

CLINICAL ENDOCRINOLOGY

BY

ALLAN WILLIAM SPENCE
M.A., M.D. (Cantab.), F.R.C.P. (London)
Physician, St. Bartholomew's Hospital, London



CASSELL AND COMPANY LIMITED
LONDON
1953

CASELL & CO. LTD
37/38 St. Andrew's Hill, Queen Victoria Street
London, E.C.4
and at
210 Queen Street, Melbourne
26/30 Clarence Street, Sydney
Haddon Hall, City Road, Auckland, N.Z.
1068 Broadview Avenue, Toronto 6
122 East 55th Street, New York
Galeria Guemes, Escritorio 518/520 Florida 165, Buenos Aires
Haroon Chambers, South Napier Road, Karachi
17 Central Avenue P.O. Dharamtala, Calcutta
P.O. Box 275, Cape Town
P.O. Box 1386, Salisbury
15 Graham Road, Ballard Estate, Bombay, 1
Islands Brygge 5, Copenhagen
Avenida 9 de Julho 1138/51, Sao Paulo
P.O. Box 959, Accra, Gold Coast
Calcada Do Carma 55-20, Lisbon
25 rue Henri Barbusse, Paris 5e

First edition 1953

ALL RIGHTS RESERVED

MADE AND PRINTED IN GREAT BRITAIN
AT THE CHAPEL RIVER PRESS
ANDOVER, HANTS
753

PREFACE

THIS book is written for the general physician and for those aspiring to become clinical endocrinologists. Stress has therefore been laid on the clinical features of endocrine diseases and diagnostic procedures and treatment have been described in some detail. To remind the reader of the debt we owe to the pioneers of the subject the historical aspects of each disease have been briefly described. As in other branches of medicine, a knowledge of physiology is, in the author's opinion, essential for the proper understanding of disordered function and for rational therapeutics, and therefore a brief account has been given of the actions of the various hormones. The anatomy of the endocrine glands has been purposely omitted because, although it is of advantage to be cognisant of the situation of these organs, this knowledge is acquired in one's preliminary studies and detailed information is more suitably obtained in textbooks of anatomy. The author has not been bold enough to include diabetes mellitus, for the reason that it is a separate branch of endocrinology and the province of physicians who devote themselves almost entirely to its study.

During the last two decades enormous strides have been made in our knowledge of endocrinology, largely through the work of the chemists and physiologists. There was a time within the memory of the author when endocrinology was the Cinderella of medicine, but now it encroaches on almost every branch and through the original investigations at the Mayo Clinic it has been shown to play an important part in diseases in which hitherto an endocrine factor had never been conceived. The result has been that almost over-night rheumatologists, ophthalmologists, dermatologists and a host of others have taken up the study of this complex subject. A vast literature has grown up, so that to keep pace with the publications relating even to only one gland is a task of some magnitude. As far as possible those authors who made the original observations have been quoted in this book, but, to avoid being cumbersome, a large number of investigators who have contributed to the subject have had to pass unmentioned, their place being taken by those who have written monographs or reviews.

The author expresses his thanks to Messrs. Butterworth & Co., Ltd., for kindly granting him permission to incorporate certain sections of his contribution to their publication "Medical Treatment; Principles and Their Application," edited by Dr. Geoffrey Evans. He also thanks Dr. Oliver Garrod for his suggestions and criticism of the chapter on Diabetes Insipidus and Mr. C. W. S. Taylor, B.Sc., A.R.I.C., of the Ciba Laboratories, Ltd., for obtaining for him certain references in respect of the chemistry of the steroid hormones. The author should record his indebtedness to that valuable book by Sir

PREFACE

Humphry Rolleston, "The Endocrine Organs in Health and Disease," which is a mine of historical information.

