

DUNCAN'S
Diseases of Metabolism
Endocrinology



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Seventh Edition

Edited by

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New Haven, Connecticut; Cancer Research Campaign Visiting
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Metabolism

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Duncan's Diseases of Metabolism — Endocrinology

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Preface

The decision to bring out a new edition of *Diseases of Metabolism* after an interval of only four years may seem to require some justification. Readers familiar with the rate of progress in the field will not, however, be surprised to learn that most of the authors were satisfied that their contributions required quite extensive revision. In addition, experience with the previous edition of this work had shown ways in which the organization of the material could be improved. As a result, we feel that we can provide a better organized and more useful book than before. The degree to which we have been successful will be determined by the reader.

The largest burden of this revision has fallen on our authors, to whom we are most grateful. Science moves so rapidly that even a thoroughly up-to-date presentation may be somewhat outmoded by the time it has passed through the processes of publication. To minimize the importance of the necessary delay following submission of the chapters, each author has been offered an opportunity to write an addendum to his chapter, to make it as current as possible. These addenda appear at the ends of the chapters for which they were written.

We have been greatly helped in this work by the advice and support of Mr. John L. Dusseau of the W. B. Saunders Company, whose experience and knowledge were essential to the completion of this task. Sally E. Bondy and Marilyn E. Feldman provided invaluable secretarial and editorial assistance, and Mrs. Virginia Simon was of great help in preparing much of the art work.

PHILIP K. BONDY

LEON E. ROSENBERG

Contents

Part III. Endocrinology

15

NEUROENDOCRINE INTERRELATIONS 951

Roger Guillemin

Hypothalamus and Adenohypophysis..... 952

Chemistry of the Hypothalamic Releasing Factors..... 955

Neuroendocrine Integration 958

References 959

16

THE ANTERIOR PITUITARY GLAND 961

Robert L. Ney

Embryology and Anatomical Relationships..... 961

Cellular Characteristics 963

The Anterior Pituitary Hormones 965

Clinical Tests of Anterior Pituitary Function 981

Diseases of the Anterior Pituitary 988

Anterior Pituitary Neoplasms..... 996

References 1003

17

THE THYROID AND IODINE METABOLISM 1009

Jacob Robbins, J. E. Rall, Phillip Gorden

Normal Structure, Function and Controls 1010

Development, Structure and Structure-Function

Relationships 1010

Thyroglobulin and Its Synthesis 1013

Iodine Metabolism and Hormone Production..... 1014

Control of Thyroid Function 1018

Agents Affecting the Thyroid 1020

Hormone Circulation and Metabolism..... 1022

Quantitative Aspects of Iodine Metabolism 1026

Effects of the Thyroid Hormones 1028

Diagnostic Procedures..... 1030

Hormones and Other Iodine Compounds in Blood..... 1030

Radioiodine Tests 1032

Evaluation of Thyroid Control Systems 1034

Tests of the Peripheral Effects of Thyroid Hormones..... 1035

Thyroid Diseases.....	1038
Anomalies.....	1038
Inherited Disorders.....	1039
Environmental Goiter.....	1043
Inflammatory Thyroid Disease.....	1047
Lymphocytic Thyroiditis.....	1049
Nontoxic Goiter and Thyroid Neoplasia.....	1051
Hyperthyroidism.....	1060
Hypothyroidism.....	1076
References.....	1085

18.

THE ADRENAL CORTEX.....	1105
Philip K. Bondy.....	
History.....	1105
Control Mechanisms.....	1106
Adrenal Anatomy.....	1110
Biosynthesis of Adrenal Corticosteroids.....	1111
The Fetal Adrenal Cortex.....	1116
Mechanism of Action of ACTH.....	1116
Inhibitors of Steroid Synthesis.....	1119
Rate of Steroid Secretion in Man.....	1119
Nutrition and Adrenal Function.....	1121
Metabolism of the Corticosteroids.....	1121
Physiological Effects of Corticosteroids.....	1125
Clinical Uses of Corticosteroids.....	1129
Tests of Adrenal Function.....	1132
Adrenocortical Insufficiency.....	1140
Adrenocortical Hyperactivity (Cushing's Syndrome).....	1147
Exogenous Hyperadrenocorticism (Hypercortisonism).....	1156
Congenital Adrenal Hyperplasia.....	1157
Schedule for Studying Patients with Adrenal Disease.....	1165
References.....	1166
Recent Developments.....	1180

