Surgical and Medical Management of Diseases of the Thyroid and Parathyroid

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Ashok R. Shaha,
MD, FACS
Cherie-Ann O. Nathan,
MD, FACS
Jyotika K. Fernandes,
MD, MBBS
Chris de Souza,
MS, DORL, DNB, FACS, FRCS
Shashank R. Joshi,
MD, DM, FRCP, FACE, FACP, FICP

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PREFACE

The thyroid gland is considered to be the master organ of the body. A provocative paper even went so far as to suggest that iodination of the thyroid gland was instrumental in conferring intelligence and thus was responsible for the evolutionary separation of humans from hominids. The thyroid gland regulates 13 vital functions of the body, including that of the brain and heart. Understanding the role of the thyroid and parathyroid glands and the consequences of their dysfunction has taken a long time to uncover. It was in 1908 that Theodor Kocher was awarded the Nobel prize for his work on the physiology, pathology, and surgery of the thyroid gland. Theodor Kocher is considered by many to be the father of thyroid surgery. The era before his work was clouded with catastrophes that surrounded thyroid surgery. Hemorrhage and sepsis were usually the cause of mortality in those days. Since then the trajectory of thyroid gland surgery has evolved swiftly. The surgeons of today are lucky to be practicing in an era when thyroid surgery has its finesse and nuances; the mortality associated with thyroid surgery is almost negligible.

The new era of endocrine surgery has started as a subspecialty. Each discipline in medicine has experienced major developments and advances. All of these have greatly increased the safety of thyroid and parathyroid gland surgery. With the advent of robotics, greatly improved radiological imaging, molecular biology, and a vast array of treatment modalities, physicians can now better treat most problems associated with tumors and dysfunctions of the thyroid and parathyroid glands.

All the editors and authors of this book understand that its contents need to be updated at frequent intervals if it is to remain relevant. It is our hope that all those who read this book will find themselves better prepared to face the challenges associated with diseases of the thyroid and parathyroid glands.

Our primary intention is to pass on relevant, meaningful, and helpful information to our readers. This in turn should help them to transform this information into useful principles in everyday practice. When physicians and patients benefit from the information obtained from this book, all of us involved in its publishing will feel that its purpose is well served.

Ashok R. Shaha
Cherie-Ann O. Nathan
Jyotika K. Fernandes
Chris de Souza
Shashank R. Joshi

ABOUT THE EDITORS

Ashok R. Shaha, MD, FACS, is an attending surgeon on the Head and Neck Service at Memorial Sloan-Kettering Cancer Center, Jatin P. Shah Chair in Head and Neck Surgery, and Professor of Surgery at Cornell University Medical College, New York. He completed his surgical training in Baroda, India and worked as a house surgeon at Tata Memorial Hospital, where he developed an interest in head and neck surgical oncology. After his arrival at Memorial Sloan-Kettering Cancer Center in 1975, Dr. Shaha did a surgical oncology fellowship completing his surgical training at Downstate Medical Center in Brooklyn, New York. Dr. Shaha returned to Memorial Hospital in 1981 as a Fellow in Head and Neck Surgery, and he joined the Department of Surgery at Downstate Medical Center in 1982 as a head and neck surgeon, rising to the rank of Professor of Surgery in 1992. During this period, he was also Chief of Head and Neck Surgery at King's County, Brooklyn VA Hospital and University Hospital. In August of 1993, Dr. Shaha moved to Sloan Kettering.

During his post-graduate training, Dr. Shaha was awarded several gold medals and was given the Golden Apple Teaching Award at Downstate Medical Center. Other awards include: Faculty Member of the AOA Honor Medical Society, the Outstanding Teacher Award at Memorial Sloan-Kettering Cancer Center in 1996, the Honor Award from the American Academy of Otolaryngology/Head and Neck Surgery, and being named Visiting Professor of the Society of Head and Neck Surgeons in 1997 and 1998. Dr. Shaha has been honored by visiting professorships at University of Santa Tomas, Manila, and Sun Yat-Sen University, Guang Zhou, China. He has been actively involved in local and national head and neck societies, as well as having been President of the New York Head and Neck Society, the American Society for Surgeons of Indian Origin, and the Brooklyn Surgical Society, and was co-president of the American Head and Neck Society, 1998–1999, and president of the New York Cancer Society, 1999–2000 and the New York Surgical Society, 2004–2005. He is a member of many scientific organizations and serves on the editorial boards of the *Journal of Surgical Oncology, Head and Neck, Annals of Surgical Oncology, Brazilian Journal of Surgery*, and *Journal of Clinical Oncology*. He is an honorary member of the Brazilian College of Surgeons, the Cuban Surgical Society, Association of Surgeons of India, the Korean Head and Neck Society, Latin Head and Neck Society, Panamanian Society of Oncology, Chilean College of Surgeons, and Costa Rican Endocrine Society, and was the Program Chairman for the Fifth International

Head and Neck Oncology Meeting in San Francisco (2000), and Conference Chairman for the Sixth International Head and Neck Meeting in 2004. Recently Dr. Shaha was the recipient of the Distinguished Service Award by the American Academy of Otolaryngology—Head and Neck Surgery and President of the American Association of Endocrine Surgeons, and was elected to the American Surgical Association. In July 2016, he delivered the Hayes Martin Lecture, and has served on the steering committee for World Congress in Thyroid Cancer.

Dr. Shaha has been academically active at national and international meetings, with approximately 650 papers, 540 of which are peer-reviewed (Pubmed and Scopus). His *curriculum vitae* includes 150 published abstracts, 63 posters, and 45 scientific exhibits. He has delivered more than 2,000 presentations nationally and internationally. His research interests include tracheal reconstruction and an experimental model of tracheomalacia and thyroid cancer. He has been actively involved in the training of head and neck fellows nationally and was chairman of the Advanced Training Council for head and neck fellowship in the United States.

Dr. Shaha has dedicated his professional career to the training of medical students and residents and has developed a preceptorship program at Cornell University Medical College in head and neck training for medical students. He was Chairman of the Advanced Training Council for Head and Neck Oncology Fellowships in the United States for ten years and recipient of the Distinguished Service Award by the Head and Neck Society twice.

Cherie-Ann O. Nathan, MD, FACS, is the Jack W. Pou Endowed Professor and Chairman of the Department of Otolaryngology/Head and Neck Surgery at LSU-Health in Shreveport, Louisiana. She is also Director of Head and Neck Oncologic Surgery and Research at the Feist-Weiller Cancer Center. She completed her Otolaryngology/Head and Neck Surgery residency and head and neck fellowship in 1995 at University of California, San Diego. She was a post-doctoral fellow at Johns Hopkins where she started her research career. Following her fellowship, she began her academic career at LSU-Health Sciences Center, Shreveport.

Her passion to improve outcomes for patients with head and neck cancer was the reason she moved from Mumbai India, where she went to medical school. She is a Surgeon-Scientist who maintains a busy practice treating head and neck cancer, thyroid, parathyroid, and salivary gland tumors, and leads an active research team. The National Cancer Institute has funded her translational research since 2000 with a focus on targeted therapy for head and neck patients. Dr. Nathan is recognized nationally and internationally for her seminal work on molecular analysis of surgical margins. She has pioneered multi-institutional clinical trials using mTOR inhibitors in HNSCC patients with both Wyeth and Novartis. She has also received NIH funding for chemoprevention of cancer with curcumin and has a patent for a curcumin chewing gum. Her new RO1 on Targeting the FGFR-2 pathway for cutaneous SCC holds potential for transplant patients with aggressive cSCC. She has published extensively. Dr. Nathan has over 180 publications in peer-reviewed jour-

nals and has authored multiple textbooks and encyclopedia chapters.

Dr. Nathan is currently the President-Elect of the American Head and Neck Society. She serves on many national committees including the NCI Steering committee, the American Cancer Society-CDC HPV Steering Committee, executive board of directors for the Head and Neck Cancer Alliance, council member for the Society of University Otolaryngology, and the Larynx Preservation Guideline Panel. She is currently co-president of the ASTRO-ASCO Multidisciplinary meeting and secretary treasurer of the Association of Academic Departments of Otolaryngology/Head and Neck Surgery. She has served on the nominating committee for the American Academy of Otolaryngology-HNS Program and is the Head and Neck CORE grants research leader. She is also associate editor for "Laryngoscope Investigative Otolaryngology." At the local level she is active, having been on the board of directors for Shreveport Medical Society, Disaster Reform committee, and the Science Museum.