The bulk of the illustrations are photographs of the author's own cases and for others he is indebted to Dr. William Evans, Mr. M. A. Falconer, F.R.C.S., Dr. A. Shapiro and Dr. D. A. G. Galton and to his colleagues and erstwhile colleagues at St. Bartholomew's Hospital, namely, Sir Francis Fraser, Sir Thomas Dunhill, Mr. Geoffrey Keynes, F.R.C.S., Dr. C. F. Harris, Mr. Rupert Corbett, F.R.C.S., Mr. John Hosford, F.R.C.S., Mr. C. Naunton Morgan, F.R.C.S., Dr. E. F. Scowen, Dr. A. W. Franklin, Dr. I. G. Williams and Dr. V. C. Medvei. Thanks are due to Messrs. Butterworth & Co., Ltd., for permission to publish Figures 2 and 3, which appear in the author's article on Acromegaly in the *British Encyclopædia of Medical Practice*, 2nd Edition and Figure 21 from *Surgical Progress* 1952, to the F. A. Davis Company for Figure 37 from the author's article in *Cyclopedia of Medicine*, to the Editor of the *British Journal of Cancer* for permission to publish Figures 42 and 43, to the Editors of the *Proceedings of the Royal Society of Medicine* for Figures 10 and 25, to the Clarendon Press for Figures 11, 12 and 36, to Messrs. John Wright & Sons for Figure 45, and to the Photographic Department of the Luton and Dunstable Hospital for Plate II. Finally, it is a pleasure to record the author's indebtedness to Mr. N. K. Harrison, A.R.P.S., and his staff of the Photographic Department, St. Bartholomew's Hospital, for their long-continued and helpful co-operation.

A. W. SPENCE

CONTENTS

	PAGE
SECTION I. THE PITUITARY GLAND AND THE HYPOTHALAMUS	
Chapter I. The Pituitary Hormones	3
The Growth Hormone	3
The Gonadotrophic Hormones	6
The Thyrotrophic Hormone	10
The Adrenocorticotrophic Hormone	10
The Lactogenic Hormone	13
Antihormones	14
The Posterior and Intermediate Lobes	16
The Hypothalamus	19
Chapter II. Tumours of the Pituitary Gland	22
Chapter III. Acromegaly	33
Gigantism	47
Chapter IV. Cushing's Syndrome	51
Chapter V. Hypopituitarism	70
Chapter VI. Hypothalamic and Posterior Pituitary Syn- dromes	88
Fröhlich's Syndrome	88
Diabetes Insipidus	92
Hand-Schüller-Christian Syndrome	100
Hyperfunction of the Posterior Lobe	101
Laurence-Moon-Biedl Syndrome	102
Polyostotic Fibrous Dysplasia	105
 SECTION II. THE THYROID GLAND	
Chapter VII. The Thyroid Hormone	115
Chapter VIII. Simple Goitre	126
Chapter IX. Toxic Goitre	140
Chapter X. Hypothyroidism	185
Cretinism	185
Myxœdema	192
Juvenile Myxœdema	204
Mild Hypothyroidism	205
Chapter XI. Tumours of the Thyroid Gland	207
Chapter XII. Thyroiditis	210
Acute Thyroiditis	210
Chronic Thyroiditis	211
Lymphadenoid Goitre	213

CONTENTS

	PAGE
SECTION III. THE PARATHYROID GLANDS	
Chapter XIII. The Parathyroid Hormone . . .	217
Chapter XIV. Hypoparathyroidism . . .	221
Pseudohypoparathyroidism . . .	228
Chapter XV. Hyperparathyroidism . . .	230
Secondary Hyperparathyroidism . . .	230
Primary Hyperparathyroidism . . .	231
Acute Hyperparathyroidism . . .	241
 SECTION IV. THE ADRENAL GLANDS	
Chapter XVI. The Adrenal Hormones . . .	245
The Medullary Hormones . . .	246
The Cortical Hormones . . .	249
The Pituitary-Adrenal System . . .	259
Stress . . .	259
Diseases of Adaptation . . .	261
Chapter XVII. Cortisone and the Adrenocorticotrophic Hormone in General Medicine . . .	263
Chapter XVIII. Addison's Disease . . .	269
Chapter XIX. Adrenal Hæmorrhage . . .	291
Chapter XX. Hyperfunction of the Adrenal Cortex . . .	297
Adrenal Virilism . . .	298
Adrenal Feminism . . .	309
Chapter XXI. Tumours of the Adrenal Medulla . . .	312
Sympathetic Nerve Cell Tumours . . .	312
Phæochromocytoma . . .	314
 SECTION V. THE MALE ORGANS OF REPRODUCTION	
Chapter XXII. The Testicular Hormone . . .	325
Chapter XXIII. Eunuchism . . .	333
Chapter XXIV. Hypogonadism . . .	338
The Male Climacteric . . .	346
Chapter XXV. Disorders of Libido . . .	349
Impotence . . .	349
Excessive Libido . . .	351
Chapter XXVI. Undescended Testes . . .	352
Chapter XXVII. Endocrine Tumours of the Testes . . .	361

