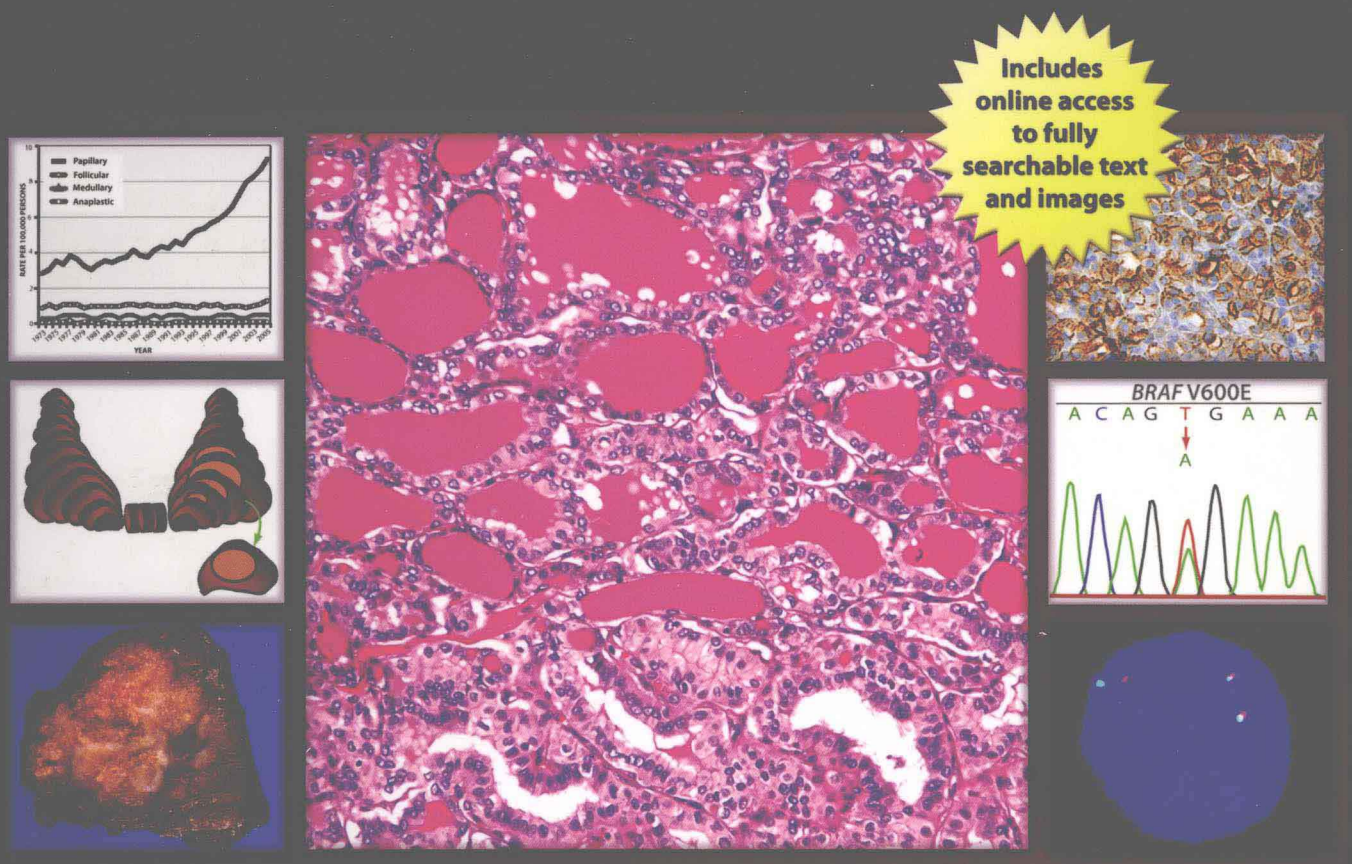
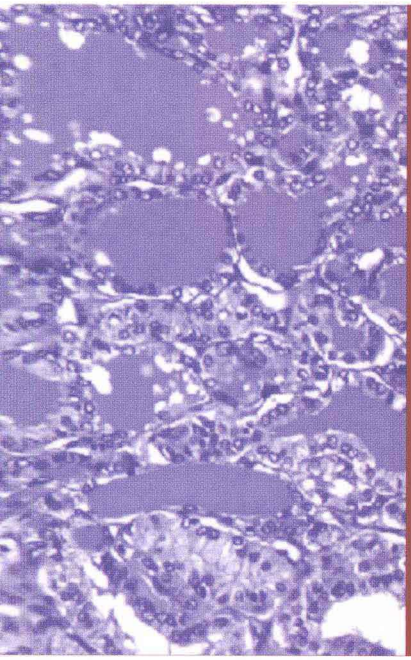
# Diagnostic Pathology and Molecular Genetics of the Thyroid

*A comprehensive guide for practicing thyroid pathology*

**Yuri E. Nikiforov**
Paul W. Biddinger
Lester D.R. Thompson




Wolters Kluwer Health | Lippincott Williams & Wilkins



# Diagnostic Pathology and Molecular Genetics of the Thyroid


EDITORS

**Yuri E. Nikiforov, MD, PhD**
Professor of Pathology
Director, Division of Molecular Anatomic Pathology
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

**Paul W. Biddinger, MD**
Professor of Pathology
Chief of Anatomic Pathology
Department of Pathology
Medical College of Georgia
Augusta, Georgia

**Lester D.R. Thompson, MD, FASCP, FCAP**
Consultant Pathologist
Department of Pathology
Southern California Permanente Medical Group
Woodland Hills, California

**Drawings by Marina N. Nikiforova, MD and Paul W. Biddinger, MD**



Wolters Kluwer Health | Lippincott Williams & Wilkins
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

*Acquisitions Editor:* Jonathan W. Pine, Jr.
*Managing Editor:* Sirkka E. Howes
*Marketing Manager:* Angela Panetta
*Associate Production Manager:* Kevin P. Johnson
*Creative Director:* Doug Smock
*Compositor:* Maryland Composition/ASI



351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106



*Printed in China*

**Library of Congress Cataloging-in-Publication Data**

Diagnostic surgical pathology and molecular genetics of the thyroid / [edited by] Yuri Nikiforov.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-7817-7459-8
1. Thyroid gland—Cancer—Diagnosis. 2. Thyroid gland—Cancer—Molecular aspects.
3. Pathology, Surgical. I. Nikiforov, Yuri.
[DNLM: 1. Thyroid Neoplasms. 2. Pathology, Surgical—methods. 3. Thyroid Diseases. WK 270 D536 2010]
RC280.T6D53 2010
616.99'444—dc22

2008039972



To purchase additional copies of this book, call our customer service department at **(800) 638-3030** or fax orders to **(301) 824-7390**. International customers should call **(301) 714-2324.**

***Visit Lippincott Williams & Wilkins on the Internet: http://www.LWW.com.*** Lippincott Williams & Wilkins customer service representatives are available from 8:30 am to 6:00 pm, EST.

CCS0109

To my parents, who live far away but who are always so close in my heart.
In loving memory of my mother-in-law, who never stopped believing in me.
To my wife and children, whose love, support, and closeness
are the biggest treasure I've ever had.

*Yuri E. Nikiforov*

To Leslie for her support, patience, and enduring love.

*Paul W. Biddinger*

Thousands brush your development as a physician;
Hundreds provide detail to your world as a pathologist;
Dozens contribute color to your knowledge and skill;
Few challenge your mind to achieve contrast;
Only one sees and creates the whole picture:
My Precious Sweet P – My Whole Wide World.

