SIXTH EDITION

YEN AND JAFFE'S

REPRODUCTIVE ENDOCRINOLOGY

Physiology, Pathophysiology, and Clinical Management

STRAUSS • BARBIERI

SAUNDERS
ELSEVIER

Yen and Jaffe's

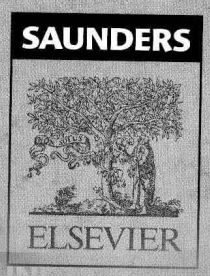
REPRODUCTIVE ENDOCRINOLOGY

Physiology, Pathophysiology, and Clinical Management

6TH EDITION

Jerome F. Strauss III, MD, PhD
Executive Vice President for Medical Affairs, VCU Health System
Dean, School of Medicine and Professor of Obstetrics and Gynecology
Virginia Commonwealth University
Richmond, Virginia

Robert L. Barbieri, MD
Kate Macy Ladd Professor, Department of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Chair, Department of Obstetrics and Gynecology
Brigham and Women's Hospital
Boston, Massachusetts



SAUNDERS
ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

YEN AND JAFFE'S REPRODUCTIVE ENDOCRINOLOGY:
PHYSIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL MANAGEMENT,
6TH EDITION

ISBN: 978-1-4160-4907-4

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment, and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on his or her own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Editors assume any liability for any injury and/or damage to persons or property arising out or related to any use of the material contained in this book.

Library of Congress Cataloging-in-Publication Data
Yen and Jaffe's reproductive endocrinology / [edited by] Jerome F. Strauss, Robert L. Barbieri.—6th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4160-4907-4
1. Human reproduction—Endocrine aspects. 2. Endocrine gynecology. 3. Generative organs—Diseases—Endocrine aspects. I. Strauss, Jerome F. (Jerome Frank) II. Barbieri, Robert L. III. Yen, Samuel S. C. Reproductive endocrinology. IV. Title: Reproductive endocrinology.
[DNLM: 1. Reproduction—physiology. 2. Endocrine Glands—physiology. 3. Endocrine System Diseases—physiopathology. WQ 205 Y4467 2009]
QP252.Y46 2009
612.6—dc22

2008037592

Acquisitions Editor: Stefanie Jewell-Thomas
Developmental Editor: Colleen McGonigal
Project Manager: Mary Stermel
Marketing Manager: Courtney Ingram
Design Direction: Ellen Zanolle
Multi-Media Producer: Adrienne Simon

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Remembrance

Samuel S. C. Yen, MD, DSc
1927–2006

In 2006, endocrinology in general, and reproductive endocrinology in particular, lost a giant in clinical and translational reproductive endocrinologic research, Samuel S. C. Yen. He was insightful and a visionary and demanded excellence from his trainees, but no more so than from himself. He was arguably the leading clinical reproductive neuroendocrinologist of his time.

He and I coedited the first four editions of this textbook, which has since been translated from English into five languages—including a pirated version from China. The genesis of our textbook was crystallized during our time at the magnificent, idyllic Rockefeller Foundation retreat, the Villa Serbelloni, at the nexus of the three legs of Lake Como in Italy. It was there, surrounded by scholars from a panoply of disciplines and countries (Sam and I were the only physicians in the group), that we had the time and freedom to finalize the chapters. We mutually selected the authors, most of whom were outstanding investigators and clinicians in the areas about which they wrote (albeit not all as expeditiously as we had hoped).

Fortunately, our first editor, John Hanley, was a true scholar who shared our passion for quality and excellence. Our original publisher, W. B. Saunders, shared that same passion.

Sam continued his insistence on excellence for each edition, and he cajoled several of our authors until they did the same.

Sam's chapters on neuroendocrine regulation of the brain and of the hypothalamic-pituitary-ovarian axis are classic. His extensive and productive collaboration with his very close friend, the Nobel Laureate Roger Guillemin, who characterized many of the hypothalamic secretagogues that Sam used in his clinical studies, enabled him to base many of his comments in the textbook on his own laboratory's studies.

Sam was hard-driving, yet charming, as demanding of himself and our authors as he was of the myriad investigators with whom he worked and trained. His was a rich, full, productive, and creative life. He was a unique and colorful individual.