CONTENTS

	PAGE
Chapter XXVIII. Disorders of the Prostate and of the	
Seminal Vesicles	363
Benign Hypertrophy of the Prostate	363
Carcinoma of the Prostate	364
Chronic Hæmospermia	366
SECTION VI. THE FEMALE ORGANS OF REPRODUCTION	
Chapter XXIX. The Ovarian Hormones	369
The Sex Hormones in Pregnancy	382
Chapter XXX. Ovarian Infantilism	387
Ovarian Agenesis (Turner's Syndrome)	392
Chapter XXXI. Disorders of Menstruation	398
Amenorrhœa	398
Functional Dysmenorrhœa	405
Intermenstrual Pain	411
Premenstrual Tension	411
Functional Uterine Hæmorrhage	413
Chapter XXXII. Disorders of Libido	424
Frigidity	424
Excessive Libido	425
Chapter XXXIII. Endocrine Tumours of the Ovary and	
Endometriosis	426
Chapter XXXIV. Disorders of Pregnancy	429
Toxæmias of Pregnancy	429
Threatened and Habitual Abortion	429
Diabetes Mellitus	431
Induction of Labour	432
Chapter XXXV. The Climacteric	434
SECTION VII. THE BREASTS	
Chapter XXXVI. Hormonal Control of the Breasts	443
Chapter XXXVII. Disorders of the Breasts	446
Under-development of the Breasts	446
Hypertrophy of the Breasts	447
Failure of Lactation	447
Suppression of Lactation and of Breast	
Engorgement	449
Persistent Lactation	450
Fibro-adenosis of the Breast (Chronic	
Mastitis)	452
Carcinoma of the Breast	455
Gynæcomastia	459

CONTENTS

	PAGE
SECTION VIII. MISCELLANEOUS DISORDERS	
Chapter XXXVIII. The Pineal Body and the Thymus Gland	467
Physiology of the Pineal Body	467
Pineal Tumours	467
Physiology of the Thymus Gland	468
Pathology of the Thymus Gland	469
Myasthenia Gravis	470
Chapter XXXIX. Intersexuality	472
Chapter XL. Sexual Precocity	485
Chapter XLI. Dwarfism and Infantilism	495
Chapter XLII. Obesity	505
Chapter XLIII. Sterility and Subfertility	524
Chapter XLIV. Hyperinsulinism	536
Chapter XLV. Œstrogens and Androgens in Miscellaneous Disorders	540
Acne Vulgaris	540
Atrophic Rhinitis	541
Bone Diseases	541
Buccal Leucoplakia and Buccal Ulceration	543
Enuresis	544
Phimosis	544
Prematurity	545
APPENDIX. Preparations and Methods of Administration of Steroid Hormones	546
REFERENCES	557
INDEX OF AUTHORS	641
GENERAL INDEX	653