The Shreveport-Bossier Commerce Department awarded her the Athena Award for community service and she received the Leonard Tow Humanism award from the Arnold Gold Foundation. The Board of Regents in Louisiana established the "Cherie-Ann O. Nathan Endowed Professorship in Otolaryngology/Head and Neck Surgery" initiated by grateful patients to honor her dedication and expertise.

Dr. Nathan is married to pulmonary and critical care physician Raghu Nathan and they have two boys Sean and Neil. Her favorite hobby is to perform with the "Nathan Family Trio" to raise money for the arts and cancer research in Shreveport.

Jyotika K. Fernandes, MD, MBBS is currently Professor in Internal Medicine—Endocrine Division at the Medical University of South Carolina, Charleston (MUSC) South Carolina. She is also Chief of the Endocrine Section at the Ralph H. Johnson Veterans Affairs Medical Center, Charleston. Dr. Fernandes completed her early medical training in India—MBBS from Christian Medical College, Ludhiana, India and MD Medicine at PGIMER (Post Graduate Institute of Medical Education and Research), Chandigarh, India.

After her move to the United States, she did her internship at Mayo Clinic Rochester, and finished her residency at University of Texas, Houston. This was followed by a joint endocrine fellowship at Baylor College of Medicine and The MD Anderson Cancer Center, Houston, Texas. Her clinical interest is endocrine neoplasias and she leads a Multidisciplinary Endocrine Neoplasia Clinic at the Hollings Cancer Center at MUSC. The Multidisciplinary Endocrine Neoplasia Clinic comprises specialists from Endocrinology, Endocrine Surgery, Head and Neck Surgery, Neurosurgery, Radiation, and Medical Oncology. Dr. Fernandes is actively involved in endocrine medical education and mentorship of the training fellows and residents at the Medical University and the VA hospital. She has authored several publications in peer-reviewed journals and is the lead investigator in several NIH and pharmaceutical trials

Chris de Souza, MS, DORL, DNB, FACS, FRCS, trained at the University of Minnesota with Dr. Michael Paparella, and completed his externship in otology and neurotology with Dr. Michael Glasscock and Dr. C. Gary Jackson at Baptist Hospital in Nashville, Tennessee. He furthered his training in India and was given the gold medal in the DORL exam from the College of Physicians and Surgeons in Mumbai, India. In 1995, Dr. de Souza was the second awardee of the Orbit Silver Medal for his work on the nose, paranasal sinuses, and skull base. In 2018, Dr. de Souza was awarded an FRCS degree by the Royal College of Surgeons of England. He was visiting assistant professor of Otorhinolaryngology—Head and Neck Surgery at the State University of New York, Brooklyn and also at the Louisiana State University Health Science Center, Shreveport, where he has conducted temporal bone surgery workshops and has held these appointments for the past 22 years. Dr. de Souza has published extensively in internationally peer-reviewed journals and several of his publications are considered landmark papers. He has published 35 postgraduate ENT medical textbooks in the United States, Germany, and India. Currently, he is editor-in-chief of the *International Journal of Head and Neck Surgery*. Dr. de Souza's current clinical appointments include senior ENT consultant at Lilavati Hospital, Tata Memorial Hospital, Holy Family Hospital, and the Holy Spirit Hospital in Mumbai, India, and he is also the coordinator for implantable hearing devices in children and adults at Holy Family Hospital. He is the Director of the Hearing Disability Clinic, as well as the Director of the Cochlear Implant Foundation.

Shashank R. Joshi, MD, DM, FRCP, FACE, FACP, FICP is the President, API (Association of Physicians of India), President of Indian Academy of Diabetes, and Past President of RSSDI (Research Society for Study of Diabetes in India). He is also an endocrinologist at Lilavati and Bhatia Hospitals. He is on the faculty at Grant Medical College and Sir JJ Group of Hospitals in Endocrinology. Dr. Joshi is a practicing endocrinologist and diabetologist who has topped all years of MBBS, MD, and DM with Gold Medals. He is a Fellow of the American College of Endocrinology, American College of Physicians and the Royal College of Physicians (Glasgow and Edinburgh). He has more than 600 research publications to his credit. He is the Hon. Emeritus Editor of JAPI (*Journal of The Association of Physicians of India*), and former editor of the *Indian Journal of Obesity*, *Indian Journal of Endocrinology and Metabolism*, and *Indian Journal of Clinical Pharmacology and Therapeutics* as well as several other leading medical journals. He is affiliated with several leading hospitals, including Lilavati and Bhatia Hospitals,

and he is the Past President of AIAARO (All India Association of Advancement for Research in Obesity, IASO Affiliate), Chapter Chair (India), and American Association of Clinical Endocrinology (AACE). He is visiting faculty to several Indian and international universities. Dr. Joshi is actively involved with evidence-based work in endocrinology including diabetes, obesity, thyroid, osteoporosis, and growth. He was awarded "International Clinician of the Year 2012" by the American College of Endocrinology. He has been conferred "Padma Shri" in 2014 by the Government of India.

CONTRIBUTORS

Adrian P. Abreo, MD
Assistant Professor of Medicine, Associate Internal Medicine Program Director, Associate Internal Medicine Student Clerkship Director
Department of Medicine, Nephrology Section
LSU Health Shreveport School of Medicine
Shreveport, Louisiana
Chapter 51

Kenneth Abreo, MD, FASDIN
Professor of Medicine, Chief, Nephrology Section, Vice Chairman
Department of Medicine, Nephrology Section
LSU Health Shreveport School of Medicine
Shreveport, Louisiana
Chapter 51

Rashi Agarwal, MD FACP
Division of Endocrinology, Metabolism, and Medical Genetics
Medical University of South Carolina
Charleston, South Carolina
Chapter 13

Joseph A. Aloi, MD, FACE, FACS
Professor of Internal Medicine
Chief, Section on Endocrinology and Metabolism
Wake Forest School of Medicine
Winston-Salem, North Carolina
Chapters 9 and 10

Steven Anderson
Specialist Registrar
Department of Surgery
Beaumont Hospital
Royal College of Surgeons Ireland
Dublin, Ireland
Chapter 26

Surender K. Arora, MD
Section Chief, Endocrinology
Overton Brooks VA Medical Center
Assistant Professor of Endocrinology
Louisiana State University Health Science Center
Shreveport, Louisiana
Chapter 47

Supreeta Arya, MD, DNB, DMRD
Professor
Department of Radiodiagnosis
Tata Memorial Centre
Mumbai, India
Chapter 21

Ameya Asarkar, MD
Staff Physician (Otolaryngology)
Overton Brooks VA Medical Center
Assistant Professor of Otolaryngology
Louisiana State University Health
Shreveport, Louisiana
Chapter 33

Shaikh Irfan Basha, MD, MBBS, MS, FRCS, ORL-HNS-Ed
Division Head Otolaryngology
Department of Surgery
Sheikh Khalifa Medical City
Abu Dhabi, United Arab Emirates
Chapter 31

Naifa L. Busaidy, MD, FACE, FACP
Associate Professor
Director, Thyroid Nodule Clinic
Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center

Houston, Texas
Chapter 39

Pankaj Chaturvedi, MS, FACS
Professor
Department of Head and Neck Surgery
Tata Memorial Hospital
Mumbai, Maharashtra, India
Chapter 22

Uma P. Chaturvedi, MD
Pathologist
BARC Hospital
Mumbai, India
Chapter 20

Bae P. Chu, MPH
Lead Health Physicist
Department of Medical Physics
Memorial Sloan Kettering Cancer Center
New York, New York
Chapter 36

Matthew D. Cox, MD
Department of Otolaryngology—Head and Neck Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Chapter 48

Jennifer R. Cracchiolo, MD
Department of Surgery, Head and Neck Service
Memorial Sloan Kettering Cancer Center
New York, New York
Chapter 29

Preeti Dhingra, MD, MBBS, MS (ENT)
Junior Consultant
ENT, Head and Neck Surgery
Lilavati Hospital and Research Centre Location
Mumbai, Maharashtra, India
Chapter 20