His like comes along very rarely.

Robert B. Jaffe, MD
University of California, San Francisco
2008

Contributors

Valerie A. Arboleda
Department of Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, California
16: *Disorders of Sex Development*

Mario Ascoli, PhD
Professor, Department of Pharmacology, Carver College of Medicine, The University of Iowa, Iowa City, Iowa
2: *The Gonadotropin Hormones and Their Receptors*

Richard J. Auchus, MD, PhD
The Charles A. and Elizabeth Ann Sanders Chair in Translational Research, Professor of Internal Medicine, Division of Endocrinology and Metabolism, University of Texas Southwestern Medical Center, Dallas, Texas
23: *Endocrine Disturbances Affecting Reproduction*

Robert L. Barbieri, MD
Kate Macy Ladd Professor, Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School; Chair, Department of Obstetrics and Gynecology Brigham and Women's Hospital, Boston, Massachusetts
10: *The Breast;* ***21:*** *Female Infertility*

Kurt Barnhart, MD, MSCE
Director, Women's Health Clinical Research Center, Assistant Dean, Clinical Trial Operations, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
34: *Contraception*

Breton F. Barrier, MD
Assistant Professor, Department of Obstetrics, Gynecology and Women's Health, University of Missouri, Columbia, Columbia, Missouri
13: *Reproductive Immunology and Its Disorders*

Enrico Carmina, MD
Professor of Endocrinology, Department of Clinical Medicine, University of Palermo, Palermo, Italy
32: *Evaluation of Hormonal Status*

Alice Y. Chang, MD, MS
Assistant Professor, Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Texas Southwestern Medical Center, Dallas, Texas
23: *Endocrine Disturbances Affecting Reproduction*

R. Jeffrey Chang, MD
Professor and Division Director, University of California School of Medicine, San Diego, California
20: *Polycystic Ovary Syndrome and Hyperandrogenic States*

Charles Chapron, MD
Professor and Chair, Obstetrics and Gynecology II, Université Descartes GHU Cochin-St. Vincent de Paul, Paris, France
33: *Pelvic Imaging in Reproductive Endocrinology*

John A. Cidlowski, PhD
Chief, Laboratory of Signal Transduction, Head, Molecular Endocrinology Group, National Institute of Environmental Health Science, National Institutes of Health, Research Triangle Park, North Carolina
5: *Steroid Hormone Action*

Donald K. Clifton, PhD
Professor of Obstetrics and Gynecology, University of Washington, Seattle, Washington
1: *Neuroendocrinology of Reproduction*

Anick De Vos, PhD
Clinical Embryologist, Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium
30: *Gamete and Embryo Manipulation*

Dominique de Ziegler, MD
Professor and Head, Reproductive Endocrine and Infertility, Obstetrics and Gynecology II, Université Descartes GHU Cochin-St. Vincent de Paul, Paris, France
33: *Pelvic Imaging in Reproductive Endocrinology*

William S. Evans, MD
Professor, Departments of Medicine and Obstetrics and Gynecology, University of Virginia, Charlottesville, Virginia
19: *Physiologic and Pathophysiologic Alterations of the Neuroendocrine Components of the Reproductive Axis*

Bart C. J. M. Fauser, MD, PhD
Professor of Reproductive Medicine; Chair, University Medical Center Utrecht, Utrecht, The Netherlands
28: *Medical Approaches to Ovarian Stimulation for Infertility*

Garret A. FitzGerald, MD
Robert L. McNeil, Jr., Professor in Translational Medicine and Therapeutics, Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
6: *Prostaglandins and Other Lipid Mediators in Reproductive Medicine*

Timothée Fraisse, MD, MSc
Joint Division Reproductive Endocrine and Infertility, University Hospitals Geneva and Lausanne, Geneva and Lausanne, Switzerland
33: *Pelvic Imaging in Reproductive Endocrinology*

Colin D. Funk, PhD
Professor, Departments of Physiology and Biochemistry, Queen's University, Kingston, Canada
6: *Prostaglandins and Other Lipid Mediators in Reproductive Medicine*