19

CATECHOLAMINES AND THE ADRENAL MEDULLA.....	1181
Robert J. Levine, Lewis Landsberg.....	
Embryology and Anatomy.....	1182
Catecholamines.....	1184
Physiologic and Pharmacologic Effects.....	1188
Inactivation and Metabolism.....	1194
Interaction of Drugs with the Sympathetic Nervous System.....	1199
Hormones and Sensitivity to Catecholamines.....	1199
Disorders of the Sympathetic Nervous System.....	1202
Pheochromocytoma.....	1203
Other Tumors of Sympathetic and Adrenal Medullary Origin.....	1217
References.....	1217

20

PARATHYROID HORMONE, CALCITONIN, VITAMIN D, BONE AND BONE MINERAL METABOLISM 1225

John T. Potts, Jr., Leonard J. Deftos

Bone Mineral Metabolism.....	1227
Calcium.....	1227
Phosphate.....	1234
Bone Metabolism and Skeletal Homeostasis.....	1237
Tissue Calcification and Bone Formation.....	1238
Bone Structure, Resorption and Remodeling.....	1247
Skeletal Homeostasis.....	1260
Methods of Estimating Bone Turnover.....	1262
Parathyroid Hormone, Calcitonin, Vitamin D and	
Calcium Homeostasis.....	1270
History.....	1270
Pharmacology and Chemistry of the Hormones and	
Vitamin D.....	1276
Physiological Effects and Biochemical Mode of Action	
of Vitamin D, Parathyroid Hormone and Calcitonin.....	1298
Synthesis, Secretion, Distribution and Metabolism of	
Vitamin D, Parathyroid Hormone and Calcitonin.....	1309
Calcium Homeostasis.....	1330
Disorders of Parathyroid Function.....	1339
Primary Hyperparathyroidism.....	1339
Secondary Hyperparathyroidism.....	1363
Hypoparathyroidism.....	1366
Metabolic Bone Disease.....	1375
Osteoporosis.....	1375
Paget's Disease (Osteitis Deformans).....	1381
Osteomalacia.....	1389
Fibrous Dysplasia.....	1401
Osteogenesis Imperfecta.....	1402
Osteopetrosis (Albers-Schoenberg's Disease).....	1403
Extraskelatal Calcification and Ossification.....	1405
Extraskelatal Calcification.....	1405
Extraskelatal Ossification.....	1407
Differential Diagnosis and Treatment of Ectopic	
Calcification and Ossification.....	1408
Medullary Thyroid Carcinoma.....	1408
References.....	1413

21

ALDOSTERONE IN HYPERTENSION AND EDEMA..... 1431

Patrick J. Mulrow

Biological Actions of Aldosterone.....	1431
Regulation of Aldosterone Secretion.....	1435
Biosynthesis.....	1440
Primary Aldosteronism and Hypertension.....	1440
Edema.....	1445

Aldosterone Secretion in Edema States.....	1446
Hypoaldosteronism	1448
Aldosterone in Normal and Toxemic Pregnancy.....	1448
References	1450

22

WATER METABOLISM AND THE NEUROHYPOPHYSIAL HORMONES	1459
--	------

Charles R. Kleeman, Helmuth Vorherr

General Concepts of Water Metabolism	1459
Diabetes Insipidus	1487
The Water Depletion (Hyperosmolar) and Water Excess (Hypo-osmolar) Syndromes	1500
Oxytocin	1513
References	1525

23

ACID-BASE BALANCE	1531
-------------------------	------

Howard Levitin

Terminology	1531
Methods	1533
Physiology of Hydrogen Ion Regulation	1535
Clinical Disorders of Acid-Base Balance.....	1537
References	1551

