MEDICAL AND SURGICAL ENDOCRINOLOGY

Medical and Surgical Endocrinology

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Preface

This largely new book has grown out of one entitled 'Clinical Endocrinology for Surgeons', which we published in 1963. Friends and reviewers were kind enough to persuade us that the title was wrong because it tended to prevent physicians and other clinicians, for whom it was suitable, from reading it. They also pointed out that laboratory workers and pre-clinical teachers found that it provided them with an account of clinical endocrinology based on the laboratory sciences and that candidates for examinations in the basic medical sciences used it for learning physiology and pathology. For these reasons we have changed the title and have tried to meet the needs of all these people.

Our first aim, as before, is to help all concerned with clinical endocrinology to understand, investigate and treat their patients. Anatomy, physiology and pathology are essential to understanding, and considerable clinical detail is required if patients are to be managed effectively. Our second aim is to help graduates and senior undergraduates to study for examinations. Our third aim is to present the clinical aspects of endocrinology to those not directly involved in the care of patients.

Endocrinology has advanced very rapidly in the past decade. The hypothalamus and the endocrine function of the gut have sprung to life, new hormones have been discovered, the interdependence of the nervous and endocrine systems has become much clearer, increasing numbers of hormones can be measured in the body fluids, the modes of action of hormones at the cellular level are being elucidated, and so on. Inclusion of much new material has increased the size of the book considerably. Many new tests of glandular function have been included. At the same time many old ones, which have been superseded in some specialized units, have been retained because the new ones are not generally available.

We believe firmly that all clinical medicine is one and that in endocrinology, as in other branches of medicine, physicians, surgeons, gynaecologists, radiodiagnosticians, radiotherapists, laboratory workers and others should, when required, work together for the solution of each patient's problems. We have therefore discussed the total management of patients from all points of view. We have discussed the indications for surgical operations and radiotherapy, and what may be expected of them, and have advised surgeons and radiotherapists what to do, without telling them in detail how to do it.

We have again attempted to provide a systematic account of clinical endocrinology, in which the essential unity of the endocrine system is emphasized. The arrangement is a little different and three new chapters have been added. The book is divided into six parts. Part 1 (the longest) describes the hypothalamus, the anterior pituitary and their dependent glands. Part 2 deals with calcium metabolism and the hormones which control it. Part 3 is concerned with the alimentary tract, including the islet cells of the pancreas. Part 4 provides a description of multiple endocrine adenopathy and of the paraendocrine syndromes. Part 5 discusses some of the endocrinological aspects of general medicine and surgery, and Part 6 is a chapter concerned with miscellaneous topics.

It is impossible for a book such as this to be up to date when it is published, because the subject is moving so fast. Indeed many alterations and additions have had to be made to chapters after their revision was thought to be complete. However, we have attempted to include everything of importance that was published up to the end of 1972 and have added a few things that have appeared since.

As before, we have not used formal references in the text, except when quoting numerical data about the results of tests (references marked*), but have included a selected list of papers and books for further reading at the end of each chapter. Some additional ones have been added at the proof stage. We have quoted SI units, when they are employed commonly, and have given them in brackets when *other* units are still in general use. A key to the abbreviations, which

we have used for units, hormones, etc. and for other terms, is provided on pp. xiv and xv and inside the back cover. A list of equivalent British and American names of drugs, hormones, etc. is given on p. xvi. We have omitted nearly all clinical photographs to prevent the book being too expensive.

We are very grateful to many present and former colleagues for their help. Dr. Mary McGeown has again written chapter 11 and has graciously accepted our editorial amendments. Five others (Mr. Cowley, Dr. Foster, Professor Johnston, Mr. McRae and Professor Sellwood) have made such considerable contributions that we have designated them 'co-authors'. In addition, the following have helped us in various ways with individual chapters and we appreciate their generous assistance:

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(15) Dr. J. Azzopardi, Dr. J. Polak;
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Belfast and London, 1974

D A D M
R B W

Abbreviations

UNITS

cm	centimetre	mosmol	milliosmole
cu	cubic	MUU	mouse uterine units
g	gram	MV	megavolt (10^6 volts)
h	hour	mv	millivolts (10^{-3} volts)
iu	international unit	ng	nanogram (10^{-9} g)
kcal	kilocalorie (4·2 kJ)	nm	nanometre (10^{-9} m)
kg	kilogram (10^3 g)	p.d.	potential difference
l	litre	pg	picogram (10^{-12} g)
m	metre	pH	$\log_{10}$ hydrogen ions per l
mCi	millicurie	rad	radiation absorbed dose (1 rad = 0·01 joule/kg)
mEq	milliequivalent		
mg	milligram (10^{-3} g)	s.d.	standard deviation
min	minute (time)	u	unit
miu	milli-international units	γ	gamma
mm	millimetre	λ	wavelength
mm^3	cubic millimetre	mCi	millicurie
mmol	millimole	μCi	microcurie
mN	millinormal	μg	microgram (10^{-6} g)
mol	mole	μm	micrometer (10^{-6} metre)
mol. wt.	molecular weight	μu	microunit