William S. Duke, MD, FACS
Department of Otolaryngology
MultiCare Health System
Tacoma, Washington
Chapter 50

Nazanene H. Esfandiari, MD, FACE
Associate Professor of Medicine
Division of Metabolism, Endocrinology, and Diabetes
University of Michigan
Ann Arbor, Michigan
Chapter 11

Jyotika K. Fernandes, MD, MBBS
Professor of Medicine
The Medical University of South Carolina
Charleston, South Carolina
Chapter 12

Dan M. Fliss, MD
Professor and Chairman
Department of Otolaryngology
Head and Neck Surgery and Maxillofacial Surgery
Director
The Interdisciplinary Center for Head and Neck Surgery Oncology
Tel Aviv Medical Center
Tel Aviv, Israel
Chapter 54

Prachi R. Gaddam, MD
Pathologist
Pathology Unit
Barl Hospital
Mumbai, India
Chapter 20

Pramod Gandhi, MD, DM
Endocrinologist
Ghandi Endocrinology Center
Nagpur, India
Chapter 3

Somali Gavane, MD
Assistant Professor of Radiology
Nuclear Medicine and Molecular Imaging
Icahn School of Medicine at Mount Sinai
New York, New York
Chapter 36

Ziv Gil, MD, PhD
Technician
Rambam Healthcare Campus, Head and Neck Service

Haifa, Israel
Chapter 41

Paul H. Graham, MD, FACS
Assistant Professor
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 28

Ravinder K. Grewal, MD
Associate Attending, Molecular Imaging and Therapy Service
Department of Radiology
Memorial Sloan Kettering Cancer Center
Associate Member, Memorial Hospital
New York, New York
Chapters 36 and 40

Neeti Kapre Gupta, MS, DNB (ENT)
Consultant Head and Neck Surgeon
Neck Clinic, Nagpur
Fellowship (Head and Neck Surgery, Tata Memorial Hospital)
Internation Fellow, IFHNOS
Chapters 16 and 17

Manjiri Gupte, MS, MRCS, DNB
Staff Physician
Department of Surgery
Division Otolaryngology
Sheikh Khalifa Medical City
Abu Dhabi, United Arab Emirates
Chapter 31

Thomas E. Heineman, MD
Department of Otolaryngology—Head and Neck Surgery
University of California, Los Angeles
Los Angeles, California
Chapter 18

Brittany Bohinc Henderson, MD, ECNU
Assistant Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
Wake Forest Baptist Health
Winston-Salem, North Carolina
Chapters 7 and 15

Jeffrey Harris Henderson, MD, CAQSM
Staff Physician
Cone Health Medical Group
Kernersville, North Carolina
Chapters 7 and 15

Robert W. A. Hone, MBBS, MCh (Otolaryngology), FRCS(Eng)
Head and Neck Fellow
Queen Victoria Hospital NHS Foundation Trust
East Grinstead, East Sussux, England
Chapter 23

James R. Howe, MD
Director
Surgical Oncology and Endocrine Surgery
Professor of Surgery
University of Iowa College of Medicine
Iowa City, Iowa
Chapter 27

Mimi I. Hu, MD
Professor
Deputy Department Chair, Clinical Affairs
Department of Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 28

Eiman Y. Ibrahim
Research Intern
Department of Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 39

Yasuhiro Ito, MD
Department of Surgery
Kuma Hospital
Kobe, Japan
Chapter 45

Emma Jakoi, PhD
Associate Research Professor
Cell Biology Department
Duke University
Durham, North Carolina
Chapter 5

Morgan Jones, MD
Assistant Professor of Medicine
University of North Carolina
Chapel Hill, North Carolina
Chapter 12

Shashank R. Joshi, MD, DM, FRCP, FACE, FACP, FICP
Professor
Endocrinologist
President, Association of Physicians of India
President, Indian Academy of Diabetes
Grant Medical College and Sir Jamshedjee Jeejeebhoy Group of Hospitals
Mumbai, Maharashtra, India
Chapters 1, 2, 4, and 6

A. I. Kaleva, BMBCh, BA (Oxon), MRCS (ENT)
ENT Registrar
Colchester General Hospital
Colchester, United Kingdom
Chapter 35

Shubhada Kane, MD
Professor & Head
Department of Pathology
Tata Memorial Hospital, HBNI University
Mumbai, India
Chapter 8

Madan Kapre, FRCS, DLO
ENT and Head Neck Surgery Consultant
Director, Neck Clinic Nagpur
President Indian Society of Thyroid Surgery
Pash President Foundation of Head and Neck Oncology
Chapters 16, 17, and 52

Kendall J. Keck, MD
General Surgery Resident
Department of Surgery
University of Iowa, Carver College of Medicine
Chapter 27

Mark Lee, BS, BA
Medical Student
Weill Cornell Medicine
Research Associate
Department of Head and Neck Surgery
The University of Texas MD Anderson Cancer Center
New York, New York
Chapter 28

Nancy Y. Lee, MD, FASTRO
Attending
Memorial Sloan Kettering Cancer Center
Vice Chair of Radiation Oncology
Experimental Therapeutics
Chief of Head and Neck Radiation Oncology
New York, New York
Chapter 37

Steven N. Levine, MD
Professor of Medicine
Department of Medicine, Section of Endocrinology and Metabolism
Louisiana State University Health Sciences Center
Shreveport, Louisiana
Chapter 46

Katherine A. Lewis, MD, MSCR
Associate Professor
Division of Endocrinology, Diabetes, and Medical Genetics
Medical University of South Carolina
Charleston, South Carolina
Chapter 13

David C. Lieb, MD, FACE, FACP
Associate Professor of Medicine
Division of Endocrinology and Metabolism
Eastern Virginia Medical School
Norfolk, Virginia
Chapter 10

Nick Lilic, MBChB, MSc
NHS Lothian Department of ENT/Head and Neck Surgery

University of Edinburgh
Edinburgh, Scotland
Chapter 38

Sonia Mahajan, MD
Nuclear Medicine Resident
Department of Radiology, Molecular Imaging, and Therapy Service
Memorial Sloan Kettering Cancer Center
New York, New York
Chapter 40

Joshua D. Maier, MD, CCD
Staff Endocrinologist
Overton Brooks VA Medical Center
Assistant Professor of Medicine
Louisiana State University Health Shreveport
Shreveport, Louisiana
Chapter 46

Kelley Michele Malloy, MD, FACS
Associate Professor
Fellowship Director, Head and Neck Surgical Oncology—Microvascular Reconstruction Fellowship
Associate Chief Clinical Officer of Surgical Services
University Hospital, Michigan Medicine
Department of Otolaryngology—Head and Neck Surgery
University of Michigan
Ann Arbor, Michigan
Chapter 34

Sanjay Mediwala, MD
Assistant Professor of Medicine
Baylor College of Medicine
Staff Endocrinologist
Michael E. DeBakey VA Medical Center
Houston, Texas
Chapter 14

Vikas Mehta, MD, MPH, FACS
Assistant Professor
Otorhino Laryngology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York
Chapters 33 and 49

Munita Menon, MD
Professor
Pathology
Homi Bhabha National Institute
Mumbai, Maharashtra, India
Chapter 19

Neha Mittal
Assistant Professor
Department of Pathology
Tata Memorial Centre
Mumbai, India
Chapter 8

Akira Miyauchi, MD
President and COO
Department of Surgery
Kuma Hospital
Kobe, Japan
Chapter 45

Yogesh More, MS, FACS
Staff Physician
Department of Surgery
Division of Otolaryngology
Sheikh Khalifa Medical City
Abu Dhabi, United Arab Emirates
Chapter 31

Shorook Na'ara, PhD
Student
Laboratory for Applied Cancer Research at Rambam
Resident
Department of Otolaryngology Head and Neck Surgery at Rambam
Technion Integrated Cancer Center
Rappaport Faculty of Medicine and Research Institute
Israel Institute of Technology, Haifa
Chapter 41

Raji T. Naidu
Pathologist
BARC Hospital
Mumbai, India
Chapter 20

Vibushitha Narendra, MD
Endocrinologist
Institute of Diabetes and Endocrinology
Ajax, Ontario, Canada
Chapter 47