Antonio R. Gargiulo, MD
Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School; Associate Reproductive Endocrinologist, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Boston, Massachusetts
13: *Reproductive Immunology and Its Disorders*

Janet E. Hall, MD
Professor of Medicine, Harvard Medical School; Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts
7: *Neuroendocrine Control of the Menstrual Cycle*

Kristin D. Helm, MD
Fellow, Division of Endocrinology and Metabolism, South Shore Hospital, South Weymouth, Massachusetts
19: *Physiologic and Pathophysiologic Alterations of the Neuroendocrine Components of the Reproductive Axis*

Mark D. Hornstein, MD
Associate Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School; Director, Division of Reproductive Endocrinology and Infertility; Director, Center for Reproductive Medicine, Brigham and Women's Hospital, Boston, Massachusetts
29: *Assisted Reproduction*

Dan I. Lebovic, MD, MA
Director, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Wisconsin School of Medicine, Madison, Wisconsin
24: *Endometriosis*

Charles Lee, PhD, FACMG
Director of Cytogenetics, Harvard Cancer Center; Associate Professor, Harvard Medical School; Associate Faculty Member, MIT Broad Institute; Clinical Cytogeneticist, Brigham and Women's Hospital, Boston, Massachusetts
31: *Cytogenetics in Reproduction*

Bruce A. Lessey, MD, PhD
Greenville Professor, University of South Carolina School of Medicine; Vice Chair, Research and Division Director, Reproductive Endocrinology and Infertility, Greenville Hospital System, Greenville, South Carolina
9: *The Structure, Function, and Evaluation of the Female Reproductive Tract*

Peter Y. Liu, MBBS, FRACP, PhD
Associate Professor and Head, Endocrinology and Metabolism, Woolcock Institute of Medical Research and ANZAC Research Institute, University of Sydney, Sydney, Australia; Associate Professor and Consultant, Concord Hospital, Concord, Australia
12: *The Hypothalamo-Pituitary Unit, Testes, and Male Accessory Organs*

Rogerio A. Lobo, MD
Professor, Columbia University College of Physicians and Surgeons; Attending Physician, New York Presbyterian Hospital; Director, REI Fellowship Program, New York, New York
14: *Menopause and Aging;* ***32:*** *Evaluation of Hormonal Status*

Nicholas S. Macklon, MB, ChB, MD,
Professor and Chair, Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht, The Netherlands
28: *Medical Approaches to Ovarian Stimulation for Infertility*

Sam Mesiano, PhD
Assistant Professor, Department of Reproductive Biology, Case Western Reserve University; Assistant Professor, Department of Obstetrics and Gynecology, University Hospitals Case Medical Center, Cleveland, Ohio
11: *The Endocrinology of Human Pregnancy and Fetoplacental Neuroendocrine Development*

Anne Elodie Millischer-Belaïche, MD
Obstetrics and Gynecology II, Université Descartes GHU Cochin-St. Vincent de Paul, Paris, France
33: *Pelvic Imaging in Reproductive Endocrinology*

Mark E. Molitch, MD
Professor of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine; Attending Physician, Northwestern Memorial Hospital, Chicago, Illinois
3: *Prolactin in Human Reproduction*

Cynthia C. Morton, PhD
William Lambert Richardson Professor of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Boston, Massachusetts
31: *Cytogenetics in Reproduction*

Ralf M. Nass, MD
Research Assistant Professor, Department of Medicine, University of Virginia School of Medicine, University of Virginia Health System, Charlottesville, Virginia
19: *Physiologic and Pathophysiologic Alterations of the Neuroendocrine Components of the Reproductive Axis*

Errol R. Norwitz, MD, PhD
Professor, Yale University School of Medicine; Co-Director, Division of Maternal-Fetal Medicine; Director, Maternal-Fetal Medicine Fellowship Program; Director, Obstetrics and Gynecology Residency Program, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale-New Haven Hospital, New Haven, Connecticut
26: *Endocrine Diseases of Pregnancy*

Tony M. Plant, PhD
Professor, Departments of Cell Biology and Physiology and Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
17: *Puberty: Gonadarche and Adrenarche*