HORMONES AND RELATED SUBSTANCES

ACTH	corticotrophin (adrenocorticotrophin)	HCC	hydroxycholecalciferol
		HCG	human chorionic gonadotrophin
ADH	antidiuretic hormone	HGH	human growth hormone
CCK	cholecystokinin-pancreozymin (CCK-PZ)	5-HIAA	5-hydroxyindole acetic acid
		HMG	human menopausal gonadotrophin
CRH	corticotrophin-releasing hormone	HMPG	4-hydroxy-3-methoxyphenylglycol
D_2	calciferol		
D_3	cholecalciferol	HPG	human pituitary gonadotrophin
DCA	deoxycortone acetate	HPL	human placental lactogen
DHA	dehydroepiandrosterone	5-HT	5-hydroxytryptamine
DHCC	dihydroxycholecalciferol	5-HTP	5-hydroxytryptophan
DHT	5α-dihydrotestosterone	HVA	homovanillic acid
DIT	diiodotyrosine	ICSH	interstitial cell-stimulating hormone
DOC	deoxycorticosterone		
DOCA	deoxycorticosterone acetate	ILA	insulin-like-activity
DOPA	dihydroxyphenylalanine	IRI	immunoreactive insulin
EPS	exophthalmos-producing substance	IZS	suspension of zinc insulin
		LATS	long-acting thyroid stimulator
FRH	follicle-stimulating hormone-releasing hormone	LH	luteinizing hormone
		LH/FSH-RH	luteinizing hormone/follicle stimulating hormone-releasing hormone
FSH	follicle-stimulating hormone		
GH	growth hormone, somatotrophin		
GRH	growth hormone-releasing hormone	LPH	lipotrophin, lipolytic hormone, fat mobilizing agent
GR-IH	growth hormone release-inhibiting hormone	LRH	lutenizing hormone-releasing hormone

LVP	8-lysine vasopressin
6-MAP	medroxy-progesterone
MIT	monoiodotyrosine
MRIH	melanocyte-stimulating hormone release-inhibiting hormone
MSH	melanocyte-stimulating hormone
NPH	neutral protamine Hagedorn insulin
NUSO	neutral soluble insulin
OGS	oxogenic steroids
OHCS	hydroxycorticosteroids
OXOS	oxosteroids
PBI	protein bound iodine
PG	prostaglandin
PMSG	pregnant mare's serum gonadotrophin
PRIH	prolactin release-inhibiting hormone
PTH	parathormone
SI	soluble insulin
T_3	triiodothyronine
T_4	thyroxine
TRH	thyrotrophin-releasing hormone
TSH	thyroid-stimulating hormone, thyrotrophin
Vit.D	vitamin D
VMA	vanilmandelic acid (4-hydroxy-3-methoxy-mandelic acid