*Lester D. R. Thompson*

# Contributors

**Paul W. Biddinger, MD**
Professor of Pathology
Chief of Anatomic Pathology
Department of Pathology
Medical College of Georgia
Augusta, Georgia

**Peter Kopp, MD**
Associate Professor
Director ad interim Center for Genetic Medicine
Division of Endocrinology, Metabolism and Molecular Medicine
Northwestern University
Chicago, Illinois

**Yuri E. Nikiforov, MD, PhD**
Professor of Pathology
Director, Division of Molecular Anatomic Pathology
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

**Marina N. Nikiforova, MD**
Assistant Professor
Associate Director, Molecular Anatomic Pathology
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

**N. Paul Ohori, MD**
Professor of Pathology
Medical Director of Cytopathology and Cytopathology Fellowship Program
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

**Raja R. Seethala, MD, FASCP**
Assistant Professor
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

**Lester D.R. Thompson, MD, FASCP, FCAP**
Consultant Pathologist
Department of Pathology
Southern California Permanente Medical Group
Woodland Hills, California

# Preface

Since the early 1990s, when several excellent textbooks devoted to thyroid pathology were published, the pathologic criteria for many thyroid lesions have been refined, new immunohistochemical markers have emerged, and a variety of novel genetic alterations responsible for the familial and sporadic forms of thyroid cancer have been discovered. Although some of these updates can be found in book chapters devoted to the pathology of thyroid tumors or nonneoplastic conditions, we felt a strong need for a book that is focused solely on the thyroid and provides the most current and complete information on nonneoplastic and neoplastic thyroid diseases. Most importantly, as molecular genetics has penetrated all fields of medicine and impacts more and more significantly on the practice of pathology, we believe that our times call for a book that provides a comprehensive description of classic morphology and molecular genetics side by side and in a single volume. In addition, as the incidence of thyroid cancer has increased dramatically in the United Sates and many other countries in the world over the last three decades, it would be beneficial to readers to find a description of the current knowledge of epidemiology, etiology, and molecular pathogenesis of each cancer type integrated with the discussion of the disease morphology.

To achieve these goals, most chapters in the book have a uniform structure and include sections dedicated to the incidence and epidemiology of a particular disease, etiology, pathogenesis and molecular genetics, and clinical presentation and imaging, followed by sections providing detailed discussions of gross and microscopic findings, as well as sections on immunohistochemistry, molecular diagnostics, electron microscopy, cytology, differential diagnosis, and treatment and prognosis. We expect that this organizational structure will allow readers to find all information pertinent to a particular disease in a single chapter and also easily search for a specific aspect of the disease, such as microscopic diagnostic features or immunohistochemistry, without reading the entire chapter.

Our intention was to provide a highly illustrated book, with ample illustrations of gross and microscopic features of every common thyroid disease, as well as drawings and diagrams summarizing diagnostic features and molecular characteristics. Two chapters are dedicated exclusively to the description of rare thyroid tumors. A separate chapter describes the principles of molecular diagnostics for those readers who wish to learn more about the general and technical aspects of molecular pathology.

We believe that the book will be useful to pathology trainees and practicing pathologists, endocrinologists, endocrine and head and neck surgeons, radiologists, internists, and scientists interested in thyroid diseases.

*Yuri E. Nikiforov, MD, PhD*
*Paul W. Biddinger, MD*
*Lester D.R. Thompson, MD*

# Acknowledgments

The book contains illustrations provided by many individuals, and we thank them for their extremely valuable contributions. Dr. Leon Barnes, Professor of Pathology at the University of Pittsburgh Medical Center generously allowed us to use his outstanding collection of gross images and rare thyroid cases; Dr. Mitchell E. Tublin, Associate Professor of Radiology at the University of Pittsburgh Medical Center contributed ultrasound images; and Dr. James M. Mountz, Professor of Radiology at the University of Pittsburgh Medical Center provided thyroid scan images for the book. The following pathologists shared rare cases of microscopic and ultrastructural images used in the book:

Dr. J. Aidan Carney, Mayo Clinic, Rochester, Minnesota
Dr. Vincenzo Eusebi, University of Bologna, Bologna, Italy
Drs. Ronald Ghossein and JinRu Shia, Memorial Sloan-Kettering Cancer Center, New York, New York
Dr. A. Nihan Haberal, Baskent University School of Medicine, Ankara, Turkey
Dr. Clara S. Heffess, Endocrine Division, Armed Forces Institute of Pathology, Washington, DC
Dr. Ricardo V. Lloyd, Mayo Clinic, Rochester, Minnesota
Dr. Vânia Nosé, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts
Dr. Robert L. Peel, Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
Dr. Ales Ryška, Department of Pathology, Charles University Medical Faculty Hospital, Hradec Králové, Czech Republic
Dr. Manuel Sobrinho-Simões, IPATIMUP, Porto, Portugal
Dr. Giovanni Tallini, University of Bologna School of Medicine, Bologna, Italy
Drs. Marco Volante and Mauro Papotti, Department of Clinical and Biological Sciences, University of Turin, Italy.

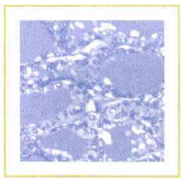
The authors would like to thank the staff members of the Molecular Anatomic Pathology Laboratory, Electron Microscopy Laboratory, Immunohistochemistry Laboratory, and In Situ Hybridization Laboratory at the Department of Pathology at the University of Pittsburgh Medical Center for help in preparing materials for the various illustrations. We would also like to thank Dr. Manoj Gandhi for fluorescence in situ hybridization images and Mr. Frank Fusco for selected gross images.

We would like to recognize Ms. Angelique M. Hudec in Dr. Yuri Nikiforov's office for her valuable help in coordinating the work on the book and her assistance in formatting and handling various book chapters. Our special thanks to Ms. Tanya Nikiforova for her assistance with editing selected chapters of the book.

We would like to express our appreciation to Mr. Jonathan W. Pine, Jr., Senior Executive Editor at Lippincott Williams & Wilkins for his enthusiasm and invaluable help with having this book published; Ms. Natalie La Roche and Mrs. Heidi Grauel from Maryland Composition; and Ms. Sirkka Howes and Mr. Kevin Johnson from Lippincott Williams & Wilkins for their professionalism and assistance during the production of this book.

We would also like to acknowledge Dr. George K. Michalopoulos, Chair of the Department of Pathology at the University of Pittsburgh School of Medicine; Dr. Samuel A. Yousem, Vice Chair for Anatomic Pathology at the University of Pittsburgh School of Medicine; Dr. Stephen Peiper, Chair of the Department of Pathology at the Medical College of Georgia; and Dr. Jeffrey D. Shiffer, Chief of the Department of Pathology at the Woodland Hills Medical Center for creating a supportive academic environment that enabled us to accomplish this challenging project.

# Contents



# Chapter 1
# Normal Anatomy and Histology

**Paul W. Biddinger**

Descriptions of the thyroid and related diseases date back to antiquity. The thyroid was identified by European anatomists during the Renaissance including Vesalius who described the *glandulas ad laryngis radicem adnatas* in Book Six of his famous work *De Humani Corporis Fabrica* of 1543. Thomas Wharton is generally credited with first using the term thyroid gland in his 1656 treatise *Adenographia*. His use of this name seems to be due to the gland's proximity to the thyroid cartilage. The term thyroid has been applied to the major cartilage of the larynx dating back at least to the time of Galen. Thyroid derives from the Greek words *thyreos,* meaning shield, and *eidos,* meaning shape, form or likeness. The *thyreos* is a narrow, oblong military shield, and its name derives from *thyra*, the Greek word for door. The thyroid cartilage indeed has a shield-like appearance.

Wharton considered the thyroid to be a pair of glands and described them as resembling an oblong fig or pear. He thought their principal function was uptake of superfluous fluids of the recurrent nerve. Other putative functions included warming the adjacent cartilages, lubricating the larynx, and contributing to the roundness and beautification of the neck.[1] Considerable advances in our understanding of the thyroid gland have occurred since the 17th century.

## MACROANATOMY

### Basic Anatomy

The thyroid gland is located in the lower anterior region of the neck at the level of the fifth, sixth, and seventh vertebrae. It is a bilobed organ joined by an isthmus and encased in a thin fibrous capsule. The right and left lobes have a somewhat conical shape with convex anterior and lateral surfaces. The lobes tend to be about 4 to 5 cm in length, 2 to 3 cm in greatest transverse dimension, and 1.5 to 2 cm in greatest anterior-posterior dimension. The isthmus is about 1 cm in greatest transverse and vertical dimensions. The location of the isthmus is variable, but it usually joins the two lateral lobes at level of the second and third tracheal rings.