LIST OF ILLUSTRATIONS

	PAGE
Fig. 1. Normal sella turcica and enlargement due to a chromo- phobe adenoma	27
Fig. 2. Acromegalic hand	39
Fig. 3. Acromegaly	40
Fig. 4. Gigantism	49
Fig. 5. Cushing's syndrome with dwarfing	58
Fig. 6. Cushing's syndrome before and after treatment	67
Fig. 7. Purpuric striæ in Cushing's syndrome	67
Fig. 8. Purpuric striæ in pulmonary tuberculosis	68
Fig. 9. Adipose gynandrisms	91
Fig. 10. Laurence-Moon-Biedl syndrome	103
Fig. 11. Polyostotic fibrous dysplasia	107
Fig. 12. Skiagram of polyostotic fibrous dysplasia	109
Fig. 13. Simple goitre	126
Fig. 14. Lingual goitre	136
Fig. 15. Toxic goitre	140
Fig. 16. Toxic goitre in a child	143
Fig. 17. A: unilateral upper lid-retraction	152
B: bilateral exophthalmos	152
Fig. 18. Pigmentation and leucoderma in toxic goitre	154
Fig. 19. Exophthalmic ophthalmoplegia	161
Fig. 20. Localized pretibial myxœdema in toxic goitre	165
Fig. 21. Chemosis before and after irradiation of the orbit	183
Fig. 22. Sporadic cretinism	189
Fig. 23. Achondroplasia	191
Fig. 24. Myxœdema	196
Fig. 25. The heart in myxœdema before and after treatment	198
Fig. 26. Myxœdema before and after treatment	204
Fig. 27. The hand in acute tetany	224
Fig. 28. Pathological appearances of generalized osteitis fibrosa	234
Fig. 29. Renal calculi in hyperparathyroidism	234

LIST OF ILLUSTRATIONS

	PAGE
Fig. 30. Radiological appearances of generalized osteitis fibrosa	236
Fig. 31. The adrenogenital syndrome before and after treatment	303
Fig. 32. Adrenal tumour demonstrated by perirenal insufflation	307
Fig. 33. Schematic diagram to illustrate Albright's conception of the pituitary-testis interrelations	332
Fig. 34. Eunuchism before and after treatment	337
Fig. 35. Eunuchoidism	342
Fig. 36. Eunuchoidism before and after treatment	345
Fig. 37. Bilateral cryptorchidism	359
Fig. 38. Average excretion rates of various hormones during pregnancy	384
Fig. 39. Turner's syndrome	394
Fig. 40. Turner's syndrome	395
Fig. 41. Failure of development of one breast	446
Fig. 42. Mammary carcinoma before and after treatment with methyltestosterone	456
Fig. 43. Pulmonary metastases of mammary carcinoma before and after treatment with testosterone	457
Fig. 44. Gynæcomastia of puberty	463
Fig. 45. Myasthenia gravis before and after treatment	471
Fig. 46. Female genital intersexuality (female pseudoherma- phroditism)	477
Fig. 47. Female genital intersexuality (female pseudoherma- phroditism)	479
Fig. 48. Hypertrophy of clitoris in female genital intersexuality	480
Fig. 49. Vagina in female genital intersexuality	480
Fig. 50. Constitutional sexual precocity	489
Fig. 51. Constitutional sexual precocity	490
Fig. 52. Genetic dwarfism	499
Fig. 53. Pituitary infantilism	500
Fig. 54. Pituitary infantilism	502
Fig. 55. Pituitary infantilism due to a craniopharyngioma	502
Fig. 56. Extreme obesity	511
Fig. 57. Extreme obesity in a young woman	512
Fig. 58. Extreme obesity in a child	514
Fig. 59. Cervical lipomatosis.	517

SECTION I

**THE PITUITARY GLAND
AND
THE HYPOTHALAMUS**

CHAPTER I

THE PITUITARY HORMONES¹

THE ANTERIOR LOBE

THE effects of hypophysectomy and the administration of specific extracts of the anterior lobe of the pituitary gland have demonstrated that the anterior lobe controls by means of its secretions the function of nearly all the other endocrine glands. There are at present six different hormones that are known to be elaborated, namely, the growth hormone, the two gonadotrophic hormones (the follicle stimulating hormone and the luteinizing or interstitial cell stimulating hormone), the thyrotrophic hormone, the adrenocorticotrophic hormone and the lactogenic hormone. The secretion of certain hormones of the anterior lobe itself, however, appears to be kept in check by the hormones of those glands which are stimulated by its specific secretions. Evidence for this statement is found in the excessive excretion in the urine of the follicle stimulating gonadotrophin that occurs after castration and in its disappearance from the urine as a result of the administration of suitable doses of oestrogen. Similarly, thyroidectomy causes an increased production of thyrotrophic hormone which is diminished or abolished by the administration of thyroid hormone. There normally exists a delicate hormonal balance between the anterior lobe of the pituitary gland and the peripheral glands, so that excessive pituitary secretion and secondary hyperactivity of the peripheral glands are prevented.