Cherie-Ann O. Nathan, MD, FACS
Jack W. Pou Endowed Professor and Chairman
Department of Otolaryngology/HNS
Louisiana State University Health—Shreveport
Director of Head and Neck Surgical Oncology
Feist-Weiller Cancer Center
Shreveport, Louisiana
Chapters 33 and 49

Kurt L. Nelson, MD
ENT Physicians of North Mississippi
Tupelo, Mississippi
Chapter 48

Iain J. Nixon, PhD, MBChB, FRCS
Senior Lecturer
NHS Lothian/Edinburgh University
Edinburgh, Scotland
Chapters 23, 35, and 38

Oluwafunmilola T. Okuyemi, MD, MSCI
Fellow Associate—Head and Neck Oncology and Microvascular Surgery
Department of Otolaryngology—Head and Neck Surgery
University of Iowa Hospitals and Clinics
Iowa City, Iowa
Chapter 53

James Paul O'Neill, FRCSI, MD, MMSc, MBA, ORL-HNS
Professor of Otolaryngology—Head and Neck Surgery
The Royal College of Surgeons in Ireland
Dublin, Ireland
Chapter 26

Gloria Ortiz, MD
Endocrinology, Diabetes, and Metabolism
Knapp Medical Center
Chapter 14

Nitin A. Pagedar, MD, MPH
Associate Professor
Otolaryngology—Head and Neck Surgery
University of Iowa
Iowa City, Iowa
Chapter 53

Prathamesh Pai, MS (ENT), DNB, DORL, MNAMS
Professor and Consultant Surgeon
Department of Head and Neck Surgical Oncology
Tata Memorial Centre
Mumbai, India
Chapter 44

Maria Papaleontiou, MD
Assistant Professor of Internal Medicine
Division of Metabolism, Endocrinology, and Diabetes
University of Michigan
Ann Arbor, Michigan
Chapter 11

Siobhan T. Pittock, MBBCh
Consultant Pediatric Endocrinology, Assistant Professor of Pediatrics
College of Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 30

Daniel L. Price, MD
Assistant Professor
Department of Otolaryngology, Head and Neck Surgery
Mayo Clinic
Rochester, Minnesota
Chapter 32

Lourdes Quintanilla-Dieck, MD, FACS
Assistant Professor
Otolaryngology Head and Neck Surgery
Oregon Health and Science University
Portland, Oregon
Chapter 55

Ashita Rastogi, DNB, Fellowship in Cancer Imaging
Assistant Professor
Department of Radiodiagnosis
Tata Memorial Hospital
Mumbai, India
Chapter 21

Ashok R. Shaha, MD, FACS
Department of Surgery, Head and Neck Service
Memorial Sloan Kettering Cancer Center
New York City, New York
Chapters 29, 33, 35, 38, and 49

Travis L. Shiba, MD
Assistant Clinical Professor
Department of Otolaryngology—Head and Neck Surgery
University of California, Los Angeles
Los Angeles, California
Chapter 18

Maisie Shindo, MD, FACS
Professor, Director of Head and Neck Endocrine Surgery
Otolaryngology
Oregon Health and Science University
Portland, Oregon
Chapter 55

Michael C. Singer, MD, FACS
Director, Division of Thyroid and Parathyroid Surgery
Department of Otolaryngology—Head and Neck Surgery
Henry Ford Health System
Detroit, Michigan
Chapter 42

Nikita Srinivasan
Research Associate
Joshi Clinic
Mumbai, India
Chapters 1, 2, and 4

Brendan C. Stack, Jr., MD, FACS, FACE
Professor
Department of Otolaryngology—Head and Neck Surgery
UAMS Thyroid Center
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Chapter 48

Jayne Ryder Stevens, MD
Department of Otolaryngology, Head and Neck Surgery
Tripler Army Medical Center
Honolulu, Hawaii
Chapter 34

Maie A. St. John, MD, PhD
Samuel and Della Pearlman Chair in Head and Neck Surgery
Co-Director, UCLA Head and Neck Cancer Program
Jonsson Comprehensive Cancer Center
David Geffen School of Medicine at UCLA
Los Angeles, California
Chapter 18

Parimal Tayde
Endocrinologist
Endocare Clinic
Nagpur, India
Chapter 3

David J. Terris, MD, FACS, FACE
Regents Professor of Otolaryngology and Endocrinology
Surgical Director of Augusta Thyroid Center
Augusta University
Augusta, Georgia
Chapter 50

Geoffrey B. Thompson, MD, FACS, FACE
Section Head, Endocrine Surgery, Mayo Clinic
Professor of Surgery
College of Medicine, Mayo Clinic
Rochester, Minnesota
Chapter 30

C. Jillian Tsai, MD, PhD
Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
Commack, New York
Chapter 37

Vidisha Tuljapurkar, MCh (Head Neck), MS (ENT)
Senior Registrar
Department of Head and Neck Surgical Oncology
Tata Memorial Centre
Mumbai, India
Chapter 44

R. Michael Tuttle, MD
Clinical Director, Endocrinology Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York
Chapters 25 and 43

Jagdeesh Ullal, MD, MS, FACE, FACP
Center for Endocrine and Metabolic Disorders
Eastern Virginia Medical School
Norfolk, Virginia
Chapter 9

Jimit Vadgama, MD, C.Diab.
Director and Head, Swaminarayan Diabetes Thyroid and Hormone Clinic
Consultant, Mahavir Multispecialty Hospital
BAPS Hospital and Green Leaf Hospital
Former Assistant Professor, Department of Medicine
Government Medical College
Surat, India
Chapter 1

Abhishek Vaidya, MD, MS, DNB, Fellowship Head-Neck Surgery
Consultant, Head and Neck Oncosurgeon
National Cancer Institute
Nagpur, India
Assistant Professor
ENT and Head and Neck
NKP Salve Institute of Medical Sciences
Nagpur, India
Chapter 22

Fernanda Vaisman, MD, PhD
Endocrinologist
National Institute of Cancer
Professor, Post Graduate Program
Federal University of Rio de Janeirol
Rio de Janeiro, Brazil
Chapters 25 and 43

Kathryn M. Van Abel, MD
Instructor
Department of Otolaryngology, Head and Neck Surgery
Mayo Clinic
Rochester, Minnesota
Chapter 32

Steven G. Waguespack, MD, FACE
Professor
Department of Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 28

Kacey B. Wanland
Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 39

Robert L. Witt, MD, FACS
Professor
Department of Otolaryngology—Head and Neck Surgery
Thomas Jefferson University
Philadelphia, Pennsylvania
Affiliate Professor
Department of Biological Sciences
University of Delaware
Newark, Delaware
Director
Head and Neck Multidisciplinary Clinic
Heten F. Graham Cancer Center, Christiano Care
Newark, Delaware
Chapter 24

Amy J. Xu, MD PhD
Resident Physician

Radiation Oncology
Memorial Sloan Kettering Cancer Center
New York City, New York
Chapter 37

Daniel Yafit, MD
Staff Physician
Department of Otolaryngology, Head and Neck and Maxillofacial Surgery
Tel-Aviv Sourasky Medical Center
Tel Aviv, Israel
Chapter 54

Mark E. Zafereo, MD, FACS
Section Chief, Head and Neck Endocrine Surgery
Associate Medical Director, Endocrine Surgery
Associate Professor, Head and Neck Surgery
The University of Texas MD Anderson Cancer Center
Division of Surgery, Department of Head and Neck Surgery
Houston, Texas
Chapter 28

This book is dedicated to

Mr. Ratan N. Tata

Chairman Emeritus of the Tata Group and of the Tata Trusts for amazing and incredible philanthropic work that has benefited millions of people all over India. The Tata Memorial Hospital named after its founder (commissioned by the Sir Dorabji Tata Trust on 28th February, 1941) and bears the Tata name, owes its existence to the Tata vision of free, competent, and comprehensive care for cancer patients regardless of their status in society.

Dr. Rajendra A. Badwe (Padmashree Awardee)

Director of Tata Memorial Centre, whose vision for the future of the Tata Memorial Hospital has taken it to new heights of excellence.

To the sacred memory of Dr. Ketayun A. Dinshaw

Director of the Tata Memorial Hospital who introduced many revolutionary changes during her tenure as director.