24

THE TESTIS	1553
------------------	------

Mortimer B. Lipsett, Richard J. Sherins

Methods of Examination	1554
Biochemistry	1557
Regulation of Gonadotropins	1561
Diseases of the Fetal Testis	1562
Testicular Diseases with Karyotype Abnormalities	1567
Congenital Anorchia.....	1570
Male Turner's Syndrome	1571
Hypogonadotropic Syndromes	1571
Cryptorchidism.....	1573
Male Infertility	1574
Tumors of the Testis.....	1575
References	1576

25

THE OVARY	1585
-----------------	------

Nathan G. Kase, Leon Speroff

Ovarian Structure and Organization	1585
Ovarian Steroid Synthesis.....	1592

Metabolic Fate of Secreted Ovarian Steroids.....	1597
Steroid Hormone Function.....	1599
Mechanism of Action of Estrogens.....	1602
Clinical Aspects of Ovarian Function.....	1603
Menarche	1605
Sexual Precocity.....	1605
Disorders of Menstrual Function	1606
Investigation of Infertility	1617
Fertility Control	1618
Hormonal Physiology of the Placenta.....	1621
References	1623
Recent Developments	1627

26

NONENDOCRINE SECRETING TUMORS.....	1629
------------------------------------	------

Thomas T. Amatruda, Jr.

Hyperadrenocorticism	1629
Hyperpigmentation	1633
Hypercalcemia.....	1633
Hypoglycemia.....	1637
Inappropriate Antidiuresis	1638
Gynecomastia and Hypergonadotropism.....	1639
Hyperthyroidism.....	1639
Erythremia.....	1640
Atypical Carcinoid Syndrome.....	1640
Multiple Endocrine Abnormalities	1641
Histological Type and Endocrine Abnormalities	1642
Miscellaneous: Growth Hormone, Prolactin, Prostaglandins.....	1643
Recapitulation and Hypothesis	1644
References	1647

27

SEROTONIN AND THE CARCINOID SYNDROME; HISTAMINE AND MASTOCYTOSIS.....	1651
--	------

Robert J. Levine

Serotonin and the Carcinoid Syndrome.....	1651
Enterochromaffin Cells	1651
Serotonin.....	1652
Kallikrein and Bradykinin	1656
Carcinoid Syndrome.....	1657
Histamine and Mastocytosis	1666
Mast Cells	1666
Histamine	1667
Mastocytosis	1672
References	1679

INDEX.....	i
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III

Endocrinology

III

Endocrinology

Neuroendocrine Interrelations

ROGER GUILLEMIN

HYPOTHALAMUS AND ADENOHYPOPHYSIS

Methods of Study
Hypothalamic-Hypophyseal Portal System
Localization of Hypophyseal Control Centers
Effects of Stimulation
Effects of Local Destruction
Effects of Drugs
Effects of Section of the Hypophyseal Stalk
Pituitary Transplantation

Control Circuits

Hypothalamic Feedback: ACTH, Gonadotropins
Pituitary Feedback: TSH
Short Loop—Pituitary-Hypothalamic Feedback

CHEMISTRY OF HYPOTHALAMIC RELEASING FACTORS

Clinical Administration of Hypothalamic Releasing Factor

NEUROENDOCRINE INTEGRATION

A generation ago we were taught that the anterior pituitary gland commands all other peripheral endocrine glands (with the unhappy exception of the parathyroids and perhaps the pancreas) and that a subtle reciprocal equilibrium between concentrations of circulating "peripheral" hormones and quantities of the corresponding pituitary hormones maintained endocrine homeostasis (feedback or push-pull theory). Thus were explained the experimental compensatory hypertrophy of peripheral endocrines following unilateral ablation, the development of goiter, the atrophy of the contralateral adrenal in the presence of a unilateral adrenal tumor, and so forth. Then followed a twilight period in which more and more aspects of this elegant construction lost their appealing clarity and heuristic value as it was realized that there were circumstances in which the simple pituitary-target organ relationship was not exclusively operative. For instance, an explanation was needed for the excretion in the urine of large quantities of corticoids during prolonged stress or exercise, an observation which was incompatible with the eucorticoidism theory postulated by the feedback system between pituitary and adrenal cortex secretion. Similarly, the extreme rapidity of the changes in pituitary ACTH secretion was realized, with increases in plasma concentration of pituitary hormones taking place in a few minutes with no evidence of preceding fall in plasma concentration of the peripheral hormones, which could have triggered the feedback system. Then clinicians and experimentators reported more and more evidence that lesions in certain areas of the base of the brain (in the hypothalamus) would produce

various syndromes of pituitary dysfunctions such as inhibition of stress-induced release of ACTH, permanent diestrus, permanent estrus with an ovarian picture reminiscent of the Stein-Leventhal syndrome and testicular atrophy.