Approximately half of all thyroid glands exhibit a pyramidal lobe, with most studies reporting an incidence in the 30% to 75% range (Fig. 1.1).[2] Some of the variation in incidence may relate to the variable size and prominence of the lobe, and hence threshold of recognition. The pyramidal lobe represents the remnant of the inferior portion of the thyroglossal duct. The lobe extends superiorly from the isthmus and may be attached to the hyoid bone by fibrous tissue. Pyramidal lobes are more frequently attached to the left side of the isthmus and in some cases attach to the left lobe itself.[2]

The tubercle of Zuckerkandl is a focal enlargement along the lateral border of the lateral lobes that is commonly observed during thyroid surgery.[3] It ranges from a slight thickening to a nodular structure 1 cm or larger. It can be found on either side or bilaterally. It has utility as a surgical landmark, because the recurrent laryngeal nerve usually courses medially, sometimes in a cleft between the tubercle and the main substance of the lateral lobe. In addition, the superior parathyroid gland is commonly found just cephalad to the tubercle.

### *Normal Weight*

Studies examining the weight of normal thyroid glands, either by direct measurement or extrapolation from volume measurement, have yielded variable means and ranges, particularly the latter.[4–8] Distillation of these findings yields an average weight of about 18 g for adult males and 15 g for adult females. The reported distributions of thyroid weights tend to show a positive skew, with a broader range of weights above the mean than below. Most of the reported weights of normal adults lie within a range of 8 to 30 g. Glands with weights in excess of 50 g have been reported, but these outliers raise questions regarding their normal status. The glands of adult females tend to be smaller than adult males, but the differences are modest and the ranges mostly overlap. Some studies have shown a positive correlation between thyroid weight and body weight, body mass index, or age.[4–9] Body weight or body mass index tends to show stronger correlation than age, but overall these correlations are weak. Thyroid weight tends to show a progressive increase in childhood and adolescence, stability in early to mid adulthood, and gradual decline in older age.[7,8] An increase in thyroid size has been reported in pregnant women.[10,11] However, most cases of enlargement may reflect iodine deficiency as opposed to an invariable physiologic response to pregnancy.

### Anatomic Relationships

The medial surfaces of the lobes abut the thyroid cartilage of the larynx and superior aspect of the trachea. The apices of the lobes are located near the oblique line of the thyroid cartilage and the bases at the level of the fourth, fifth or sixth tracheal ring. The superomedial aspects of the lateral lobes are adjacent to the inferior pharyngeal constrictors and posterior portions of the cricothyroid muscles. The common carotid artery, internal jugular vein, and vagus nerve, encased within the carotid sheath, course along the posterolateral aspects of the lateral lobes (Fig. 1.2). The recurrent laryngeal nerves are located in the tracheoesophageal grooves in proximity to the posteromedial aspects of the lateral lobes. The superior branch of the external laryngeal nerve usually courses to the cricothyroid muscle immediately posterior to the superior poles of the lateral lobes.

The thyroid gland is encased by the pretracheal fascia, anchoring the gland to the trachea and correlating with the movement of the gland during swallowing. The sternothyroid muscle is located immediately anterior to the thyroid. Muscles anterior to the sternothyroid are the thyrohyoid, sternohyoid, superior belly of the omohyoid, and the anterior border of the sternocleidomastoid.

### Vascular Supply

The blood supply to the thyroid is via the right and left superior thyroid arteries and right and left inferior thyroid arteries (Fig. 1.3). The superior thyroid arteries derive from the external carotid arteries, and the inferior thyroid arteries derive from the subclavian arteries via the thyrocervical trunks. An inconstant artery, the thyroidea ima, occasionally arises from the brachiocephalic trunk, aortic arch, or left common carotid and ascends along the anterior midline of the trachea to reach the thyroid in

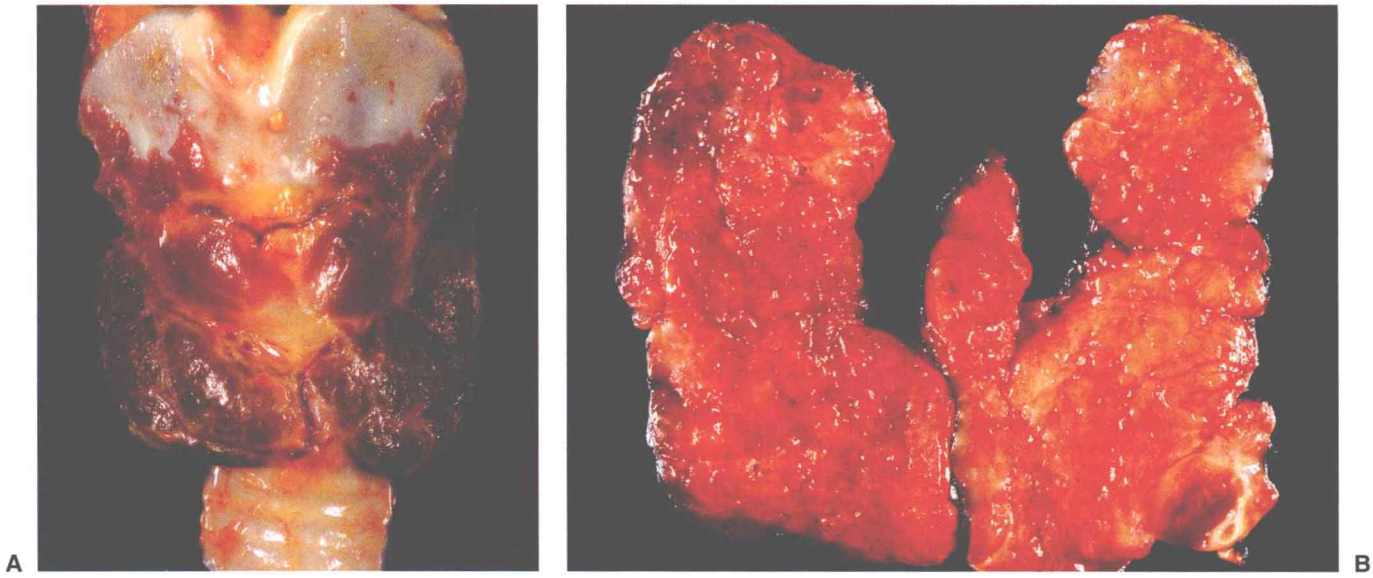



**FIGURE 1.1. Gross photographs of thyroid glands. (A)** Bilobed thyroid and its relationship to the trachea and thyroid cartilage. **(B)** Thyroid with prominent pyramidal lobe.