Section I
Introduction

1

ANATOMY AND DEVELOPMENT OF HYPOTHALAMIC PITUITARY THYROID AXIS

Shashank R. Joshi, Jimit Vadgama, and Nikita Srinivasan

Introduction: Development and Anatomy of the HPT Axis

Thyroid hormones are our body's most widely active hormones, critically required for neuronal development, growth, energetic metabolism, and even thermogenesis. They also affect the hepatic metabolism of various nutrients, the cardiovascular system, and fluid balance. The hypothalamus-pituitary-thyroid (HPT) axis determines amount or the set point of hormone production by the thyroid gland.

The thyroid gland is responsible for synthesis and controlled release of triiodothyronine (T3) and thyroxine (T4) hormones. T4 is the highest secreted hormone of the thyroid gland, while T3, though of less amount, is a more highly active hormone than T4, and they both act via nuclear receptors to exert effects throughout the body. T3 is also important for negative feedback effects on thyroid stimulating hormone (TSH; thyrotropin) secretion from the pituitary and for thyrotropin-releasing hormone (TRH) synthesis and release at the hypothalamus, respectively. TSH, by the anterior pituitary, is the main regulator of thyroid gland development, growth, and hormone synthesis and secretion. The secretion of TSH is in turn from positive input by TRH from the hypothalamus and the negative feedback THS level in blood.

Hypothalamic Part of the HPT Axis: Development and Anatomy

The hypothalamus is an evolutionarily ancient part of the brain which is formed by multiple small nuclei with diverse variety of functions. It is located above the midbrain and just below the thalamus. It forms the ventral diencephalon. The diencephalon is considered an embryologic area of the vertebrate neural tube region that gives rise to forebrain structures of the posterior region. In the early embryo, neuroectoderm of the forebrain (**prosencephalon**) primary brain vesicle divides to form two secondary brain vesicles, telencephalon (endbrain, cortex) and diencephalon. The historical description is that the diencephalon ventrolateral wall, intermediate zone proliferation generates the primordial hypothalamus. But a recent "Prosomeric model"[1,2] based on gene expression in the mouse, suggests an overall different origin of the hypothalamus arising from the

telencephalon. Hypothalamus development also occurs differentially in male and female embryos, described as part of neural sexual dimorphism.

The hypothalamus integrates diverse sensory and hormonal inputs and provides coordinated responses through motor outputs to key regulatory sites.[3] The various nuclei of the hypothalamus act as a conduit between the central nervous system and the endocrine systems via the pituitary gland (hypophysis) by synthesizing and secreting neurohormones. This way it regulates multiple homeostatic functions of the body (eg, circadian rhythms, metabolic rate, hunger, thirst, body temperature).[4]

The hypothalamus is roughly diamond shaped in sagittal section and is composed of numerous fiber tracts and nuclei which are situated symmetrically near and about the third ventricle of brain. At the caudal end, the hypothalamus extends up to the periaqueductal gray matter of the midbrain, and at the rostral end it extends from the anterior commissure, lamina terminalis, and optic chiasm.[5]

The nuclei of the hypothalamus are divided into three groups depending on the blood supply they receive[4]:

1. Anterior or chiasmatic region (anterior cerebral and anterior communicating arteries)
2. Median or tuberal region (the posterior communicating artery)
3. Posterior or mammillary region (the posterior communicating, posterior cerebral, and basilar arteries)

These groups can be further segregated into three functional areas:

1. lateral,
2. medial, and
3. periventricular

Anterior hypothalamic nuclei include the medial/lateral preoptic, periventricular, supraoptic, suprachiasmatic, and anterior/lateral hypothalamic nuclei. The medial preoptic nucleus generates gonadotropin-releasing hormone (GnRH). The supraoptic nucleus and the paraventricular nucleus are composed primarily of neurosecretory cells, which produce oxytocin and vasopressin.[4]

The paraventricular nucleus also contains important endocrine-related neurons, composed of two major parts: a lateral part containing magnocellular neurons and a medial part with parvocellular neurons. The parvocellular neurosecretory neurons project into the median eminence, where their axon terminals release very critical hormones directly into the hypothalamic-pituitary portal system. The hormones include TRH, GnRH, growth hormone–releasing hormone (GHRH), corticotropin-releasing hormone (CRH), and somatostatin. TRH neurons are in the medial and periventricular parvocellular subdivisions, which are the main hypophysiotropic neurons regulating the HPT axis.[6] A few TRH-producing neurons are also located in the anterior subdivision of the parvocellular neurons, but they are functionally distinct from the above-mentioned hypophysiotropic neurons and their secreted TRH exerts other effects on the central nervous system centered on food intake and thermoregulation.

The suprachiasmatic nucleus of the hypothalamus lies directly dorsal to the optic chiasm and optic tracts. This proximity permits afferents from the retina, as well as some fibers from visual pathways, which allows this nucleus to act as a dominant regulator of circadian rhythms and circardian variations of TRH/TSH release.

Tuberal nuclei control satiety and the hypothalamic-pituitary-gonadal (HPG) axis.

The posterior/mammillary nuclei are a component of the limbic system and play a role in recognition of memory.[4]

Median Eminence and Hypophyseal Portal System

The location of the median eminence places it in a central position to serve both as an afferent sensory organ and as a connecting link between the hypothalamus and the pituitary gland.[8] The hypophyseal portal system is a special and second portal system of the body, which allows the hypothalamus to secrete neurohormones in it and

further regulate anterior pituitary gland function. The hypothalamus nuclei, as mentioned above, secrete vesicles containing hypophysiotropic ("releasing") hormones (eg, TRH, GnRH, CRH, GHRH, somatostatin, and dopamine) at the portal capillary plexus, and these hormones reach the anterior pituitary gland by passing through the small fenestrated capillary endothelium. Arterial blood supply to the pituitary is derived from two branches of the internal carotid artery itself, called the superior and inferior hypophyseal arteries.[7]

Thyrotropin-Releasing Hormone

TRH, the short peptide hypophysiotropic hormone, is the tripeptide pyroGlu-His-Pro-NH2. The human TRH pre-prohormone gene encodes six copies of the TRH peptide sequence, which are then processed by two prohormone convertases, PC1 and PC2, carboxypeptidase E, and peptidylglycine α-amidating mono-oxygenase (PAM) enzymes before the final TRH molecule is formed.[8]

The Pituitary Part of the HPT Axis: Development and Anatomy

The pituitary gland, also called the master gland of body, is situated within the sella turcica ("Turkish saddle," because of its shape). Along with the hypothalamus, the pituitary gland orchestrates the structural integrity and function of endocrine glands of whole body.[8] The pituitary gland is contiguous with the hypothalamus via the pituitary stalk. The pituitary gland consists of the predominant anterior lobe, the posterior lobe, and a vestigial intermediate lobe.

All vertebrates have a pituitary gland, and its basic structure has remained essentially the same. The posterior lobe, or neurohypophysis, develops from the diencephalic floor of the brain and remains connected to the brain. The adenohypophysis/anterior part of the gland comprises around two-thirds of the whole pituitary gland and is derived from the oral ectoderm (Rathke's pouch) (from the adjacent ectoderm of the head or mouth). The sella turcica forms the thin bony roof of the sphenoid sinus and is located at the base of the skull. The optic chiasm is directly above the diaphragma sella and is located anterior to the pituitary stalk. The posterior pituitary gland, in contrast to the anterior pituitary, is directly innervated by the supraopticohypophyseal and tuberohypophyseal nerve tracts of the posterior stalk. The anterior pituitary gland consists of five differentiated cell types that secrete six hormones. Thyrotrophs (also called thyrotropes) are endocrine cells present in the anterior pituitary comprising less than 5% of the total adenohypophyseal cell population, and they produce TSH, in response to TRH from the hypothalamus, and regulate the function of the thyroid gland. Thyrotrophs are discussed in detail in a separate chapter. Blood supply of the pituitary is described above.

TSH is a 28-kD glycoprotein hormone secreted from thyrotrophs of the pituitary gland and is made up of two subunits, alpha and beta. The alpha subunit has a common structure among follicle-stimulating hormone, luteinizing hormone, and human chorionic gonadotropin. The beta subunit, on the other hand, is specific for TSH only.