Today we teach our students that, for the most part, the center of control of the adenohypophyseal functions is to be found in the hypothalamus, that the feedback relationships between peripheral hormone levels and adenohypophyseal secretions are for the most part transhypothalamic, and that the hypothalamic control over the pituitary functions is exerted through the secretion of hypothalamic hormones or releasing factors, which may be called hypophysiotropic substances or hormones.

The purpose of this short review will be to describe briefly the principal tenets of the current concepts in neuroendocrinology without going into any of the techniques that were involved in acquiring the pertinent knowledge. Key references to several reviews or specific articles will be given for the reader who might want to go into the mechanisms of how these were obtained.

This review will discuss first the relationships between the hypothalamus and the adenohypophysis; we will then outline a more generalized concept of neuroendocrine relationships involving other parts of the central nervous system and describe some of the neurohormonal reverberating circuits which are one of the fundamental aspects of neuroendocrinology.*

*There will be no discussion here of control of the secretion of antidiuretic hormone, oxytocin and aldosterone since this will be covered in Chapters 21 and 22.

HYPOTHALAMUS AND ADENOHYPOPHYSIS

Methods of Study

Our current information about the endocrinology of the hypothalamus was acquired through the simple intellectual and experimental processes which have led to all basic knowledge in endocrinology: The deficiency syndrome produced by the classic surgical removal of the suspected endocrine tissue was achieved here by localized destruction of various parts of the hypothalamus through stereotactically placed electrical coagulations, removing the hypothalamic influence from the pituitary connections by isolating the pituitary gland in peripheral grafts or by *in vitro* explantation or incubation. Replacement therapy was achieved by injecting hypothalamic extracts into the animals with hypothalamic destruction and studying the functions of the anterior pituitary or simply by adding these extracts to the isolated pituitary and studying its release of hormones. Recently it has become possible to measure with some degree of reliability variations in the concentration of the hypothalamic hormones in hypothalamic portal blood sampled under various experimental conditions. A unique feature of neuroendocrinology has been the study of the electrical activity of hypothalamic nuclei as modified by the levels of circulating hormones and also the induction of the release of a specific pituitary hormone by the electrical stimulation of the pertinent hypothalamic areas.

Hypothalamic-Hypophyseal Portal System

There is general agreement^{10,11} that connections between the hypothalamus and the anterior pituitary are not provided through tracts of nerve fibers (as in the case of hypothalamus to posterior pituitary), but rather through a vascular link in the form of a system of portal vessels. The primary plexus of this system of vessels is to be found in a contact area between ventral hypothalamus and pituitary stalk called the median eminence. Axon

terminals from the cells of hypothalamic nuclei come into close contact with the capillaries of this primary plexus, and presumably there is passage of the hypothalamic releasing factors into the blood stream of these capillaries. The substances are distributed through collecting veins in the pituitary stalk into the adenohypophyseal parenchyma by the secondary plexus of capillaries of this hypothalamo-hypophyseal portal system (Fig. 15-1). Precise localization of the origin of a given releasing factor cannot be given in terms of specific hypothalamic nuclei as they have been described by the neuroanatomists. Rather, the neuroendocrine areas in the hypothalamus appear to be somewhat diffuse if we consider the considerable overlapping of hypophysiotropic activities related to one area or another (Fig. 15-2). This point of the exact hypothalamic origin of specific releasing factors requires further investigation; in its present and perhaps final state of affairs, the question is reminiscent of the conclusions reached by the neurophysiologists not many years ago regarding the absence of specific localizations in the hypothalamus, for instance, for sympathetic and parasympathetic integration. The nature of the cells in the hypothalamus that manufacture and secrete the hypophysiotropic hormones is not known.