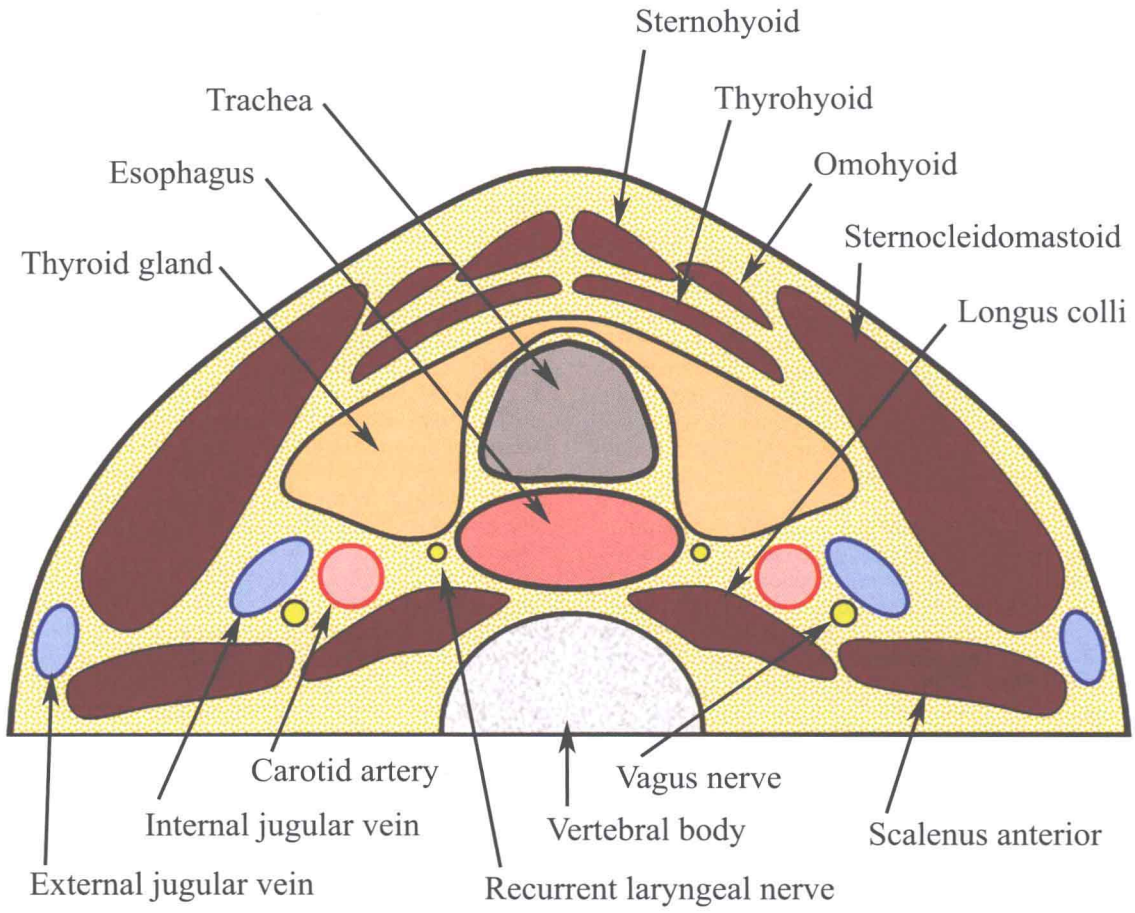



**FIGURE 1.2. Anatomic relationships of thyroid to other structures of neck at level of the fifth cervical vertebra.**

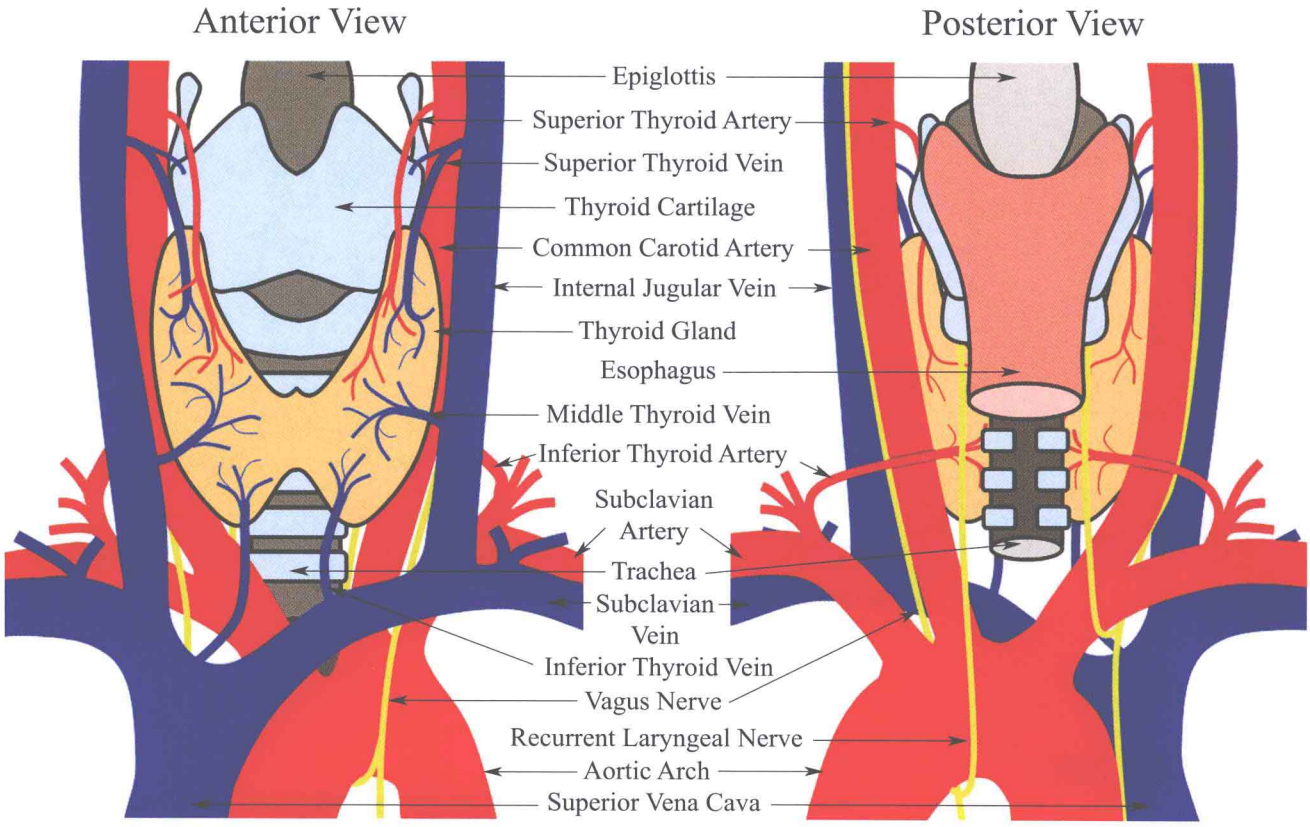



**FIGURE 1.3. Vascular supply of thyroid.**

the region of the isthmus. Venous drainage is via a plexus that leads to the superior, middle, and inferior thyroid veins. The superior and middle veins drain into the internal jugular veins, and the inferior veins join the brachiocephalic veins. A dense capillary plexus encompassing the follicles lies between the arterial and venous vessels.

## Lymphatic Drainage

The lymphatic drainage flows from vessels in the perifollicular connective tissue to a subcapsular network. Lymphatic vessels leave the gland in proximity to veins and extend to a number of regional lymph nodes (Fig. 1.4). The most proximate nodes are located in the anterior, or central, compartment of the neck and collectively compose the level VI nodes. These include those immediately adjacent to the thyroid gland (perithyroidal or pericapsular nodes) as well as prelaryngeal, pretracheal, and paratracheal lymph nodes. A midline prelaryngeal node found anterior to the cricothyroid membrane and superior to the isthmus is alternatively known as the Delphian node. Lymphatic drainage involves other regional lymph nodes, including the internal jugular (particularly levels III and IV), superior mediastinal, supraclavicular, spinal accessory, retropharyngeal, and to a limited extent, the submandibular and submental (level I) lymph nodes.

## Innervation

The thyroid is innervated by nerves originating from the superior and middle sympathetic cervical ganglia. These nerves release noradrenaline from interfollicular adrenergic nerve terminals.[12] Cholinergic nerve fibers also have been demonstrated in the thyroid, suggesting a role of the parasympathetic nervous system in the regulation of thyroid function.[13]

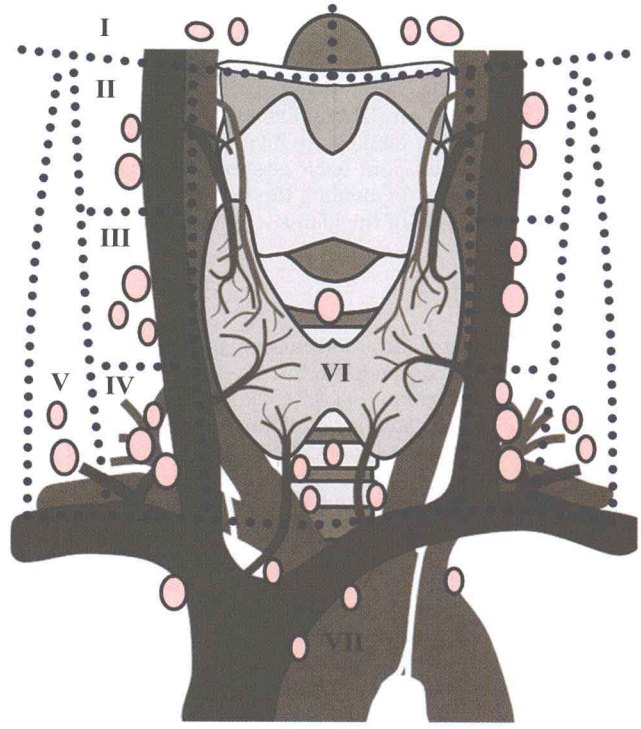



**FIGURE 1.4. Regional lymph nodes draining thyroid with designation of levels I–VII.** Level I, anterior triangle; level II, upper jugular; level III, middle jugular; level IV, lower jugular; level V, posterior triangle; level VI, central compartment; level VII, upper mediastinal.

