Diagnosis and Management of Pituitary Disorders
Contemporary Endocrinology

P. Michael Conn, Series Editor

Diagnosis and Management of Pituitary Disorders, edited by Brooke Swearengen and Beverly M. K. Biller, 2008

A Case-Based Guide to Clinical Endocrinology, edited by Terry F. Davies, 2008

Type 2 Diabetes Mellitus: An Evidence-Based Approach to Practical Management, edited by Mark N. Feinglos and Mary Angelyn Bethel, 2008

Autoimmune Diseases in Endocrinology, edited by Anthony P. Weetman, 2008


The Metabolic Syndrome: Epidemiology, Clinical Treatment, and Underlying Mechanisms, edited by Barbara Caleen Hansen and George A. Bray, 2008

Genomics in Endocrinology: DNA Microarray Analysis in Endocrine Health and Disease, edited by Stuart Handwerger and Bruce Aronow, 2008


Endocrine-Disrupting Chemicals: From Basic Research to Clinical Practice, edited by Andrea C. Gore, 2007

When Puberty is Precocious: Scientific and Clinical Aspects, edited by Ora H. Pescovitz and Emily C. Walvoord, 2007


The Leydig Cell in Health and Disease, edited by Anita H. Payne and Matthew Phillip Hardy, 2007


Evidence-Based Endocrinology, edited by Victor M. Montori, 2006

Stem Cells in Endocrinology, edited by Linda B. Lester, 2005

Office Andrology, edited by Phillip E. Patton and David E. Battaglia, 2005


Androgens in Health and Disease, edited by Carrie Bagatell and William J. Bremner, 2003

Endocrine Replacement Therapy in Clinical Practice, edited by A. Wayne Meikle, 2003

Early Diagnosis of Endocrine Diseases, edited by Robert S. Bar, 2003

Type I Diabetes: Etiology and Treatment, edited by Mark A. Sperling, 2003


Developmental Endocrinology: From Research to Clinical Practice, edited by Erica A. Eugster and Ora Hirsch Pescovitz, 2002

Osteoporosis: Pathophysiology and Clinical Management, edited by Eric S. Orwoll and Michael Blziotes, 2002
Diagnosis and Management of Pituitary Disorders

Edited by

Brooke Swearingen, MD
Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

and

Beverly M. K. Biller, MD
Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Humana Press
This book presents a comprehensive update on the current diagnostic and treatment options for the management of disease of the sella, with an emphasis on pituitary adenomas. Over the past several decades, the techniques of molecular biology have been employed to investigate the pathogenesis of these tumors, as discussed by Drs. Lania, Mantovani, and Spada in Chapter 1. Their pathological analysis is discussed by Drs. Gejman and Hedley-Whyte in Chapter 2. The evaluation of patients presenting with sellar disease is based both on modern endocrine techniques, as discussed by Dr. Snyder in Chapter 3, as well as new imaging modalities, as discussed by Drs. Lysack and Schaefer in Chapter 4. Since Harvey Cushing first plotted visual fields, the intimate anatomic relationship between the sella and the optic structures has required careful neuro-ophthalmologic evaluation in these cases; this is discussed by Drs. Cestari and Rizzo in Chapter 5. The management of secretory adenomas remains challenging. Prolactinomas, since the introduction of medical treatment in the 1980s, have been primarily managed with dopamine agonists as discussed by Drs. Shibli-Rahhal and Schlechte in Chapter 6. The diagnosis of acromegaly, discussed by Dr. Clemmons in Chapter 7, is made by hormonal testing and depends on reliable GH and IGF-1 assays. The treatment of acromegaly, once primarily a surgical disease, is now increasingly amenable to new medical agents, including somatostatin analogs and growth hormone receptor antagonists. The relative advantages of these approaches are discussed by Dr. Freda, and Drs. Buchfelder and Nomikos, in Chapters 8 and 9, respectively. The patient with Cushing’s disease requires an extensive and sophisticated endocrine evaluation before undergoing transsphenoidal surgery, as outlined by Drs. Findling and Raff in Chapter 10. The surgical approach is described by Dr. Kelly in Chapter 11, with options for medical treatment discussed by Drs. Lindsay and Nieman in Chapter 12. The diagnosis and treatment of the uncommon TSH adenomas is described by Drs. Zemskova and Skarulis in Chapter 13. Nonfunctioning tumors currently remain the province of the neurosurgeon, as discussed by Drs. Muh and Oyesiku in Chapter 14. Drs. Chandler and Barkan describe the surgical techniques used to remove sellar tumors in Chapter 15, while Drs. Barkan, Blank, and Chandler address
the perioperative management of patients with these lesions in Chapter 16. Although advances in medical treatment and surgical techniques have made its use less frequent, radiation therapy continues to have an important role in the management of these patients, as described by Drs. Shih and Loeffler in Chapter 17. Finally, a number of specialized and clinically important topics arise in caring for patients with pituitary disorders. The diagnosis and management of inflammatory disease of the pituitary is discussed by Drs. Ulmer and Byrne in Chapter 18, the management of apoplexy by Drs. Russell and Miller in Chapter 19, and the management of pituitary disease during pregnancy by Dr. Molitch in Chapter 20. Modern imaging techniques will sometimes demonstrate an incidental sellar abnormality when none was suspected; the evaluation of these patients is described by Dr. Frohman in Chapter 21. Although pituitary adenomas are relatively less common in children, other sellar pathologies, especially craniopharyngiomas, are more important and their endocrine management is critical in the developing child; these topics are discussed by Drs. Stanley, Prabhakaran, and Misra in Chapter 22. Finally, the management of cystic disease of the sella can be an especially thorny problem, and therapeutic options are described by Drs. Snyder, Naidich, and Post in Chapter 23.