Staci Pollack, MD
Assistant Professor of Obstetrics and Gynecology and Women's Health, Associate Reproductive Endocrinology and Infertility Fellowship Director, Albert Einstein College of Medicine, New York, New York
18: *Nutrition and the Pubertal Transition*

Alex J. Polotsky, MD, MSc
Assistant Professor of Obstetrics and Gynecology and Women's Health, Albert Einstein College of Medicine; Attending Physician, Montefiore Medical Center, New York, New York
18: *Nutrition and the Pubertal Transition*

David Puett, PhD
Regents Professor of Biochemistry and Molecular Biology, University of Georgia, Athens, Georgia
2: *The Gonadotropin Hormones and Their Receptors*

Catherine Racowsky, PhD
Associate Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School; Director, Assisted Reproductive Technology Laboratory, Brigham and Women's Hospital, Boston, Massachusetts
29: *Assisted Reproduction*

Turk Rhen, PhD
Assistant Professor of Biology, University of North Dakota, Grand Forks, North Dakota
5: *Steroid Hormone Action*

Jessica Rieder, MD, MS
Assistant Professor, Department of Pediatrics, Division of Adolescent Medicine, Albert Einstein College of Medicine; Attending Physician, Department of Pediatrics, Division of Adolescent Medicine, Children's Hospital at Montefiore, New York, New York
18: *Nutrition and the Pubertal Transition*

Richard J. Santen, MD
Professor of Medicine, University of Virginia Health Sciences System, Charlottesville, Virginia
27: *Breast Cancer*

Nanette Santoro, MD
Professor and Director, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology and Women's Health, Albert Einstein College of Medicine/Montefiore Medical Center, New York, New York
18: *Nutrition and the Pubertal Transition*

Courtney A. Schreiber, MD, MPH
Assistant Professor of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania
34: *Contraception*

Danny J. Schust, MD
Associate Professor of Obstetrics, Gynecology and Women's Health; Chief, Division of Reproductive Endocrinolgy and Infertility, Department of Obstetrics, Gynecology and Women's Health, University of Missouri, Columbia, Missouri
13: *Reproductive Immunology and Its Disorders*

Peter J. Snyder, MD
Professor of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
15: *Male Reproductive Aging*

Wen-Chao Song, PhD
Professor, Department of Pharmacology, Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
6: *Prostaglandins and Other Lipid Mediators in Reproductive Medicine*

Robert A. Steiner, PhD
Professor, Departments of Obstetrics and Gynecology and Physiology and Biophysics, University of Washington, Seattle, Washington
1: *Neuroendocrinology of Reproduction*

Elizabeth A. Stewart, MD
Professor, Department of Obstetrics and Gynecology, Mayo Clinic College of Medicine; Senior Associate Consultant, Mayo Clinic, Rochester, Minnesota
25: *Benign Uterine Disorders*

Jerome F. Strauss III, MD, PhD
Executive Vice President for Medical Affairs, VCU Health System; Dean, School of Medicine and Professor of Obstetrics and Gynecology, Virginia Commonwealth University, Richmond, Virginia
4: *The Synthesis and Metabolism of Steroid Hormones;* ***8:*** *The Ovarian Life Cycle;* ***9:*** *The Structure, Function, and Evaluation of the Female Reproductive Tract*

Robert N. Taylor, MD, PhD
Willaford Leach-Armand Hendee Professor and Vice Chair for Research, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia
24: *Endometriosis*

Stephen F. Thung, MD, MSCI
Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine; Director, Yale Maternal-Fetal Medicine Practice; Director, Yale Diabetes during Pregnancy Program, New Haven, Connecticut
26: *Endocrine Diseases of Pregnancy*

Paul J. Turek, MD, FACS, FRSM
Former Professor and Endowed Chair in Urologic Education, Department of Urology, Obstetrics, Gynecology and Reproductive Sciences, University of San Fransiscco; Director, The Turek Clinic, San Francisco, California
22: *Male Infertility*

André Van Steirteghem, MD, PhD
Emeritus Professor, Faculty of Medicine, Vrije Universiteit Brussel; Honorary Consultant, Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium
30: *Gamete and Embryo Manipulation*