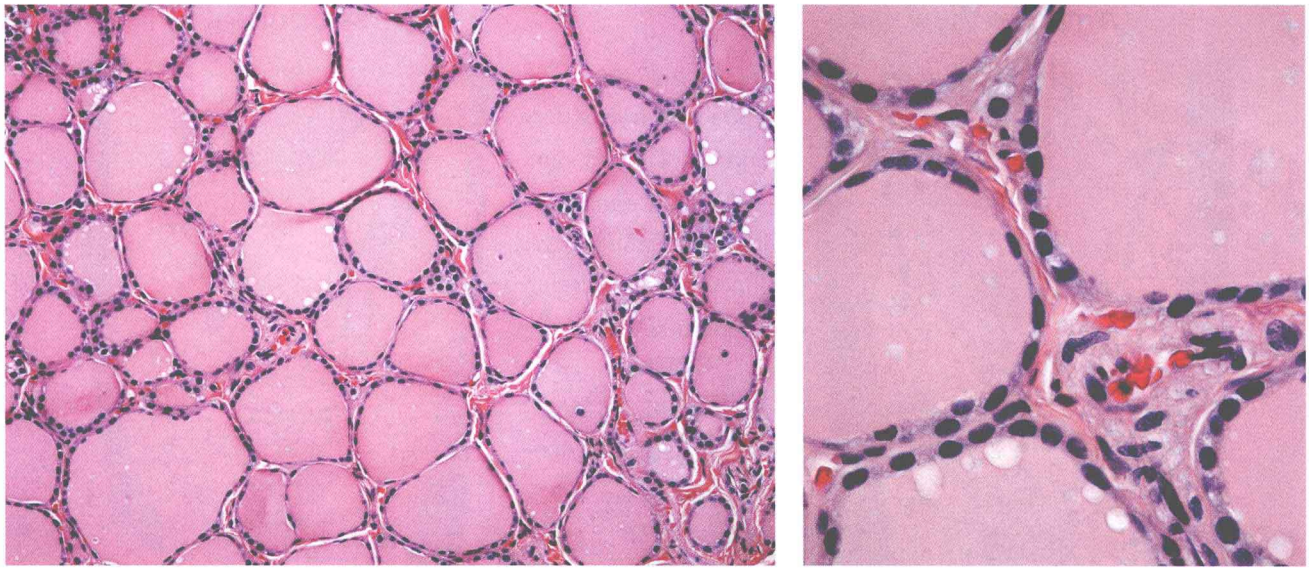


**FIGURE 1.5. Low- and high-power photomicrographs of normal follicles.**

## MICROANATOMY

### The Follicle

The follicle is the distinctive basic unit of the thyroid gland (Fig. 1.5). It is a spherical structure that usually has a polyhedral appearance due to the abutment of adjacent follicles. Each follicle is lined by a single layer of follicular cells with apices in contact with a central extracellular collection of colloid. The bases of the follicular cells lie along a thin fibrovascular stroma rich in a capillary network that encompasses the follicle. Normal thyroid glands usually contain between 500,000 to 1.5 million follicles.[7] The size of most normal follicles lies in the range of 50 to 500 μm with an average size of about 200 μm. Thyroid lobules are formed by groups of 20 to 40 follicles. The lobules are invested by a thin layer of fibrous connective tissue, and each is supplied by small arterial branch. The fibrous tissue dividing the lobules is eventually contiguous with the capsule of the gland.

#### *Colloid*

The colloid within the central follicular space contains thyroglobulin, an iodinated glycoprotein that is the precursor of triiodothyronine ($T_3$) and thyroxine ($T_4$). Colloid has an amorphous eosinophilic appearance and is highlighted by periodic acid–Schiff and thyroglobulin stains. The intensity of staining with hematoxylin and eosin can vary. The colloid in follicles with low activity usually shows more intense eosinophilia compared with colloid in follicles with a high level of hormone synthesis and release. Colloid in these latter follicles may also show scalloping or small vacuoles at the interface with follicular cells, a sign of endocytotic resorption. Larger, round to oval clear spaces are common within colloid, and some of these spaces may contain calcium oxalate crystals. Colloid generally has a homogeneous appearance. However, it can contain particulate-like clumps of material that are more intensely eosinophilic or slightly basophilic (Fig. 1.6). This histologic finding seems more common in active follicles, but it is unclear whether this is a manifestation of increased synthetic activity or a nonspecific artifact.[14]

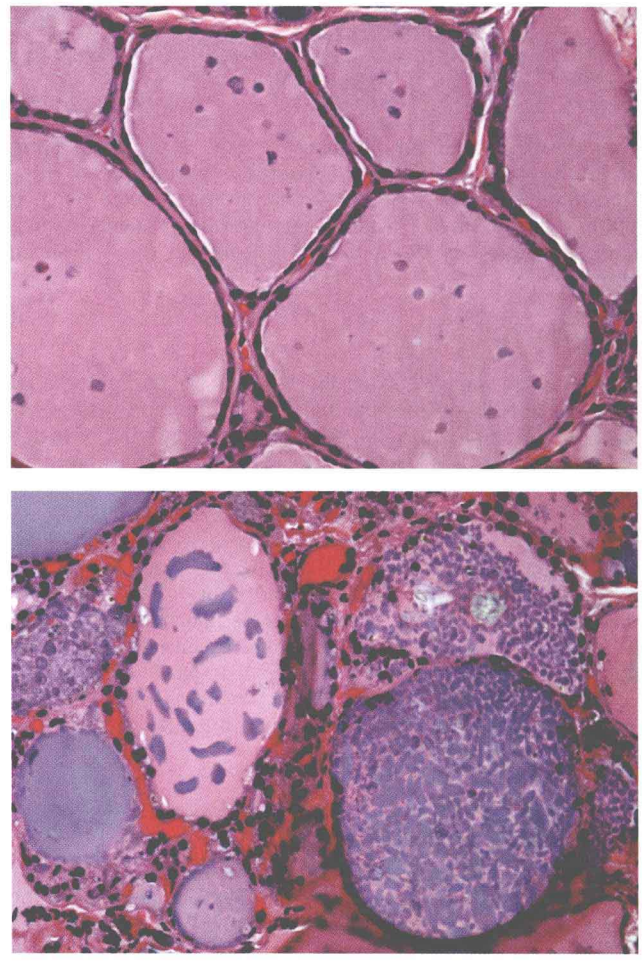


**FIGURE 1.6. Photomicrographs showing particulate material within colloid.** The top image shows a relatively subtle accumulation, while the bottom image is an extreme example of the phenomenon.

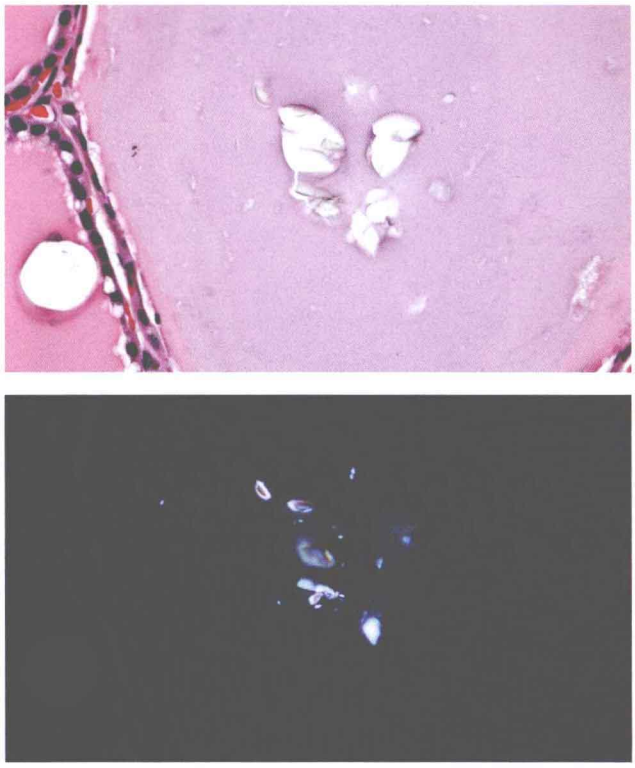


**FIGURE 1.7. Calcium oxalate crystals within follicles.** The crystals are birefringent when viewed through polarizing filters *(bottom)*.