It has been a pleasure to work with some of the leading authorities in the field of pituitary disease in the preparation of this volume and we would like to thank them both for their contributions to this volume and their commitment to the field of pituitary education. In addition, we would like to thank Dr. Michael Conn and Richard Lansing of Springer publishing for conceiving this project and asking us to participate in it, and the editorial staff at Springer for their expert assistance in preparing the volume.

Brooke Swearingen, MD
Beverly M. K. Biller, MD
Contents

Preface .............................................................................................................. v
Contributors ................................................................. ix
Color Plate .................................................................................................. xiii

1. Molecular Pathogenesis of Pituitary Adenomas ...................... 1
   *Andrea Lania, Giovanna Mantovani, and Anna Spada*

2. Pathology of Pituitary Adenomas ........................................... 17
   *Roger Gejman and E. Tessa Hedley-Whyte*

3. Endocrinologic Approach to the Evaluation of Sellar Masses .... 39
   *Peter J. Snyder*

4. Imaging of the Pituitary Gland, Sella, and Parasellar Region .... 45
   *John T. Lysack and Pamela W. Schaefer*

5. Neuro-ophthalmology of Sellar Disease .................................. 93
   *Dean M. Cestari and Joseph F. Rizzo III*

6. Prolactinomas: Diagnosis and Management .......................... 125
   *Amal Shibli-Rahhal and Janet A. Schlechte*

7. Acromegaly: Pathogenesis, Natural History, and Diagnosis .... 141
   *David R. Clemmons*

8. Acromegaly: Medical Management ....................................... 151
   *Pamela U. Freda*

9. Acromegaly: Surgical Management ...................................... 171
   *Michael Buchfelder and Panagiotis Nomikos*

10. Cushing’s Disease: Diagnostic Evaluation ......................... 187
    *James W. Findling and Hershel Raff*
11. Cushing’s Disease: *Surgical Management* ....................... 203  
   *Daniel F. Kelly*

12. Cushing’s Disease: *Medical Management* ....................... 223  
   *John R. Lindsay and Lynnette K. Nieman*

13. Thyrotropin-secreting Pituitary Adenomas ....................... 237  
   *Marina S. Zemskova and Monica C. Skarulis*

14. Non-functioning Adenomas: *Diagnosis and Treatment* ........... 271  
   *Carrie R. Muh and Nelson M. Oyesiku*

15. Pituitary Surgery: *Techniques* .................................. 289  
   *William F. Chandler and Ariel L. Barkan*