Thyroid Glandular Part of the HPT Axis: Development and Anatomy

Origin-wise the thyroid gland derives from a diverticulum of the pharynx. The gland originates at the base of the tongue and then during further development migrates downward. Its relation with the base of the tongue is evidenced by and related to the foramen cecum. This downward course is along the midline and reaches the final place nearby the trachea in the center of the neck. This downward course is finally indicated by a duct called the thyroglossal duct. Many a time, few remnants of this duct remain prominent (or fail to disappear) into adult life, where they produce mucus-filled cysts called thyroglossal cysts.

The adult or developed thyroid has an appearance of a Greek shield as described in ancient literature and is composed of two lobes which are

pear shaped, surrounding the two sides of the trachea. They are joined together by an isthmus. The adult gland weighs around 15 g. In size and weight, it is the largest endocrine gland of the human body. In half of adults, a median lobe can be found arising from the isthmus, which should be noted during surgery and never to be missed in total thyroidectomy.[9] Apart from this median lobe during surgery, the two other important things to note by a surgeon are the four parathyroid glands at each pole of the two thyroid lobes and the recurrent laryngeal nerve. The gland is encapsulated by connective tissue, invaginates the gland many times, and forms small lobules. One lobule is made up of around 30 follicles and each follicle represents a fully independent functional unit of the thyroid gland. The adult thyroid gland contains around 3 million follicles.[10] Each follicle has a single line of epithelium, which are called thyroid follicular cells or thyrocytes. The thyroid gland also contains neuroendocrine C cells, also called parafollicular C cells, and they comprise only 0.1 % of the gland. C cells are derived from the ultimobranchial body, (from the fourth pharyngeal pouch) and later on migrates to the thyroid gland.[11] The apex of the thyroid follicular cells is pointed toward the lumen of the follicle, which contains colloid (containing a large amount of protein called thyroglobulin), while the basolateral surface is directed toward the interfollicular space[12] and contains the TSH receptors.

Blood supply of the thyroid gland varies significantly, but generally it is supplied by the superior thyroid artery, inferior thyroid artery, and lowest accessory thyroid arteries.[13] The circulation is markedly increased in Graves' disease and can be felt over the gland or auscultated also. The venous drainage of the thyroid gland drains via superior, lateral, and inferior thyroid veins. The oncologically significant lymphatic drain occurs into cervical lymph nodes.

Functional Part of HPT Axis

After increase in concentration of TRH in humans, serum TSH levels rise within a few minutes only[14] and is followed by a rise in serum thyroid hormone levels. TRH action on the pituitary is blocked by previous treatment with thyroid hormone, which forms an important negative feedback control of pituitary TSH release. TRH is also a potent prolactin-releasing factor (PRF) and involved in the regulation of prolactin (PRL) secretion. Stimulatory effects of TRH are initiated by binding of the peptide to its G protein coupled receptor on the cell membrane of the thyrotrophs.[15] Thyroid hormone itself and somatostatin antagonize the effects of TRH and interfere with its binding also. Binding on these receptors starts a cascade of intracellular reactions and leads to secretion and glycosylation of TSH hormone.[16]

So, regulation of thyrotropin release is controlled by these two related elements: negative feedback by thyroid hormone and open-loop neural control by hypothalamic hypophysiotropic factors (Figure 1–1).

TSH secreted in blood, via circulation, then binds to a specific G protein coupled receptor on the basolateral membrane of thyroid follicular cells, which is followed by intracellular cascade of reactions, and regulates the hormone synthesis function of the thyroid gland.[16]

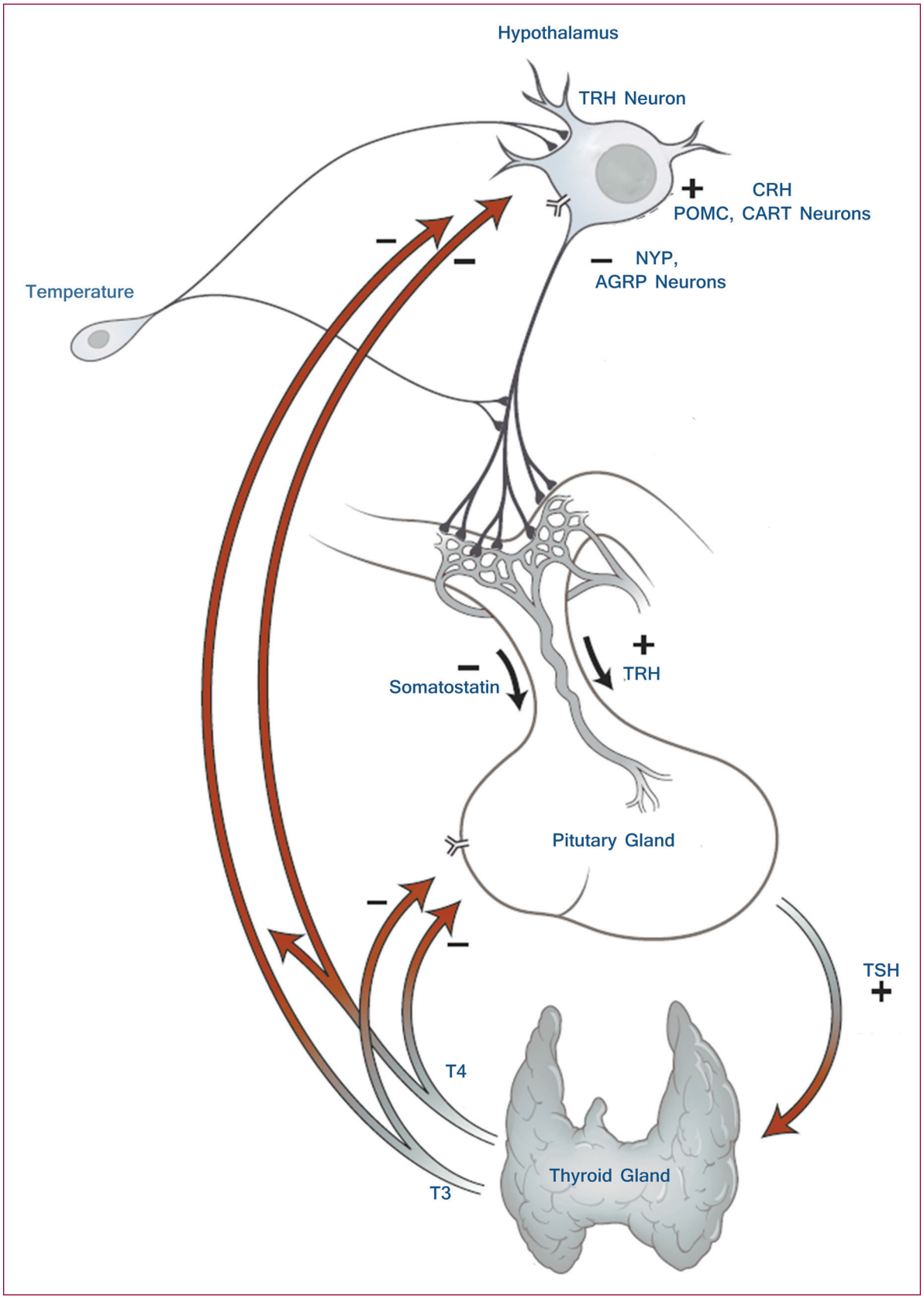

Figure 1–1. Regulation of the HTP axis. *Source:* adapted from Melmed S, Polonsky K, Larsen P, Kronenberg H. *Williams Textbook of Endocrinology.* 13th ed. Elsevier; 2016:212–214.

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2

ANATOMY AND PATHOLOGY OF THYROTROPHS

Shashank R. Joshi and Nikita Srinivasan

Introduction

The pituitary gland, also called the master gland of the body is situated within the sella turcica ("Turkish" saddle, because of its shape). The name "pituitary" was given from the Greek word *ptuo* and Latin word *pituita*, which mean phlegm, reflecting its nasopharyngeal origin. Along with the hypothalamus, the pituitary gland orchestrates the structural integrity and function of endocrine glands of whole body.[1] The pituitary gland is contiguous with the hypothalamus via the pituitary stalk. The anterior pituitary gland consists of five differentiated cell types that secrete six hormones. Thyrotrophs (also called thyrotropes) are endocrine cells present in the anterior pituitary which produce thyroid stimulating hormone (TSH), in response to thyrotropin releasing hormone (TRH) from the hypothalamus, and regulate the function of the thyroid gland. The hypothalamic-pituitary-thyroid (HPT) system plays a very important role in intrauterine development, growth, and cell level basal metabolism. This is done by regulating thyroid hormone availability, and its action is controlled by many complex mechanisms at the cellular targets.