THE GROWTH HORMONE

HISTORICAL NOTE

That the pituitary gland secreted a hormone concerned with growth was long suspected as a result of clinical observations; gigantism was connected with hyperactivity of the gland and dwarfism was observed to be sometimes associated with its destruction. In the experimental field Aschner (1909) demonstrated that removal of the pituitary gland from puppies caused arrest of growth and of development. This work was subsequently confirmed in the rat by Smith (1926) and by many other investigators. The proof of the existence of a growth hormone was supplied by Evans and Long (1921), who reported the experimental

¹ For references see page 557.

CLINICAL ENDOCRINOLOGY

production of gigantism in rats by daily injections of extract of the anterior lobe of the pituitary gland over a prolonged period. The growth hormone (termed by H. M. Evans "somatotropin") was isolated in pure form by Li and Evans (1944). It is a protein, readily destroyed by pepsin and trypsin, with a molecular weight of 44,250 (Li, Evans and Simpson, 1945).

ACTIONS

Growth. The growth hormone causes gain in body weight through its direct action on the tissues and not through the mediation of other endocrine glands. Li and Evans (1948) injected pure growth hormone into adult female rats six days a week for 435 days and observed that growth continued during the whole period with no sign of lack of responsiveness. The average gain in weight was 289 g., compared with 57 g. in the control animals; the average body length of the experimental rats was 45.5 cm., of the control animals 40.9 cm. The weights of the liver, kidneys, heart, stomach and intestine of the injected rats per 100 g. of body weight remained practically the same as in the control animals.

The site of action of growth hormone in promoting growth of bone appears to be localized mainly in the proliferating zone of the epiphyseal cartilages (Freud, Levie and Kroon, 1939). After hypophysectomy the dimensions of the epiphyseal plate are reduced and a calcium barrier appears between the epiphysis and the diaphysis, preventing longitudinal growth. The administration of growth hormone leads to the rapid disappearance of this "closing membrane" and restores the dimensions of the cartilaginous plate by stimulating firstly chondrogenesis and later osteogenesis (Kibrick, Becks, Marx and Evans, 1941).

The growth promoting action of growth hormone is enhanced by the administration of thyroid hormone. Evans, Simpson and Pencharz (1939) observed that excessive growth produced by anterior pituitary extracts is not dependent on the presence of the thyroid gland, but is greater when the thyroid gland is present; that the promotion of the growth of thyroidectomized or thyroidectomized-hypophysectomized animals in excess of normal secured by anterior pituitary extracts is maximal only if the thyroid hormone is administered at the same time; and that thyroid hormone, which promotes the growth of thyroidectomized animals, does not have this effect when it is administered to thyroidectomized-hypophysectomized animals.

Metabolism. Growth hormone has been shown to cause nitrogen retention, a reduction in the level of the blood amino acids, an increase in the protein content and a decrease in the fat content of the carcass, an increase of the plasma alkaline phosphatase and an increase of the plasma inorganic phosphorus (Li and Evans, 1948). The hormone thus promotes the anabolism of protein. Nitrogen retention leads to

THE PITUITARY GLAND

water retention and the water content of animals treated with growth hormone is significantly higher than in the control animals. This fluid retention accounts for the obese appearance of the animals treated with growth hormone. Young (1945) suggested that depletion of the fat stores was due to increased combustion of fat to supply the necessary energy for the building up of protein into muscle.