Johannes D. Veldhuis, MD
Professor of Medicine and Clinical Investigator, Mayo Clinic College of Medicine; Consultant, Division of Endocrinology, Diabetes, Metabolism, Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
12: *The Hypothalamo-Pituitary Unit, Testes, and Male Accessory Organs*

Eric Vilain, MD, PhD
Professor of Human Genetics, Pediatrics, and Urology; Chief, Medical Genetics, Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California
16: *Disorders of Sex Development*

Carmen J. Williams, MD, PhD
Clinical Investigator, Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
8: *The Ovarian Life Cycle*

Selma Feldman Witchel, MD
Associate Professor, Department of Pediatrics, University of Pittsburgh School of Medicine; Associate Professor, Division of Endocrinology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
17: *Puberty: Gonadarche and Adrenarche*

Preface

The year 2008 marked the 30th anniversary of the clinical success of in vitro fertilization and embryo transfer, a technology that has revolutionized the treatment of infertility. This landmark event came about through the marriage of reproductive biology, endocrinology, and gynecology, in what was at the time a new model of translational science. Today, the field of reproductive endocrinology continues to be broad-based with contributions from the fields of developmental and reproductive biology, neuroscience, genetics and genomics, endocrinology, gynecology, obstetrics, andrology, pediatrics, pathology and laboratory medicine, and diagnostic imaging, among others. The multiple disciplines and their respective perspectives have brought forth what can arguably be considered the greatest medical advance in the past century: the capacity of humans to master the process of reproduction. The 6th edition of *Yen and Jaffe's Reproductive Endocrinology* has been expanded to reflect the position of our field as the nexus of basic and clinical research, and as a source of innovation that shapes the scientific foundations of physiology and medicine. The editors thank the chapter authors, both old and new, for delivering the insightful synthesis of their topics. In many instances, advances in research and clinical practice have resulted in substantial changes in scope and direction that necessitated critical appraisal of information offered in the 5th edition.

Since the previous edition of this text, we lost Samuel S. C. Yen, one of the founders of contemporary reproductive endocrinology and one half of the brilliant team that birthed this text. As noted in the remembrance, his legacy is profound, and the editors once again acknowledge his transformative influence on the field.

Jerome F. Strauss III, MD, PhD
Richmond, Virginia

Robert L. Barbieri, MD
Boston, Massachusetts

Contents

PART I

Endocrinology of Reproduction

PART II

Pathophysiology and Therapy

PART III
Reproductive Technologies

PART I

Endocrinology of Reproduction

CHAPTER 1

Neuroendocrinology of Reproduction

Donald K. Clifton and Robert A. Steiner

Historical Perspective[1]

ENDOCRINOLOGY TAKES FLIGHT

In 1849, A. A. Berthold conducted the first known experiment in endocrinology—long before the word *endocrinology* was invented. He castrated roosters and showed that after the surgery, the animals lost the ability to crow, their combs drooped, and they stopped chasing hens. Berthold went on to show that if he transplanted testes from other roosters into the castrated animals, the newly transplanted organs would survive and the roosters became sexually rejuvenated—crowing, strutting, and mounting the hens, as they did before castration. Berthold observed that the transplanted testes became revascularized and thus revitalized—despite having no obvious regeneration of nerve supply to the organ. Berthold deduced correctly that without the action of nerves, the testes must release blood-borne substances that are transported to distant target sites in the body and thus support the secondary sex characteristics of the rooster and its behavior.

THE ANTERIOR PITUITARY AND NEUROHYPOPHYSIS

The thought that the pituitary gland serves some physiologic function can be traced to the first century AD, when Galen postulated that the pituitary was a sump for wastes distilled from the brain—an idea that was also championed by the Belgian physician and anatomist Andreas Vesalius in the middle of the 16th century. However, the true physiologic significance of the pituitary traces its roots to the late 19th and early 20th century with early attempts of physiologists to perform hypophysectomies and study the outcome on survival, growth, and reproduction. The work of Harvey Cushing, Bernard Aschner, and others established that the pituitary was indeed important and that experimental manipulations or tumors of the pituitary were associated with disorders of growth, metabolism, adrenal function, and reproduction. Also in the 19th century, Ramón y Cajal described a neural tract that led from the brain to the neural lobe of the pituitary, and in the mid 1920s, it was recognized that the supraoptic and paraventricular nuclei in the hypothalamus were the origins of this neural tract. Cushing observed that the anterior lobe of the pituitary was highly vascularized, and he postulated that this organ was anatomically and physiologically distinct from the pars intermedia, which he incorrectly thought was part of the "neural lobe." Confusion about the anatomy of the pituitary persisted until the mid 1930s, when G. B. Wislocki and L. S. King finally got it right.