Anatomy

The pituitary gland consists of the predominant anterior lobe, the posterior lobe, and a vestigial intermediate lobe. The anterior part of the gland comprises around two-thirds of the whole pituitary gland and is derived from the oral ectoderm (Rathke's pouch), while the posterior pituitary gland is derived from the diencephalon. The sella turcica forms the thin bony roof of the sphenoid sinus and is located at the base of the skull. The optic chiasm is directly above the diaphragma sella and is located anterior to the pituitary stalk. The posterior pituitary gland, in contrast to the anterior pituitary, is directly innervated by the supraopticohypophyseal and tuberohypophyseal nerve tracts of the posterior stalk.

Five differentiated hormone-secreting endocrine cell types are present in the anterior pituitary gland (Table 2–1)[1]:

1. **Corticotroph cells** secrete pro-opiomelanocortin (POMC) peptides, which includes adrenocorticotropic hormone (ACTH).
2. **Somatotroph cells** secrete growth hormone (GH).

Table 2–1. Five Differentiated Hormone-Secreting Endocrine Cell Types Present in the Anterior Pituitary Gland

Cell Type (Hormone)	Percent Cells	Chromosomal Gene Locus	Regulation	Affected Hormones	Effects
Somatotrophs (growth hormone) **GH**	45–50	17q	Growth hormone–releasing hormone (GHRH)	Insulin-like growth factor (IGF-1) and somatostatin	Linear and somatic growth. Metabolism (lipids and proteins carbohydrates)
Lactotrophs (prolactin) **PRL**	15–25	6	Thyrotropin releasing hormone (TRH) and estrogen	Dopamine	Lactation
Gonadotrophs (luteinizing hormone and follicle stimulating hormone) **FSH/LH**	10	β-11p; β-19q	Gonadotropin releasing hormone (GnRH) Estrogen late follicular phase of menstrual cycle	Estrogen Progesterone Testosterone (on FSH) Inhibin	Sex steroids production. Folliculogenesis and ovulation in female, spermatogenesis in male.
Thyrotrophs (thyroid stimulating hormone) **TSH**	5	α-6q; β-1p	TRH	T4, T3, Somatostatin	Thyroid hormone production
Corticotrophs (adrenocortico-tropin) **ACTH**	15–20	2p	Corticotropin releasing hormone (CRH)	Cortisol	Glucocorticoid and dehydroepiandros-terone (DHEA) production

3. **Thyrotroph cells** secrete the common glycoprotein α-subunit and the specific TSH (thyrotropin) β-subunit.
4. **Gonadotroph cells** secrete the α- and β-subunits for both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
5. **Lactotroph cells** secrete prolactin (PRL).

Each cell type is under highly specific signal controls from the hypothalamus and other hormonal, biochemical, or genetic signals.

Arrangement of cells: Secretory cells of the anterior pituitary are generally zonal in distribution. This is most evident in horizontal sections, in which the gland can be divided into a midline "mucoid wedge" and lateral "wings"[2] (Figure 2–1).

Thyrotroph Cells

The earliest light microscopic cell staining studies differentiated all pituitary cell types by their reactions with different dyes. Trichrome stains differentiated three types of cells. The red cells were called acidophils, the blue cells were called basophils, and the colorless cells were called chromophobes. Thyrotrophs are basophils and stain with the PAS (**periodic acid Schiff)** reagent. Thyrotrophs are one of the least common secretory cells of the pituitary gland and comprise approximately 5% of the total secretory anterior pituitary cells[1] (Figure 2–2). They are located mostly in the anteromedial areas of the pituitary gland. Thyrotrophs are identified by their content of very small

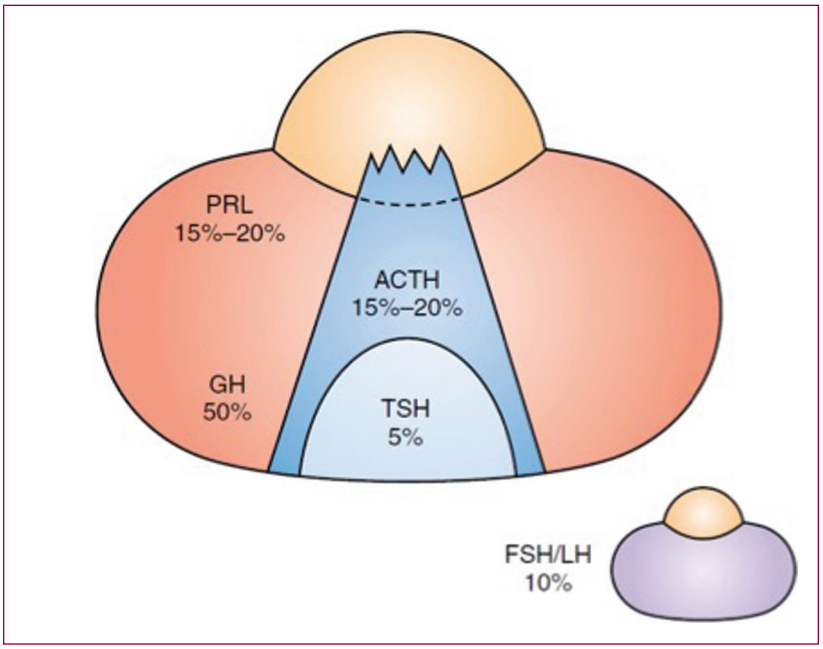

Figure 2–1. Schematic depiction of the distribution of secretory cells in the normal pituitary. Note the central mucoid wedge and the lateral wings. Gonadotroph cells are generally distributed widely (*inset*).[2]

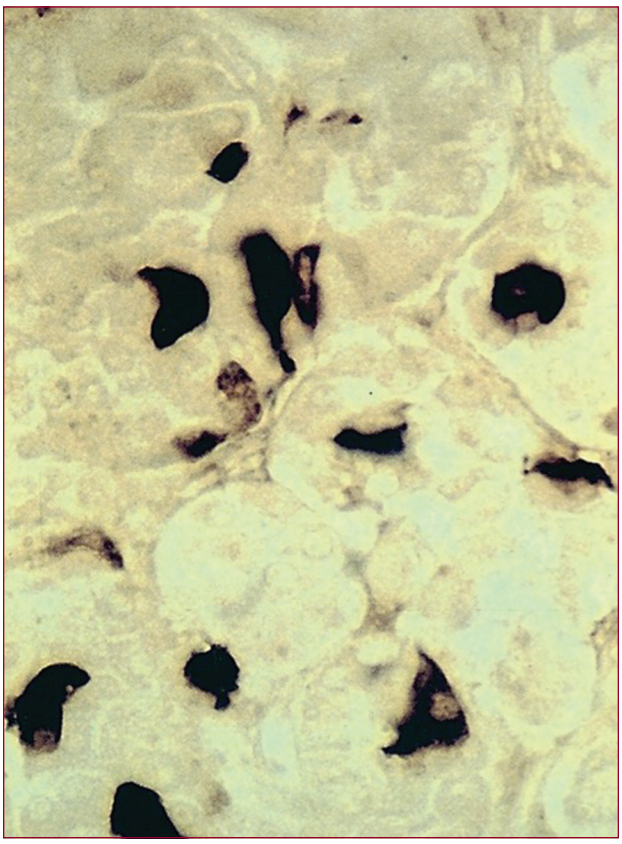

Figure 2–2. Normal thyrotrophs have angular cell bodies with elongated processes.[1] [From Asa S. L. (1997). Tumors of the pituitary gland. In J. Rosai (Ed.), *Atlas of tumor pathology*, series III, fascicle 22 (p. 19). Washington, DC: Armed Forces Institute of Pathology.]

secretory granules (100–150 nm in diameter) and dilated profiles of rough endoplasmic reticulum. They are smaller than the other cell types and are irregularly shaped with flattened nuclei and relatively small secretory granules. They secrete TSH hormone.