### *Crystals*

The presence of calcium oxalate crystals within colloid is a common finding.[15,16] Crystals appear as small, clear, refractile foci and are birefringent when viewed with polarizing filters (Fig. 1.7). These crystals begin to appear during childhood and adolescence and become more prevalent as adults age. Calcium oxalate crystals have potential utility in distinguishing thyroid from parathyroid tissue.[17]

## Follicular Cells

Follicular cells have eosinophilic cytoplasm and round to slightly oval nuclei. The nuclei are located basally and have finely granular chromatin and inconspicuous nucleoli. Follicular cells vary in size and shape from low cuboidal to columnar, and this correlates with their level of thyroid hormone synthesis (Fig. 1.8). Cells with a low synthetic level have a low cuboidal appearance, and relatively abundant colloid occupies the lumen. This appearance of follicles is sometimes designated as the resting state. In contrast, follicular cells stimulated to produce more thyroid hormone exhibit columnar morphology. Histologic sections of normal adult thyroid glands usually show follicular cells with cuboidal to low cuboidal features.

### *Ultrastructure*

Ultrastructural examination of follicular cells reveals junctional complexes of desmosomes and terminal bars linking cells along their lateral borders near the apices. The bases of the cells abut a basal lamina that separates them from the interstitial stroma and fenestrated capillary network (Fig. 1.9). The nuclei are basally located. Granular endoplasmic reticulum and mitochondria are readily identifiable components of the cytoplasm. The supranuclear region contains a Golgi complex that increases in prominence with increased activity. The apical region contains Golgi-derived dense secretory vacuoles that transport glycoproteins to the plasmalemma for exocytosis into the follicular lumen. Lysosomes are prominent cytoplasmic components. This includes both primary and secondary lysosomes. The latter, also known as phagolysosomes, represents the fusion of primary lysosomes with colloid taken into the cytoplasm by endocytosis. Numerous apical microvilli are present, their length increasing when hormonal synthesis is stimulated.

### *Immunohistochemistry*

Follicular cells exhibit cytoplasmic positivity in sections immunohistochemically stained for thyroglobulin and low molecular weight cytokeratins (Fig. 1.10).[18–21] Coexpression of vimentin has also been noted.[18–20] Normal follicular cells express transcription factors including thyroid transcription factor-1 (TTF-1), TTF-2, and PAX8.[22,23] Thyrotropin receptor and thyroperoxidase (TPO) can also be demonstrated immunohistochemically in normal follicular cells.[22,24,25] Growth factors and their receptors are also expressed, including epidermal growth factor (EGF), transforming growth factor-alpha (EGF-α), and epidermal growth factor receptor (EGF-R) (Table 1.1).[26,27]

## C Cells

C cells, also known as parafollicular cells, are another component of the follicle. These cells, which produce calcitonin, are found singly or in small groups dispersed between or peripheral to the

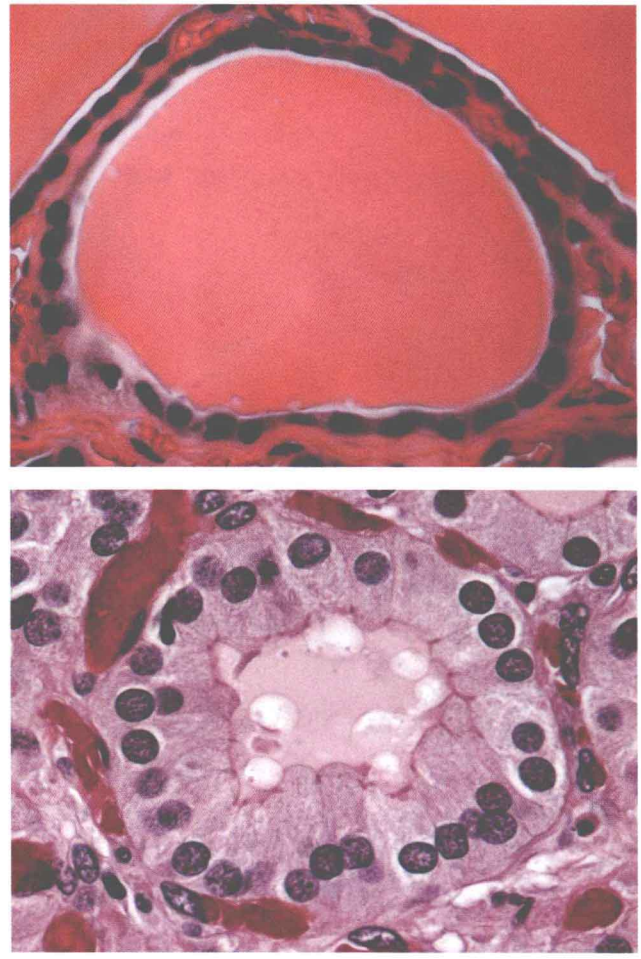


**FIGURE 1.8. Photomicrographs of cuboidal *(top)* and columnar *(bottom)* follicular cells.** The columnar cells are from a case of diffuse toxic hyperplasia (Graves disease).

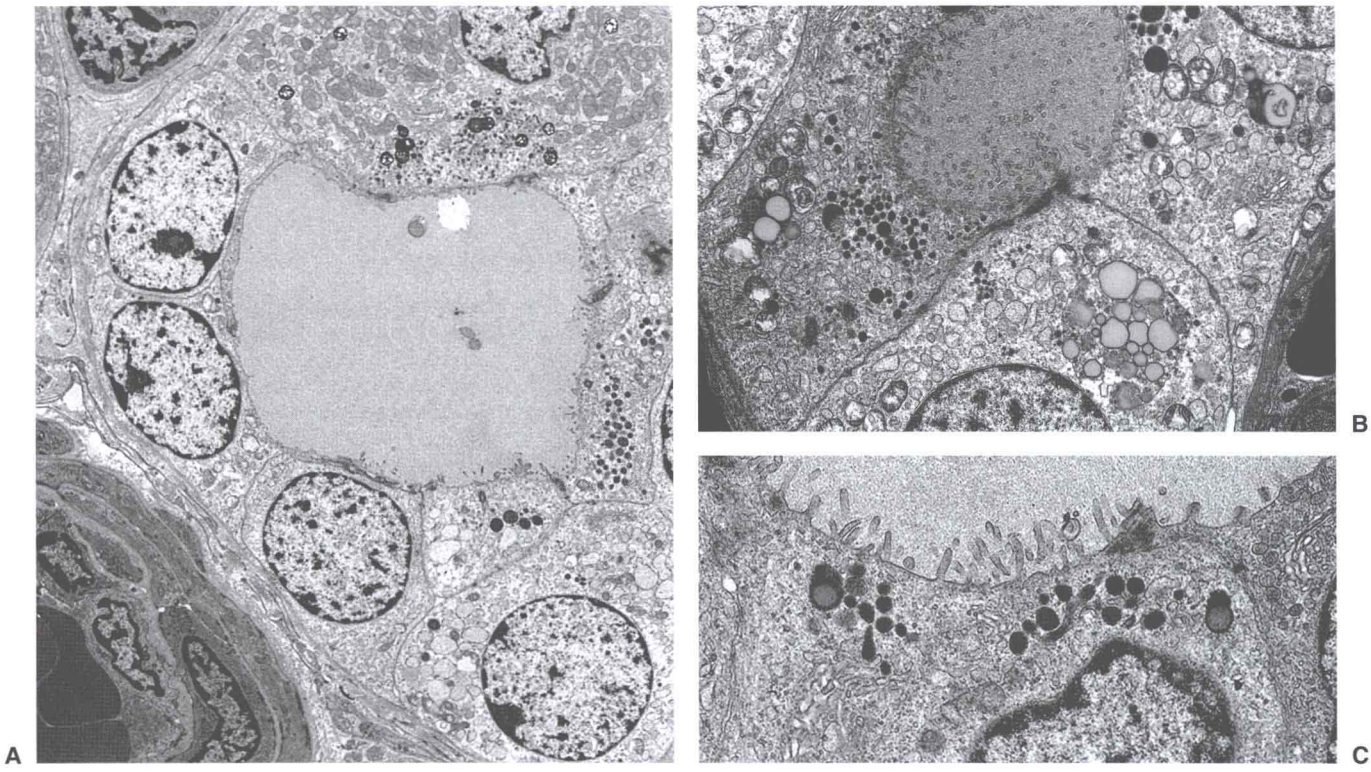



**FIGURE 1.9. Electron photomicrographs of follicular cells. (A)** Low-power view showing follicular cells surrounding the central colloid-filled cavity. A blood vessel is evident in the lower left corner. **(B)** Multiple follicular cells around central colloid *(upper center)*. Numerous microvilli project into the colloid. Multiple lysosomes are evident in the apical cytoplasm of the centrally located follicular cell. **(C)** High-power view showing luminal microvilli as well as dense secretory vacuoles and several phagolysosomes in the apical cytoplasm.