Localization of Hypophyseal Control Centers

Effects of Stimulation. Electrical stimulation of various regions of the hypothalamus by implanted electrodes produces secretion of various pituitary hormones. Stimulation of the posterior hypothalamus is followed by secretion of ACTH, whereas stimulation of more anterior areas will trigger secretion of TSH. Somewhere in between is an area which upon stimulation will produce ovulation in suitably prepared animals, hence is related to secretion of gonadotropins (LH and FSH). Possibly this midhypothalamus area is under the command of a somewhat more anterior area, the interplay between the two areas regulating basal secretion of gonadotropins as opposed to "spurt" secretion as in the triggering of ovulation.^{3,11,14}

FIGURE 15-1. A, Diagrammatic representation of the pituitary vascularization on a sagittal section (anatomy of the cat). Principal landmarks of the diagram relating to the portal circulation: 1, 2, 3—hypophyseal arteries resolving into (4) short loops, and (5) long loops of the primary plexus of the portal system. The primary plexus is in intimate contact with nerve fibers and terminals (not shown on diagram) of hypothalamic origin. The primary plexus collects in veins (6), spreading into capillaries (7) throughout the parenchyma of the adenohypophysis, constituting the secondary plexus of the portal system. This is eventually drained into veins (8, 9) leaving the pituitary. 10, Capillary net of posterior pituitary draining into posterior hypophyseal vein (11); 12, intermediate lobe; RI, infundibular recess of the third ventricle. Arrows indicate direction of blood flow.

B, Sagittal section of median eminence (pituitary of the pig) after intracarotid injection of India ink. Three types of capillary loops of the primary plexus may be seen: 1, short loop; 2, medium size loops; 3, long loops. The latter extend in a rich network immediately below the ependyma. RI, Infundibular recess, LA, anterior lobe. (× 50.)

C, Sagittal section of median eminence (pituitary of the dog) after intracarotid injection of India ink. AC, long loops of the primary plexus with (a) ascending part, (b) subependymal part, and (c) descending part. (× 150.) (All figures courtesy of Professor H. Duvernoy, Department of Anatomy, School of Medicine of Besançon, France.)

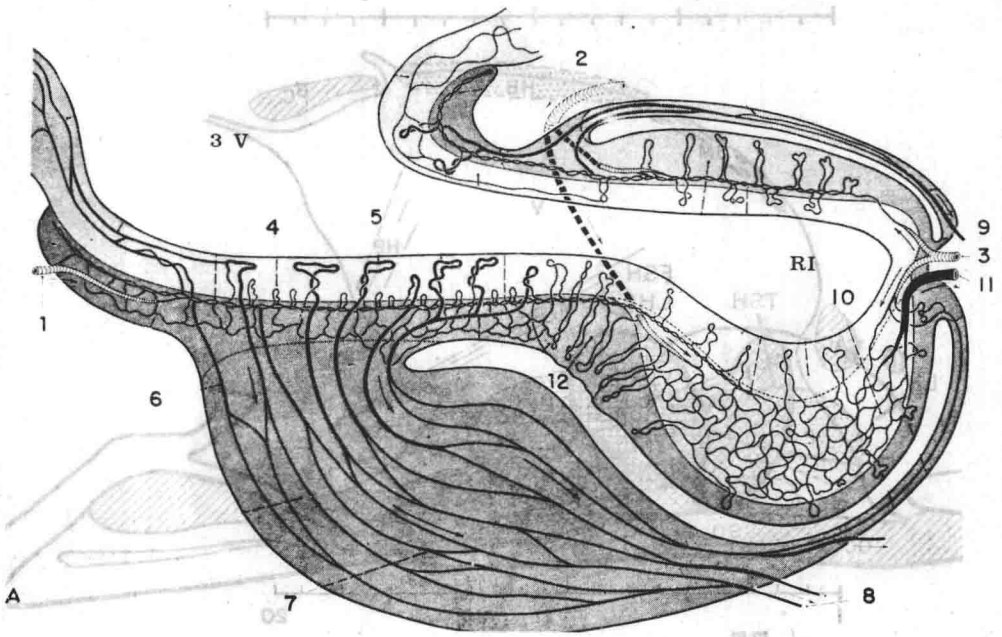


FIGURE 15-1 See opposite page for legend.