ANTERIOR PITUITARY AS A SOURCE FOR GONADOTROPINS

The turn of the 20th century brought with it the first clue that the gonads were somehow physiologically linked to the pituitary gland. In 1905, Fichera reported that castration produced a gross enlargement of the pituitary gland and the appearance of large vacuolated cells—"castration cells." In 1926, working independently, Philip Smith and Bernard Zondek showed that daily injections of fresh pituitary glands into immature mice and rats would induce precocious puberty in recipient animals. In 1927, Smith and E. T. Engle showed that hypophysectomy would prevent sexual maturation, thus establishing a critical role for the pituitary in reproduction. In the early 1930s, Zondek also proposed that the pituitary produced two "gonadotropic" hormones, which he termed *Prolan A* (FSH) and *Prolan B* (LH), and shortly thereafter, H. L. Fevold and

F. L. Hisaw, working at the University of Wisconsin, successfully isolated and purified these two hormones, which came to be known as *luteinizing hormone* (LH) and *follicle-stimulating hormone* (FSH).

PROLACTIN AND LACTATION

In the late 1920s, the idea that the pituitary gland plays some role in lactation grew from observations that daily injections of extracts from the anterior pituitary would stimulate mammary gland development in rabbits. In the early 1930s, Oscar Riddle conducted experiments in pigeons and ring doves, showing that secretion of crop milk in birds was stimulated by the same hormone that induced milk secretion in mammals, and Riddle named this hormone *prolactin*. A spate of experimental work over the next several decades would establish that prolactin has complicated effects on the reproductive axis in mammals—acting as a luteotropic factor in some species, but inhibiting FSH secretion (and thus estrous cyclicity) in others. The isolation of prolactin from growth hormone would not come until 1962, when R. W. Bates and his colleagues finally separated these closely related molecules and thus helped to explain 30 years of confusing experimental results involving studies of "pituitary extracts" on growth, reproduction, and lactation.

THE HYPOTHALAMIC–PITUITARY–GONADAL (HPG) AXIS

As early as 1901, Alfred Frohlich had described a clinical syndrome termed *urogenital dystrophy*, which was associated with damage to the pituitary gland and basal forebrain, but for the next 40 years, it remained controversial whether the condition was caused by damage to either the hypothalamus or the pituitary. Nevertheless, by 1930, it had become clear that experimental manipulations of the anterior pituitary gland (e.g., hypophysectomy) could influence gonadal function and likewise that alterations in gonadal function (i.e., castration) would influence the cellular architecture of the pituitary. These observations led Dorothy Price and Carl Moore to postulate that there was a reciprocal relationship between the pituitary and gonads, such that pituitary hormones stimulate gonadal function, whereas gonadal hormones inhibit "gonadotropin" secretion—a concept that has come to be known as *gonadal steroid negative feedback*. The idea that the brain might also be involved in this process was presaged by studies in the late 1920s of coitally induced ovulation in rabbits, but Walter Holweg and Karl Junkmann were the first to argue that the brain serves as an intermediary target for gonadal hormones, and then in turn controls the activity of the anterior pituitary. Later in the 1930s, F. H. Marshall, G. W. Harris, and others went on to show that stimulation of the brain and hypothalamus, in particular, could induce ovulation in the rabbit. In the early 1940s, Frederick Dey, working at Northwestern University, showed that discrete lesions placed in the hypothalamus could induce either constant estrus or diestrus in the rat. This work established the idea that different areas of the hypothalamus coordinate particular aspects of reproductive cyclicity. By the late 1940s, experiments conducted by J. W. Everett, C. H. Sawyer, and J. E. Markee clearly showed in the rat and rabbit that ovulation could be either blocked or induced by drugs that act on the central nervous system, thus reinforcing the idea that the brain plays a central role in the events that trigger ovulation. Although it had also become evident that communication between the brain and the pituitary was essential for pituitary function, the anatomic basis for this communication (later discovered to be the pituitary portal vessels) remained unappreciated for many years. In fact, it remained dogmatic that the brain–pituitary connection must be "neural," notwithstanding the anatomic observations of A. T. Rasmussen, who had reported finding very few nerve fibers in the anterior pituitary.