Evans, Meyer, Simpson and Reichert (1932) produced a diabetic state in dogs by the daily injection of a preparation of pituitary growth hormone for 8-9 months and the condition persisted for some weeks after the treatment was stopped. Young (1937) induced permanent diabetes in two dogs by the daily injection of anterior pituitary extract; the disorder differed from that caused by pancreatectomy in that the animals were able to survive without the administration of insulin. The islets of Langerhans showed disappearance of the cytoplasmic granules of the beta cells or extensive hyalinization of the cellular tissue (Richardson and Young, 1938). The factor responsible for these changes was known as the diabetogenic hormone. Young (1940), who had observed that diabetogenic preparations of the anterior lobe usually possessed growth promoting activity, suspected that the growth hormone and the diabetogenic principle might be identical, and later pure growth hormone was found to be diabetogenic in the cat and in the dog (Cotes, Reid and Young, 1949; Campbell, Davidson, Snair and Lei, 1950).

STANDARDIZATION

There are three methods for the standardization of growth hormone that may be employed.

(1) *Body growth of normal female rats.* The preparation to be assayed is injected intraperitoneally or subcutaneously into groups of at least 10 normal female rats, 5 to 6 months of age and weighing 220 to 280 g., for 20 days (17 injections). A unit is contained in that daily dose which causes a total increase of weight of 40 g. during this period (Evans, Uyei, Bartz and Simpson, 1938).

(2) *Body growth of hypophysectomized female rats.* Nine intra-peritoneal injections of the preparation are given in 10 days to groups of 10 completely hypophysectomized female rats, 28 to 30 days of age at operation, starting 10 to 14 days after the operation. A unit is the daily dose which causes an average gain in weight of 10 g. (Evans, Uyei, Bartz and Simpson, 1938).

(3) *Tibia of hypophysectomized rats.* The preparation is injected intraperitoneally daily for 4 days into hypophysectomized female rats, 26 to 28 days of age at operation, starting 12 to 13 days after the operation. The animal is killed 24 hours after the last injection, the right tibia is split, stained with silver nitrate and sodium thiosulphate and the uncalcified portion of the epiphysis is measured. The initial

CLINICAL ENDOCRINOLOGY

effects of growth hormone consist mainly of chondrogenesis and the resulting increase in the width of the cartilage is, within certain limits of dosage, proportional to the quantity of growth hormone injected (Evans, Simpson, Marx and Kibrick, 1943).

THE GONADOTROPHIC HORMONES

HISTORICAL NOTE

For many years before the demonstration in 1926 that the anterior lobe of the pituitary gland secreted a hormone essential for the normal development and function of the gonads this relationship was strongly suggested by clinical and laboratory observations. Experimentally it had been shown that hypophysectomy caused atrophy of the reproductive system (Crowe, Cushing and Homans, 1910; Aschner, 1912) and that the injection of anterior lobe extracts into normal female rats produced excessive luteinization of the ovaries (Evans and Long, 1922). The work of Smith (1926, 1927), of Zondek and Aschheim (1926) and later of other investigators demonstrated conclusively that the anterior lobe maintained and controlled the activity of the ovaries and testes. The administration of gonadotrophic extracts to immature rats or mice induced precocious sexual maturity, ovulation and the formation of corpora lutea.

Fluhmann (1929) and Zondek (1930) observed that women at the menopause or after castration contained in their blood and urine a gonadotrophic hormone the effect of which was predominantly follicle stimulating. Fevold, Hisaw and Leonard (1931) first separated pituitary gonadotrophic extracts into two fractions—one which caused maturation of the follicles of the ovaries and the other which brought about luteinization after the follicles had been stimulated to activity by the follicle stimulating fraction. These discoveries led to the conception that there were two gonadotrophic hormones—the follicle stimulating hormone and the luteinizing hormone. It was later shown that the follicle stimulating factor stimulated spermatogenesis in the male animal, but had little or no effect on the testicular interstitial tissue (Smith, Engle and Tyndale, 1934). Stimulation of the interstitial tissue was found to be brought about by the luteinizing substance and therefore the term interstitial cell stimulating hormone was applied to this hormone rather than luteinizing hormone because lutein tissue does not occur in the male organism.

The interstitial cell stimulating hormone was isolated in pure form from the anterior lobes of sheep and swine by Li, Simpson and Evans (1940) and by Shedlovsky and his colleagues (1940) independently. The hormone behaves as a homogeneous protein. The follicle stimulating hormone has not yet been isolated, but almost pure preparations