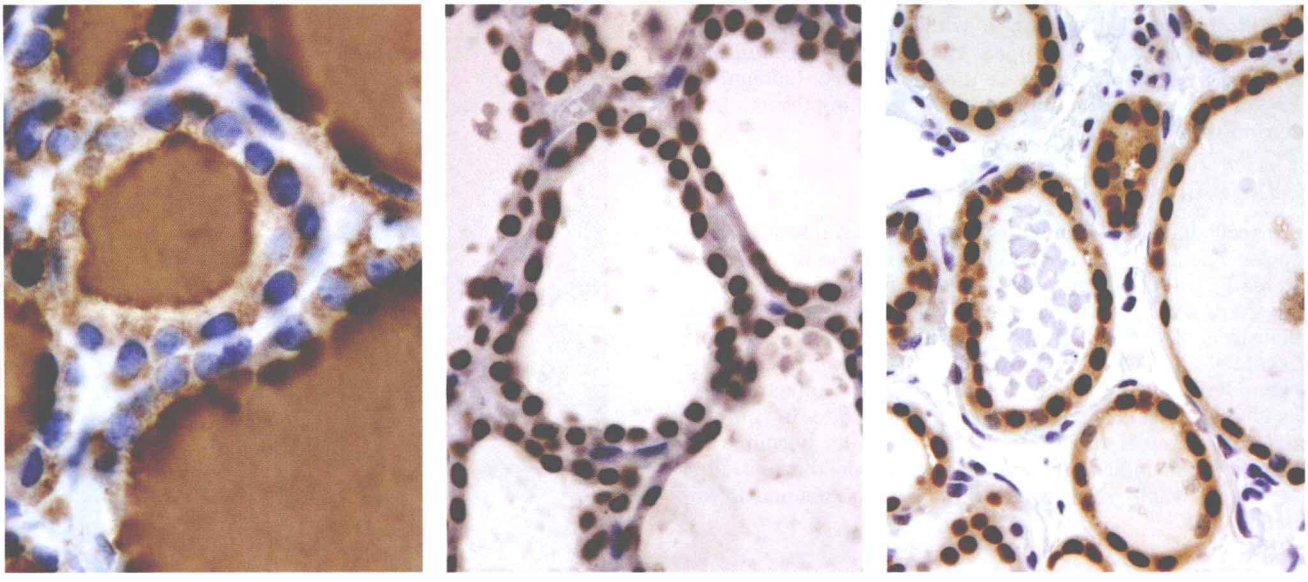


**FIGURE 1.10. Follicular cells immunostained for thyroglobulin *(left)*, TTF-1 *(center)*, and PAX8 *(right)*.**

**Table 1.1 IMMUNOHISTOCHEMICAL EXPRESSION OF THYROID CELLS**

| Follicular Cells | C-cells |
|---|---|
| Thyroglobulin | Calcitonin |
| Low-molecular-weight cytokeratins | Low-molecular-weight cytokeratins |
| Thyroid transcription factor-1 (TTF-1) | Calcitonin gene-related peptide |
| Thyroid transcription factor-2 (TTF-2) | Thyroid transcription factor-1 (TTF-1) |
| PAX8 | Carcinoembryonic antigen (CEA) |
| Vimentin | Chromogranin A |
| Thyroperoxidase (TPO) | Synaptophysin |
| TSH receptor | Various neuroendocrine peptides |
| Epidermal growth factor (EGF) | |
| Epidermal growth factor receptor (EGFR) | |
| Transforming growth factor-alpha (TGFα) | |

follicular cells. However, even those C cells that are peripheral to follicular cells and appear to be interfollicular are still encompassed by the basal lamina of the follicle.[28] C cells are separated from the colloid by the cytoplasm of overarching follicular cells.

C cells cannot be identified reliably in routine hematoxylin and eosin stained sections. Histologic features suggestive of C cells include cytoplasm that is clear to faintly granular and nuclei that are larger and more finely granular than adjacent follicular cells.[29] C cells vary in shape from polygonal to round to spindled. The C cells in glands of neonates and children tend to be polygonal and relatively large compared with adults.[30,31]

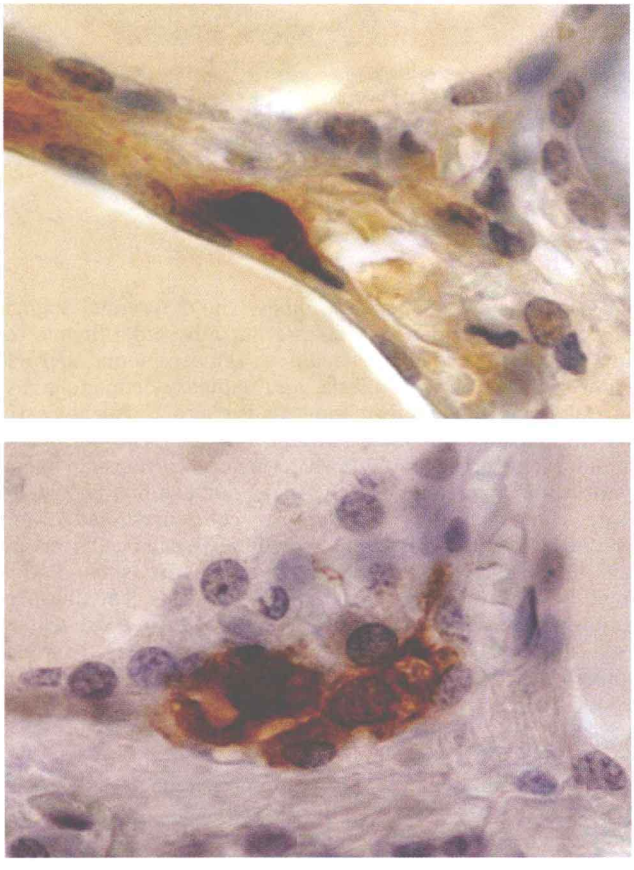


**FIGURE 1.11. Photomicrographs of normal C cells (calcitonin immunostain).**

### *Immunohistochemistry*

Stains for argyrophilic granules highlight the cytoplasm of C cells, but the most specific and common method of identification is an immunohistochemical stain for calcitonin (Fig. 1.11).[32,33] In addition to calcitonin, immunohistochemical studies of C cells have demonstrated positive staining for calcitonin gene-related peptide, low-molecular-weight cytokeratins, carcinoembryonic antigen (CEA), chromogranin, TTF-1, cholecystokinin-2, helodermin, and a number of other neuroendocrine peptides.[33–38]

### *Distribution in Thyroid*

C cells are relatively scant, comprising 0.1% or less of the total thyroid cell mass.[31,39] In addition, they are not evenly distributed throughout the thyroid. Most are found in the middle to upper-mid region of the lateral lobes, corresponding to the site of fusion of the ultimobranchial bodies with the medial thyroid anlage during embryogenesis (see Chapter 2).[29,31,40] Few, if any, C cells are present in the upper or lower poles or isthmus.