GENERAL

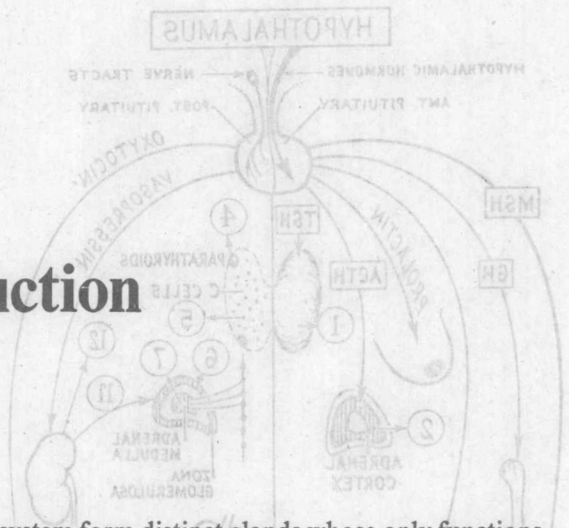
AFIP	Armed Forces Institute of Pathology (U.S.)
AIU	absolute iodine uptake
AMP	adenosine monophosphate
A-P	anterio-posterior
ATP	adenosine triphosphate
APUD	amine, precursor uptake, decarboxylase
Au	gold
BEI	butanol extractable iodine
BMR	basal metabolic rate
B.P.	British Pharmacopoeia
C-cells	calcitonin-secreting cells
CA_2	second colloid antigen
CAH	congenital adrenal hyperplasia
CBG	corticosteroid-binding globulin
CFT	complement fixation test
C.N.S.	central nervous system
CoA	coenzyme A
CPK	creatine phosphokinase
C.S.F.	cerebrospinal fluid
C.V.P.	central venous pressure
DBH	dopamine β-hydroxylase
DNA	deoxyribonucleic acid
E.C.F.	extra-cellular fluid
E.C.G.	electrocardiogram
EDTA	ethylenediamenetetraacetic acid
E.E.G.	electroencephalogram
E.S.R.	erythrocyte sedimentation rate
F.	female
FFA	free fatty acid
FTI	free thyroxine index
GFR	glomerular filtration rate
GTT	glucose tolerance test
H & E	haematoxylin and eosin
Hg	mercury
HIOMT	hydroxyindole-O-methyl-transferase
I.C.F.	intra-cellular fluid
IHC	idiopathic hypoglycaemia of childhood
i.m.	intramuscularly
INH	isoniazid
i.v.	intravenous or intravenously
I.V.P.	intravenous pyelogram
JG	juxtaglomerular
M.	male
MAO	monoamine-oxidase
MEA	multiple endocrine adenopathy
MIF	migration inhibition factor
mRNA	messenger ribonucleic acid
MTA	anaplastic malignant teratoma
MTI	malignant intermediate teratoma
MTT	malignant trophoblastic teratoma
NPN	non-protein nitrogen
p.	page
PAS	periodic acid Schiff or sodium aminosalicylate
Pco_2	partial pressure of carbon dioxide
PES	paraendocrine syndrome
PII	plasma inorganic iodide
RAI	radioiodine
RDS	repiratory distress syndrome
RNA	ribonucleic acid
RUR	resin uptake ratio
S	seminoma
SHBG	sex hormone-binding globulin (protein)
TBA	thyroid-binding albumin
TBG	thyroid-binding globulin
TBP	thyroid-binding protein
TBPA	thyroid-binding pre-albumin
TD	differentiated teratoma
TNM	tumour, nodes and metastases classification
TRC	tanned red cell
TTPR	Testicular Tumour Panel and Registry
U.S.P.	United States Pharmacopoeia
u.v.	ultraviolet
WDHA	watery diarrhoea, hypokalaemia, achlorhydria
WHO	World Health Organization
Y	yttrium
Z–E	Zollinger–Ellison

Glossary of equivalent British and American (U.S.A.) names of drugs, hormones, etc used in this book

BRITISH	AMERICAN
Actinomycin D	Dactinomycin
Adrenaline	Epinephrine
Calciferol (D_2)	Ergocalciferol (D_2)
Deoxycortone	Desoxycorticosterone
Dibenyline (Phenoxybenzamine)	Dibenzyline (Phenoxybenzamine)
Dibotin (Phenformin)	DBI (Phenformin)
Dibotin SA	DBI-TD
Dimelor (Acetohexamide)	Dymelor (Acetohexamide)
L-Dopa	Levodopa
L-Thyroxine Sodium	Sodium levothyroxine
Isoprenaline	Isoproterenol
Lignocaine	Lidocaine
Methandienone	Methandrostenolone
Methohexitone	Methohexital
Metyrapone	Methopyrapone
Noradrenaline	Norepinephrine
Norethisterone	Norethindrone
Oestradiol	Estradiol
Oestriol	Estriol
Oestrone	Estrone
Orciprenaline	Metaproterenol
17-oxogenic steroid	17-ketogenic steroid
17-oxosteroid	17-ketosteroid
Phenytoin	Diphenylhydantoin
Rastinon (Tolbutamide)	Orinase (Tolbutamide)
Rogitine (Phentolamine)	Regitine (Phentolamine)
Soluble insulin	Regular insulin
Stilboestrol	Diethylstilbestrol
Tolanase (Tolazamide)	Tolinase (Tolazamide)

Contents

Introduction



Living organisms are remarkable in that they maintain their integrity and their capacity to reproduce in a hostile world. The animal body does so by means of a highly delicate and complex organization which is controlled mainly through the nervous and endocrine systems; and these, as we shall see, are so closely related as to be almost one.

Endocrinology, although a young branch of biological science, is now approaching maturity. Most of the secretions of the endocrine tissues have been identified, many can be estimated by precise analytical methods and a large number of them have been synthesized. Much is known of the chemical processes involved in their biosynthesis, and those concerned with their biological effects are now being elucidated. The endocrine tissues must be considered as a closely integrated system which influences many of the metabolic processes of the body in health and disease. They are involved not only in the diseases which are commonly regarded as endocrine in nature but also in such common processes as growth and pregnancy, the response of the body to infection and trauma, and the development of cancers of the breast and prostate.