In the early 1930s, G. T. Popa and U. Fielding reported finding blood vessels that connected the basal forebrain to the anterior pituitary gland. However, they incorrectly deduced that blood flowed from the pituitary to the brain—not the other way around. In 1935, using microscopy, B. Houssay visualized the blood vessels along the pituitary stalk in the toad and observed blood flowing from the brain to the pituitary. One year later, G. B. Wislocki and L. S. King performed careful histologic studies of the median eminence and pituitary and described a dense capillary bed that drained blood from the median eminence, which collected into the large portal vessels along the infundibular stalk, and in turn fed a secondary capillary bed in the pars distalis (anterior pituitary). This came to be known as the *hypothalamo-hypophysial portal system*.

The notion that there is a humoral (instead of neural) connection between the hypothalamus and the anterior pituitary was seeded by the early observations of J. C. Hinsey and J. E. Markee in the rabbit, showing that coitally induced ovulation persists in rabbits with severed cervical sympathetic nerves. They deduced that some substances must somehow diffuse from the posterior lobe (neurohypophysis) into the anterior pituitary to control its function. The exact method by which the brain communicates with the pituitary remained controversial (and unproven) until an elegant series of investigations by J. D. Green, G. W. Harris, and D. Jacobsohn provided compelling evidence that humeral agents must be released by the brain into the hypophysial portal system, which then spews "hypophysiotropic factors" into the anterior pituitary to regulate its function. However, it still was not clear precisely how the brain could control all aspects of pituitary function—i.e., the secretion not only of the gonadotropins, but also of growth hormone, prolactin, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). Although it had been postulated by J. D. Green, G. W. Harris, and S. M. McCann that the brain produces separate excitatory and inhibitory factors that regulate the various pituitary hormones, proof of the existence of such factors (e.g., thyrotropin-releasing hormone [TRH], somatostatin, gonadotropin-releasing hormone [GnRH], corticotropin-releasing hormone [CRH]) was not forthcoming until the final isolation, characterization, and purification of these "hypophysiotropic hormones" in the early 1970s by R. Guillemin, A. Schally, and their coworkers, for which they received the Nobel Prize in 1977.

PRIMATES ARE PHYSIOLOGICALLY UNIQUE[2]

Until the early 1970s, the foundation of modern reproductive neuroendocrinology had been built on studies of *infra* primate species—most notably, the rabbit, rat, mouse, and sheep. Classical studies in these nonprimate species established basic principles that apply to *all mammals*—such as the negative feedback regulation of gonadotropin secretion by sex steroids and the stimulatory action of GnRH on pituitary gonadotropes. However, there are fundamental aspects of the neuroendocrine regulation of reproduction that are dramatically different among species and several that are unique to higher primates, such as Old World monkeys, the great apes, and humans. These include the cellular and molecular mechanisms that govern the onset of puberty, the circuitry that triggers the preovulatory surge of gonadotropins, and circadian inputs to GnRH neurons. The neuroendocrine mechanisms that control these processes are different in higher primates compared with rodent and ovine species. Thus, caution must be exercised when making generalizations and drawing inferences based on work performed in certain laboratory animals because the data may or may not apply to humans. This fact has implications that extend beyond physiology into the realms of pathophysiology and the translational relevance of the various models of disorders of reproduction.