TSH activity from the pituitary gland was first identified by Eduard Uhlenhuth in 1926. He showed that injecting bovine pituitary gland extract causes enlargement of thyroid gland follicular cells. TSH as a hormone was purified in the 1960s and found to have two subunits.[3]

TRH secreted by neurons in the paraventricular nucleus of the hypothalamus stimulates TSH secretion from thyrotrophs.[4] TSH is a glycoprotein hormone comprising a 28-kDa heterodimer of two subunits, α and β.[5] The α-subunit is common to hormones like TSH, LH, FSH, and **human chorionic gonadotropin** (hCG), whereas the β-subunit is unique to TSH and it confers specificity of TSH action separately from other hormones. Production of the mature heterodimeric TSH molecule requires complex co-translational glycosylation and folding of nascent α- and β-subunits.[6] Appropriate glycosylation is required for accurate molecular folding and subsequent combination of α- and β-subunits within the rough endoplasmic reticulum and Golgi apparatus. This TSH glycosylation is regulated by both TRH and T3 in opposite directions for maintaining the negative and positive feedbacks of the HPT axis. Increased TRH or low T3 level increases oligosaccharide addition to the TSH molecule.[7]

Disorders of Thyrotrophs and TSH Secretion

TSH Deficiency

TSH deficiency is most commonly seen as a part of pan-hypopituitarism. It can be defects in development of the whole pituitary gland or follow surgical removal of the gland or part of it. Pituitary damage may result in functional TSH deficiency, often without a clearly demonstrable reduction in serum TSH levels.

Congenital isolated TSH deficiency, a very rare condition, may arise from mutational defects of either the TSH hormone or TRH receptor genes. Cell differentiation in the developing pituitary gland is affected by genetic disorders of pituitary gland development. They give rise to TSH deficiency as a component of multiple pituitary hormone deficiencies. These genes with mutations include LHX3, PROP1, and POU1F1.[1]

Clinical Features of TSH Deficiency

The consequences of TSH deficiency are similar to features of thyroid hormone deficiency, which in childhood can cause physical and mental growth retardation, while in adults it causes multiple clinical features of hypothyroidism, including low **basal metabolic rate**, weight gain, hypothermia, constipation, fluid retention, hair and skin changes, or frank myxedema. They will be discussed in detail in coming chapters.

Assessment of the HPT Axis and TSH Deficiency

Most thyrotroph disorders can be diagnosed by measuring basal TSH and thyroid hormone levels. TSH measurement is not helpful in diagnosing central hypothyroidism, which is identified by concurrent measurement of thyroid hormone levels. However, only around one-third of patients with secondary hypothyroidism have low TSH levels.[8] The deficiency is usually associated with low T4 hormone levels along with low, normal, or (rarely) mildly elevated TSH levels (a similar profile may be seen in critically ill patients).

However, a TRH stimulation test may be required to effectively assess the integrity of the HPT axis.[9] In this test, intravenous TRH (200–500 μg) is given and TSH levels are measured regularly at 15 minutes before administration and at 0, 15, 30, 60, and 120 minutes.

In normal persons, TSH levels rise and may peak up to 22-fold higher than basal levels after 30 minutes.[10] Also after administration of T3 hor-

mone, the basal TSH levels fall, and TRH-stimulated TSH levels are also attenuated.

In subjects with secondary hypothyroidism due to any pituitary disease, TSH levels fail to increase in response to TRH administration.

Thyrotropin-Secreting Pituitary Tumors[11]

The identification of thyrotropin-secreting pituitary adenomas (TSPAs) depends mainly on the presence of raised serum thyroid hormones along with increased or normal TSH levels, for which brain imaging helps sometimes. The combination of hyperthyroidism, a pituitary mass, and excessive TSH production demonstrated using a TSH bioassay was first described in 1960.[12]

They are usually very rare tumors and represent only 0.6% of the adenomas found in postmortem cases,[13] but around 0.9% to 1.5% of pituitary adenomas in surgical cases.[14,15] TSH-secreting tumors, similar to the rest of the pituitary adenomas, are usually monoclonal in origin.[16] Still, the exact mechanisms for pituitary cell transformation into adenoma remain unidentified.

A number of etiologic factors are proposed which either alone or with other of these factors interact and eventually transform and promote tumor cell proliferation. They include underexpression of tumor suppressor genes, mostly those involved in cell cycle regulation, mutations in pituitary tumor-susceptibility genes, overactivation of cell-signaling pathways for proliferation, and dysfunctioning of hormone-regulatory pathways.[17]

Pituitary Thyrotroph Hyperplasia in Long-Standing Hypothyroidism

Hypothyroidism not only leads to loss of thyroid hormone feedback inhibition to TRH and TSH hypersecretion, but also leads to proliferation of TSH-secreting cells which can cause overt compensatory hyperplasia of thyrotrophs. Sometimes thyrotroph hyperplasia is associated with prolactin cell hyperplasia and hyperprolactinemia, mostly due to sustained hypothalamic TRH stimulation.[18] Histological staining shows the normal anterior pituitary acinar pattern, but each acini are larger, and contain many large pale cells called *thyroidectomy cells*. They have eccentric nuclei and abundant vacuolated cytoplasm in them; characteristically present in the pituitaries of patients with untreated protracted hypothyroidism and experimentally induced hypothyroid rats. These hyperplasic cells probably derive from division of pre-existing thyrotrophs as well as from differentiation of stem cells into mature TSH-secreting cells. Many times in addition to this, growth hormone and TSH bihormonal cells, which are also called *thyrosomatotrophs*, have been identified in similar patients or rats, supporting the hypothesis of transdifferentiation of somatotrophs to thyrotrophs, which leads to formation of thyroid cell hyperplasia.[19] Rarely, thyrotroph hyperplasia to adenoma transformation can occur, and has been reported in a few cases with long-standing untreated hypothyroidism.[20,21]

Impaired Thyroid Hormone Negative Feedback

Negative feedback of T3, T4 thyroid hormones on TRH or TSH secretion can be defective and may be responsible for pathogenesis of TSH-secreting tumors. TSH levels do not suppress after administration of thyroid hormones in most patients of TSPA. One possible explanation can be increase in expression or activity of deiodinase enzymes, which leads to reduced T3 hormone concentration in the adenoma.

Other causes include[11]:

- Hypothalamic signaling is altered by increased hypothalamic hormone stimulation or, alternatively, defective action of inhibitory hypothalamic hormones.
- TRH or its receptor mutations lead to abnormally increased activation of the TRH receptor or of its signal transduction pathway.

- Dopamine (DA) receptor blockers like metoclopramide and domperidone can increase TSH concentration both in euthyroid and hypothyroid subjects.
- Loss of heterozygosity at the somatostatin SSTR5 locus has been described in one TSH secreting adenoma that was associated with unusual tumor aggressiveness and resistance to treatment with somatostatin analogues.[21]
- Multiple mechanisms via alterations in pituitary transcription factors like Pit-1; familial/genetic syndromes (MEN 1); multiple oncogenes, tumor suppressor genes, and growth factors; or abnormal cell signaling pathways like I3K/AKT/mTOR have been studied for their pathogenesis in TSPA.

Clinical Features

TSPA generally presents with hyperthyroidism without suppression of TSH levels along with diffusely enlarged goiter. The pituitary mass can cause compression effects like those on optic chiasma depending on size of adenoma. Co-secretion of GH or LH/FSH may be associated with TSPA and will manifest their other symptoms also.

Management

With increased awareness of the disease and improvement in diagnostic techniques, these tumors are readily detected. Earlier diagnosis at initial stage of tumor growth improves the long-term prognosis. Pituitary microsurgery is the mainstay of TSPA management, providing a good chance of remission for early small size tumors, or improvement of symptoms by debulking larger tumors. Somatostatin analogues can also be used as second-line management after unsuccessful surgery or relapse, in view of their high effectiveness in controlling tumoral hypersecretion and tumor growth. Radiotherapy is usually reserved for somatostatin unresponsive cases.

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