   *Ariel L. Barkan, Howard Blank and William F. Chandler*

17. Radiation Therapy for Pituitary Adenomas ....................... 321  
   *Helen A. Shih and Jay S. Loeffler*

18. Lymphocytic Hypophysitis and Inflammatory Disease  
    of the Pituitary .................................................. 339  
   *Stephan Ulmer and Thomas N. Byrne*

19. Pituitary Apoplexy ................................................ 353  
   *Steven J. Russell and Karen Klahr Miller*

20. Pituitary Tumors and Pregnancy ............................... 377  
   *Mark E. Molitch*

21. Management of Pituitary Incidentalomas ........................ 399  
   *Lawrence A. Frohman*

22. Sellar and Pituitary Tumors in Children ....................... 411  
   *Takara Stanley, Rajani Prabhakaran, and Madhusmita Misra*

23. Cystic Lesions of the Sella ................................. 445  
   *Brian J. Snyder, Thomas P. Naidich, and Kalmon D. Post*

Subject Index .......................................................... 467
Contributors

Ariel L. Barkan, MD • Professor, Departments of Internal Medicine and Neurosurgery, University of Michigan Medical Center, Ann Arbor, MI
Howard Blank, MD • Fellow, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan Medical Center, Ann Arbor, MI
Michael Buchfelder, MD, PhD • Professor and Chairman, Department of Neurosurgery, University of Erlangen-Nuremberg, Erlangen, Germany
Thomas N. Byrne, MD • Clinical Professor of Neurology and Health Sciences and Technology, Harvard Medical School, Massachusetts General Hospital, Boston, MA
Dean M. Cestari, MD • Assistant Professor of Ophthalmology, Massachusetts Eye & Ear Infirmary, Harvard Medical School, Boston, MA
William F. Chandler, MD • Professor, Departments of Neurosurgery and Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI
David R. Clemmons, MD • Kenan Professor of Medicine, UNC School of Medicine, Chapel Hill, NC
James W. Findling, MD • Director, Endocrine-Diabetes Center, Aurora St. Luke’s Medical Center, Clinical Professor of Medicine, Medical College of Wisconsin, Milwaukee, WI
Pamela U. Freda, MD • Associate Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York, NY
Lawrence A. Frohman, MD • Professor Emeritus of Medicine, Section of Endocrinology, Metabolism, and Diabetes, University of Illinois at Chicago, Chicago, IL
Roger Gejman, MD • Research Fellow in Neuropathology, Massachusetts General Hospital, Research Fellow in Pathology, Harvard Medical School, Boston, MA
E. Tessa Hedley-Whyte, MD • Professor of Pathology, Harvard Medical School, Neuropathologist, Massachusetts General Hospital, Boston, MA
Daniel F. Kelly, MD • Director, Neuroendocrine Tumor Center, John Wayne Cancer Institute at Saint John’s Health Center, Santa Monica, CA
Andrea Lania, MD, PhD • Endocrine Unit, Department of Medical Sciences, Fondazione Policlinico, IRCCS, University of Milan, Milan, Italy
Contributors

John R. Lindsay, MD • Altnagelvin Hospital, Western Health and Social Care Trust, Londonderry, UK

Jay S. Loeffler, MD • Herman and Joan Suit Professor of Radiation Oncology, Harvard Medical School, Chair, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA

John T. Lysack, MD, FRCP • Clinical Assistant in Neuroradiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Giovanna Mantovani, MD, PhD • Endocrine Unit, Department of Medical Sciences, Fondazione Policlinico, IRCCS, University of Milan, Milan, Italy

Karen Klahr Miller, MD • Neuroendocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Madhusmita Misra, MD, MPH • Assistant in Pediatrics, Pediatric Endocrinology Unit, MassGeneral Hospital for Children, Assistant in Biology, Neuroendocrine Unit, Massachusetts General Hospital, Assistant Professor of Pediatrics, Harvard Medical School, Boston, MA