ANATOMY OF THE ENDOCRINE SYSTEM

No anatomical classification of the endocrine system is entirely satisfactory (fig. 1). Its constituent parts are derived from all three germ layers and in many instances (the anterior pituitary, the adrenal glands and the thyroid gland, for instance) derivatives of two different layers are combined. While some parts of the system form distinct glands whose only functions are endocrine, others are scattered as separate cells or as clumps of cells in organs which have other important, and sometimes more important, functions.

Much of the endocrine system, however, is related developmentally, anatomically or functionally to the nervous system, and since the two are so interdependent, it seems important and convenient to base the classification on this relationship (table I).

Hypothalamus and dependent glands

The hypothalamus (AI), which is part of the brain and under the control of the higher nervous centres, is the most important part of the endocrine system. It controls directly the anterior pituitary gland (adenohypophysis) (AI1) and, indirectly (via the pituitary), several other glands, namely the adrenal cortex, the gonads and the major part of the thyroid. Part of the hypothalamus (AI2) extends into the posterior pituitary (neurohypophysis) to form a single anatomical and functional unit. Nuclei within the hypothalamus, or closely related to it, (AI3) control the sympathetic nervous system, which includes the adrenal medulla.

Endocrine glands and tissues of neural crest origin

Another group of widely separated endocrine tissues (AII) is derived (or probably derived) in early fetal life from the neural crest, which is formed from the neural folds. They are thus, embryologically, derivatives of the nervous system, and share with the primitive neural crest

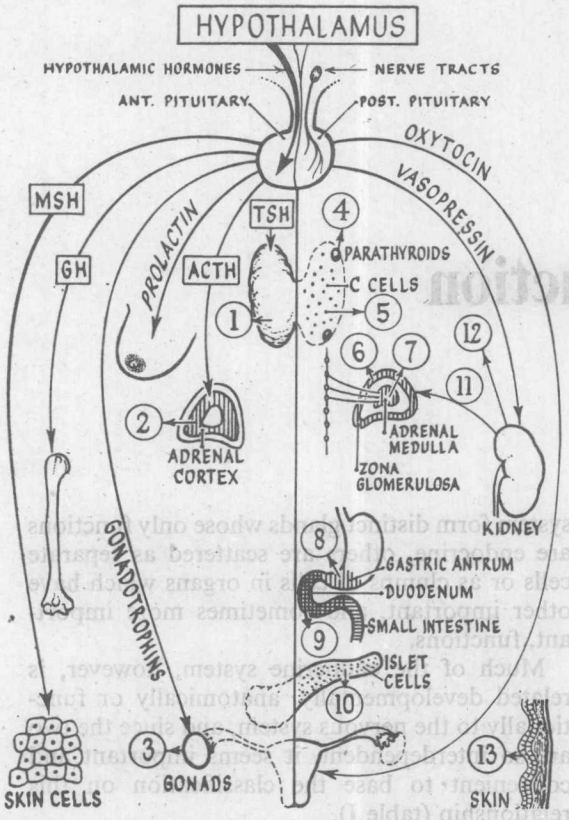


Fig. 1 The endocrine system. Glands and structures on the *left* are influenced largely by the hormones of the anterior pituitary, while those on the *right* are not.

→ indicates that the hormone shown controls the gland or tissue to which the arrow is directed. The pineal and the thymus are omitted, because their endocrinological roles are uncertain.

1 = thyroid hormones
2 = cortisol and sex hormones
3 = sex hormones
4 = parathormone
5 = calcitonin
6 = aldosterone
7 = catecholamines
8 = gastrin
9 = alimentary hormones
10 = insulin, glucagon
11 = renin
12 = erythropoietin
13 = vitamin D

certain structural and histochemical characteristics. Although they become separated from the central nervous system anatomically, some develop important secondary connections with it through the autonomic nerves. These tissues, unlike the glands controlled by the hypothalamus, comprise endocrine cells or clusters of cells within other organs, most of which are not primarily endocrine in nature. They include the parafollicular cells of the thyroid, the endocrine cells of the alimentary tract and the islet cells of the pancreas. Other cells of this series, particularly some in the alimentary tract, the bronchi and the carotid body, and the melanocytes of the skin, whose characteristics suggest an endocrine function, have no known secretions. The whole of the sympathetic nervous system (already listed under AI) and possibly some of the cells of the anterior pituitary (those secreting ACTH and MSH) are also of neural crest origin.