Neuroendocrine Anatomy[3]

NEURONS AND GLIA

The brain has two predominant cell types—neurons, which constitute approximately 10% of the brain, and glia, which make up the other 90%. Neurons represent a highly differentiated and phenotypically diverse array of excitable cells that receive, transduce, and relay information through action potentials and the release of neurotransmitters and neuromodulators at synaptic junctions. Glia comprise several general types of non-neuronal cells, the most numerous of which are astrocytes. Astrocytes can respond to neurotransmitters, neuromodulators, and hormones, and they may provide substrates and signals to neurons and thus regulate their activity and metabolism (e.g., insulin-like growth factor-1, transforming growth factor α and β). Changes in the activity of astrocytes have been linked to the mechanisms that control the onset of puberty. Astrocytes have highly motile processes that may cover nerve terminals (and thus restrict secretion) or retract to expose nerve terminals and allow unrestricted neurosecretion. Pituicytes are modified glial cells that reside in the neural lobe of the pituitary, and their movable processes either ensheath or expose nerve terminals that release oxytocin or vasopressin. Oligodendocytes are cells that form the myelin sheaths around axons, allowing neurons to conduct action potentials rapidly across long distances without decrement. Ependymal cells are epithelial cells (often ciliated), which line the third ventricle. The end feet processes of these cells govern exchange between the parenchyma of the brain and the fluid-filled ventricular cavities of the brain.

NEUROTRANSMITTERS, NEUROMODULATORS, AND THEIR RECEPTORS

Communication in the brain is mediated through synaptic transmission involving three classes of neurotransmitters—amino acids, biogenic amines, and neuropeptides. Examples of amino acid transmitters include acetylcholine (excitatory), glutamate and aspartate (excitatory), glycine (inhibitory), and γ-aminobutyric acid (GABA), which is predominantly inhibitory but may also be excitatory. The biogenic amines include the catecholamines (e.g., norepinephrine, epinephrine, dopamine) and the indoleamine serotonin. There are many neuropeptides that act as neurotransmitters, neuromodulators, or hypophysiolotropic factors in the brain. These include proopiomelanocortin (POMC) and its derivatives, including α-melanocyte-stimulating hormone and β-endorphin); neuropeptide Y (NPY); growth hormone–releasing hormone (GHRH); TRH; CRH; somatostatin; vasoactive intestinal peptide (VIP); vasopressin; oxytocin; cholecystokinin; peptide PYY; neurotensin; angiotensin II; galanin-like peptide (GALP); kisspeptin (and other RF amides, including gonadotropin-inhibitory peptide); galanin; neurokinin B; dynorphin; enkephalin; GnRH; and others. In some cases, the function of these neurotransmitters is clear—e.g., GnRH stimulates the release of the gonadotropins—but in other (most) cases, the physiologic function of a particular factor either is unknown or is complex and diverse (e.g., NPY, which has functions in feeding behavior and reproduction, but is likely to play other physiologic roles as well). These various neurotransmitters have multiple receptors and cellular mechanisms of action (e.g., five receptor subtypes for NPY), which adds layers of complexity to their divergent and diverse functions.

HYPOTHALAMIC NEUROANATOMY AND LIMBIC INPUTS

The hypothalamus is part of the diencephalon. It lies rostral to the midbrain and caudal to the forebrain. The hypothalamus is bounded dorsally by the thalamus, posteriorly by the mammillary bodies, and anteriorly by the lamina terminalis and optic chiasm, and the third ventricle splits the hypothalamus bilaterally (Figs. 1-1 and 1-2). The hypothalamus receives rich input from the autonomic areas and reticular nuclei of the brain stem, particularly the catecholaminergic cell groups (many of which have neuropeptides as cotransmitters, such as galanin and NPY). The hypothalamus also receives dense innervation from the limbic areas of the forebrain, including the hippocampus, amygdala, septum, and orbitofrontal cortex.

The hypothalamus serves as the primary site for the integration and regulation of many important physiologic processes. These include homeostatic control of temperature, metabolism, and body weight, aspects of cardiovascular function, physiologic adaptation to stress, regulation of growth, reproduction (including sexual behavior), and lactation. Although the regulation of these complex processes depends on the circuitry of the hypothalamus (and its afferent inputs), the control of these systems cannot be defined on the basis of strict anatomic criteria.