Mark E. Molitch, MD • Professor of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Carrie R. Muh, MD, MS • Department of Neurological Surgery, Emory University School of Medicine, Atlanta, GA

Thomas P. Naidich, MD • Director of Neuroradiology, Professor of Radiology and Neurosurgery, Irving and Dorothy Regenstreif Research Professor of Neuroscience (Neuroimaging), Mount Sinai Medical Center, New York, NY

Lynnette K. Nieman, MD • Senior Investigator, RBMB, NICHD, Associate Director, IETP, NICHD-NIDDK, Reproductive Biology and Medicine Branch, NICHD, National Institutes of Health, Bethesda, MD

Panagiotis Nomikos, MD • Senior Neurosurgeon, Department of Neurosurgery, Hygeia Hospital, Marousi, Greece

Nelson M. Oyesiku, MD, PhD, FACS • Professor and Vice-Chairman, Department of Neurological Surgery, Emory University School of Medicine, Atlanta, GA

Kalmon D. Post, MD • Professor of Neurosurgery, Mount Sinai Medical Center, New York, NY

Rajani Prabhakaran, MD • Fellow, Pediatric Endocrinology, MassGeneral Hospital for Children, Harvard Medical School, Boston, MA

Hershel Raff, PhD • Director, Endocrine Research Laboratory, Aurora St. Luke’s Medical Center, Professor of Medicine, Medical College of Wisconsin, Milwaukee, WI

Joseph F. Rizzo III, MD • Associate Professor of Ophthalmology, Massachusetts Eye & Ear Infirmary, Harvard Medical School, Boston, MA
STEVEN J. RUSSELL, MD, PhD • Instructor in Medicine, Harvard Medical School, Assistant in Medicine, Massachusetts General Hospital, Boston, MA

PAMELA W. SCHAEFER, MD • Associate Director of Neuroradiology, Clinical Director of MRI, Massachusetts General Hospital, Associate Professor of Radiology, Harvard Medical School, Boston, MA

JANET A. SCHLECTE, MD • Professor of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA

AMAL SHIBLI-RAHAL, MD • Assistant Professor of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA

HELEN A. SHIH, MD, MS, MPH • Instructor in Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

MONICA C. SKARULIS, MD • Clinical Endocrinology Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

BRIAN J. SNYDER, MD • Department of Neurosurgery, Mount Sinai Medical Center, New York, NY

PETER J. SNYDER, MD • Professor of Medicine, University of Pennsylvania, Philadelphia, PA

ANNA SPADA, MD • Professor of Endocrinology, Endocrine Unit, Department of Medical Sciences, Fondazione Policlinico, IRCCS, University of Milan, Milan, Italy

TAKARA STANLEY, MD • Fellow, Pediatric Endocrinology, MassGeneral Hospital for Children, Harvard Medical School, Boston, MA

STEPHAN ULMER, MD • Institute of Neuroradiology, University Hospital of Schleswig-Holstein, Kiel, Germany

MARINA S. ZEMSKOVA, MD • Associate Investigator, Clinical Endocrinology Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD
The following color illustrations are printed in the insert.

Chapter 2

Fig. 1: Prolactinoma composed of cells with chromophobic cytoplasm arranged in a diffuse architectural pattern (A). Prolactinoma with small, hyperchromatic cells after dopamine agonist therapy (B). Positive immunohistochemical reaction for PRL with diffuse (C) and paranuclear patterns (D) in two prolactinomas.

Fig. 2: Densely granulated somatotroph pituitary adenoma with acidophilic and densely granulated cytoplasm (A), strong positive immunoreaction for GH (B) and diffuse immunohistochemical staining pattern for CAM 5.2 (C). Sparsely granulated somatotroph pituitary adenoma with a chromophobic and less granular cytoplasm (D). The same tumor as in (D) with slightly positive reaction for GH (E) and the dot-like positive reaction with CAM 5.2 corresponding to fibrous bodies (F).

Fig. 3: ACTH-producing pituitary tumor composed of densely granular basophilic cells (A) with strong positive immunohistochemical reaction for ACTH (B).