Endocrine glands and tissues mainly independent of nervous system

Finally a group of endocrine glands and tissues (B) is apparently mainly independent of the nervous system. It includes the parathyroids, part of the adrenal cortex, parts of other organs and tissues, and the blood.

PHYSIOLOGY OF THE ENDOCRINE SYSTEM

Hormones

The endocrine system produces its effects by elaborating hormones. These are substances which stimulate or inhibit the function of cells, without themselves being used as sources of energy. Their actions are physiological and they are effective in very low concentrations. Most known hormones are secreted directly into the blood by specialized groups of cells and are carried to other responsive cells, where they exert their effects. In some cases the lymphatics provide an important, and occasionally the major, channel of entry into the blood. Some hormones do not follow this simple pattern. A few, such as angiotensin II, are formed from precursors in the blood, and dihydrotestosterone, an active hormone, is formed from its inactive precursor, testosterone, within androgen-responsive target cells. Vitamin D (which is a hormone by definition) has several singular features. It is synthesized in an inactive form in the skin, under the influence of sunlight, and is carried by the blood to the liver and to the kidneys, where it is converted into active derivatives. In the absence of sunlight, closely related compounds, supplied as vitamins in the diet, provide adequate substitutes.

The nervous and endocrine systems are closely related functionally as well as anatomically. Neurotransmission at synapses in the central and

Table I Classification of the endocrine system (The pineal and the thymus are omitted, because their endocrinological roles are uncertain)

Key:
BLOCK CAPITALS indicate Endocrine glands or tissues.
Words in *italics* indicate Hormones
⟶ indicates that hormone preceding *controls* hormone, gland or tissue following.
: indicates that gland or tissue preceding secretes hormone(s) following.

A. Endocrine glands and tissues related to nervous system.

I. Hypothalamus and dependent glands

1. **HYPOTHALAMIC NUCLEI SECRETING TROPHIC HORMONES:**

	ANTERIOR PITUITARY: Hormones	**Target Glands and Tissues**	**Main Hormones**
a. Releasing hormones (RH)			
i. *Growth hormone—RH* ⟶	*GH* ⟶	All tissues	—
ii. *Thyrotrophin—RH* ⟶	*TSH* ⟶	THYROID (follicular cells):	*Thyroxine and triiodothyronine*
iii. *Corticotrophin—RH* ⟶	*ACTH* ⟶	ADRENAL CORTEX (inner zones):	*Cortisol, androgens oestrogens*
iv. *Follicle-stimulating hormone—RH* ⟶	*FSH* ⟶	OVARY: Testis (tubules)	*Oestrogens* —
v. *Luteinizing hormone—RH* ⟶	*LH* ⟶	OVARY: TESTIS (Leydig cells):	*Progesterone* *Testosterone*
b. Inhibiting hormones (IH)			
i. *Prolactin release—IH* ⟶	*Prolactin* ⟶	Breast	—
ii. *Melanocyte-stimulating hormone—IH* ⟶	*MSH* ⟶	Melanocytes	—

2. **HYPOTHALAMIC NUCLEI RELATED TO POSTERIOR PITUITARY (NEUROHYPOPHYSIS):**
   a. *Antidiuretic hormone* ⟶ Renal tubules
   b. *Oxytocin* ⟶ Uterus and breast
3. **HYPOTHALAMIC (OR CLOSELY RELATED) NUCLEI CONTROLLING SYMPATHETIC NERVOUS SYSTEM**
   ADRENAL MEDULLA and SYMPATHETIC NERVOUS TISSUE: *Catecholamines*

II. Endocrine glands and tissues derived (or probably derived) from neural crest

1. THYROID (PARAFOLLICULAR CELLS): *calcitonin*
2. ALIMENTARY TRACT (ENDOCRINE CELLS): *gastrin, secretin, cholecystokinin, enteroglucagon, enterogastrone, etc., 5-hydroxytryptamine*
3. PANCREATIC ISLET CELLS: *insulin, glucagon*

B. Endocrine glands and tissues apparently mainly independent of nervous system

1. PARATHYROIDS: *parathormone*
2. SKIN: *vitamin D* (precursor)
3. ADRENAL CORTEX (zona glomerulosa): *aldosterone*
4. KIDNEY: *renin, vitamin D* (active), *erythropoietin*
5. BLOOD: *angiotensin II, kinins*
6. LIVER: *vitamin D* (active)
7. OTHER TISSUES: *histamine, prostaglandins*
8. PLACENTA: *gonadotrophin, placental lactogen, thyrotrophin, progesterone, oestrogens*