Fig. 4: Gonadotropic pituitary adenoma with a papillary pattern (A); perivascular pseudorosettes (B); and focal and weak expression of beta-FSH (C). Ultrastructural appearance of a tumor cell with oncocytic changes, i.e., many mitochondria (D).

Fig. 5: Craniopharyngioma composed of cords and islands of squamoid epithelium limited by columnar cells (A). Some cavities contain keratin material (*) (B). A cystic area has a thin epithelial wall(C) and adjacent inflammatory reaction with many foamy macrophages (D) (hematoxylin and eosin stain).

Fig. 6: Germinoma with a dense lymphocytic population and scattered groups of bigger round tumor cells with clear cytoplasm (arrows) (hematoxylin and eosin stain).
Fig. 7: Granular cell tumor composed of closely apposed acidophilic cells with bland nuclei and granular cytoplasm (hematoxylin and eosin stain).

Fig. 9: Lymphocytic hypophysitis with a dense inflammatory infiltrate including lymphocytes and plasma cells. Scattered pituitary cells are seen between the inflammatory cells (arrows) (hematoxylin and eosin stain).

Chapter 5

Fig. 6: Horizontal section of the visual pathways. The visual fields demonstrate the correlation of lesion site and field defect. (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.)

Fig. 7: Localization and probable identification of masses by pattern of field loss. Junctional scotomas occur with compression of the anterior angle of the chiasm (sphenoid meningiomas). Bitemporal hemianopia results from compression of the body of the chiasm from below (e.g., pituitary adenoma, sellar meningiomas). Compression of the posterior chiasm and its decussating nasal fibers may cause central bitemporal scotomas (e.g., hydrocephalus, pinealoma, craniopharyngioma). (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.)

Fig. 9: Parasympathetic and sympathetic innervation of the iris muscles. (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.)

Fig. 10: (A) Early papilledema. The optic disk of an 18-year-old man 2 weeks after he had complained of diplopia arising from sixth cranial nerve palsies caused by increased intracranial pressure. Note the minimal evidence of edema. (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.) (B) Developed papilledema. The optic disk of a 36-year-old woman who suffered headache and blurred vision for 2 months. Fully developed disk edema present—note the engorged veins and peripapillary hemorrhages. (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.) (C) Chronic papilledema. Severe and chronic disk edema in a 27-year-old very obese woman who has pseudotumor cerebri. Note that the disk cup is obliterated and hard exudates are present. (Reproduced with permission, Yanoff M, Duker JS,
Secondary optic atrophy from chronic papilledema. The same 27-year-old obese female patient 5 months later. Note the secondary optic atrophy has developed fully. The disk margins appear hazy or “dirty.” (Reproduced with permission, Yanoff M, Duker JS, editors. Ophthalmology, 2nd ed. St Louis, Mo: Mosby; 2004.)

**Fig. 11:** Optic disk tilting and the resulting visual field defects. (A, B) Visual fields demonstrate bilateral relative superotemporal defects not respecting the vertical midline. (C, D) Fundus photos show bilateral tilted disks, with flattening of the inferonasal disk margins. (Reproduced with permission from The American Academy of Ophthalmology, Basic and Clinical Science Course, Section 5: Neuro-ophthalmology 2005–2006.)

**Fig. 18:** Acute compressive optic neuropathy in pituitary apoplexy. (A, B) Fundus photographs in a patient with acute severe visual loss bilaterally. The optic disks appear relatively normal. (C, D) Axial (left) and sagittal (right) MRI scans show a large pituitary tumor with suprasellar extension. Inhomogeneity within the tumor represents hemorrhage and infarction. (Reproduced with permission from The American Academy of Ophthalmology, Basic and Clinical Science Course, Section 5: Neuro-ophthalmology 2005–2006.)

**Chapter 13**

**Fig. 1:** TSH-oma cells by light microscopy (40× magnification). H&E stain shows significant cytological and nuclear pleomorphism of tumor cells.

**Fig. 2:** Immunohistochemical staining of TSH-oma (40× magnification). Tumor cells show positive reaction for TSH. The intensity of staining is variable from cell to cell.