### *Ultrastructure*

The most distinctive ultrastructural feature of C cells is membrane-bound secretory granules within the cytoplasm. These electron-dense granules are the storage site of calcitonin. Type I granules measure 280 nm, and the smaller and denser Type II granules are 130 nm in diameter.[41] The cytoplasm also contains rough endocytoplasmic reticulum, a distinct Golgi complex, numerous mitochondria, and free ribosomes. Nuclei are round to oval with finely granular chromatin. Proximity to capillary blood vessels, a characteristic of endocrine cells, is also evident at the ultrastructural level.

## Solid Cell Nests

Solid cell nests are interfollicular aggregates of cells resembling squamous or transitional epithelium. Solid cell nests are found in normal thyroid glands, and most investigators consider them to be remnants of the ultimobranchial bodies.[42–44] Evidence supporting this view includes histologic and ultrastructural similarities between solid cell nests and ultimobranchial bodies, the presence of C cells within some solid cell nests, and the relatively high density of C cells in the thyroid tissue surrounding solid cell nests.[43] In addition, solid cell nests are most frequently found in the middle third of the lateral lobes, a region corresponding to the usual site of fusion of the ultimobranchial bodies with the medial thyroid anlage during embryonic development.

### *Morphologic Features*

Solid cell nests are microscopic findings and their incidence varies, in large part depending on the extensiveness of sampling. They range from 50 to 1000 μm in greatest dimension.[45] Solid cell nests are interspersed between follicles and are irregularly shaped although typically well demarcated (Fig. 1.12). A number of investigators have reported a basal membrane around solid cell nests, but this has not been a universal finding.[42–44,46] The cells range from polygonal to round to spindle shaped, and they have a compact arrangement. Distinct intercellular bridges are not typically seen; however, desmosomes are evident ultrastructurally. The nuclei have finely granular chromatin, and nucleoli are absent or inconspicuous. Some nuclei exhibit longitudinal grooves. Most have relatively scant amphophilic cytoplasm, but cells with more abundant clear cytoplasm are also seen. Some solid cell nests are associated with a cystic region containing mucin. Follicular structures containing central colloid, an inner lining of

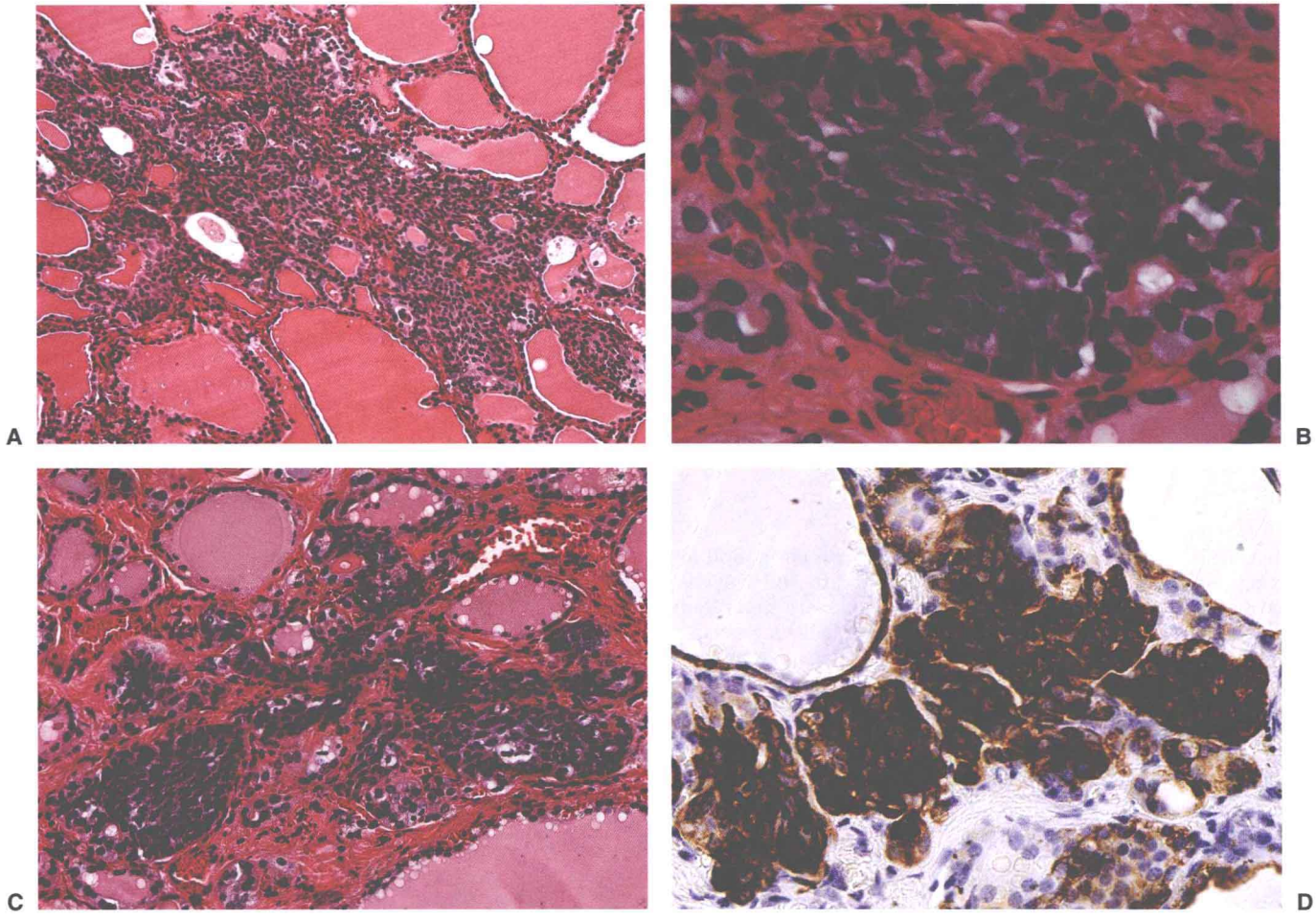



**FIGURE 1.12. Solid cell nests (SCN).** **(A)** Low-power photomicrograph of relatively large SCN. **(B)** High-power photomicrograph from the same SCN showing the squamoid appearance of the cells. **(C)** Low-power photomicrograph of smaller SCN. **(D)** Section of the same SCN as shown in panel C immunostained for low-molecular-weight cytokeratin (CAM 5.2 cytokeratin).

follicular cells, and an outer rim of solid cell nest type cells can be seen. Interpretations vary whether these represent mixed follicles derived entirely from solid cell nests or solid cell nests encircling follicles derived from the medial anlage.

## *Immunohistochemistry*

Immunohistochemical studies have shown consistently positive staining for low molecular weight cytokeratins and variable staining for carcinoembryonic antigen. Variable results have also been reported for high molecular weight cytokeratins. One study found that solid cell nests strongly express p63.[47] Solid cell nests may contain a minority population of C cells that are highlighted by a calcitonin immunostain. The C cells correspond to cells with clear cytoplasm seen in hematoxylin and eosin stained sections. The C cells also show nuclear staining for TTF-1 in contrast to the main cells of the nests.[47] Most studies have not shown staining for thyroglobulin. Isolated cells positive for thyroglobulin have been reported and interpreted as suggesting that solid cell nests may be a source of follicular epithelium.[48] An alternative interpretation is thyroglobulin-positive cells represent entrapped follicular epithelium.

## *Differential Diagnosis*

Solid cell nests are incidental findings. The differential diagnosis includes focal squamous metaplasia, intrathyroidal thymic remnant, primary or metastatic squamous cell carcinoma, thyroglossal duct cyst, C-cell hyperplasia, and papillary or medullary microcarcinomas. Squamous metaplasia is characteristically associated with chronic inflammation, and multiple scattered foci are common. The presence of Hassall corpuscles helps to identify thymic remnants. Solid cell nests do not exhibit the cytologic atypia characteristic of squamous cell carcinoma. Immunostaining for calcitonin can help distinguish solid cell nests from C-cell hyperplasia and medullary carcinoma since staining should be absent or only focal in solid cell nests. The absence of staining for p63 may also be useful to distinguish solid cell nests from C-cell hyperplasia and medullary carcinomas, as well as papillary microcarcinomas.

## *Neoplastic Potential*

Solid cell nests may play a role as the precursor for primary mucoepidermoid carcinomas of the thyroid (see Chapter 15).[49,50] Studies suggest the possibility that solid cell nests may be capable

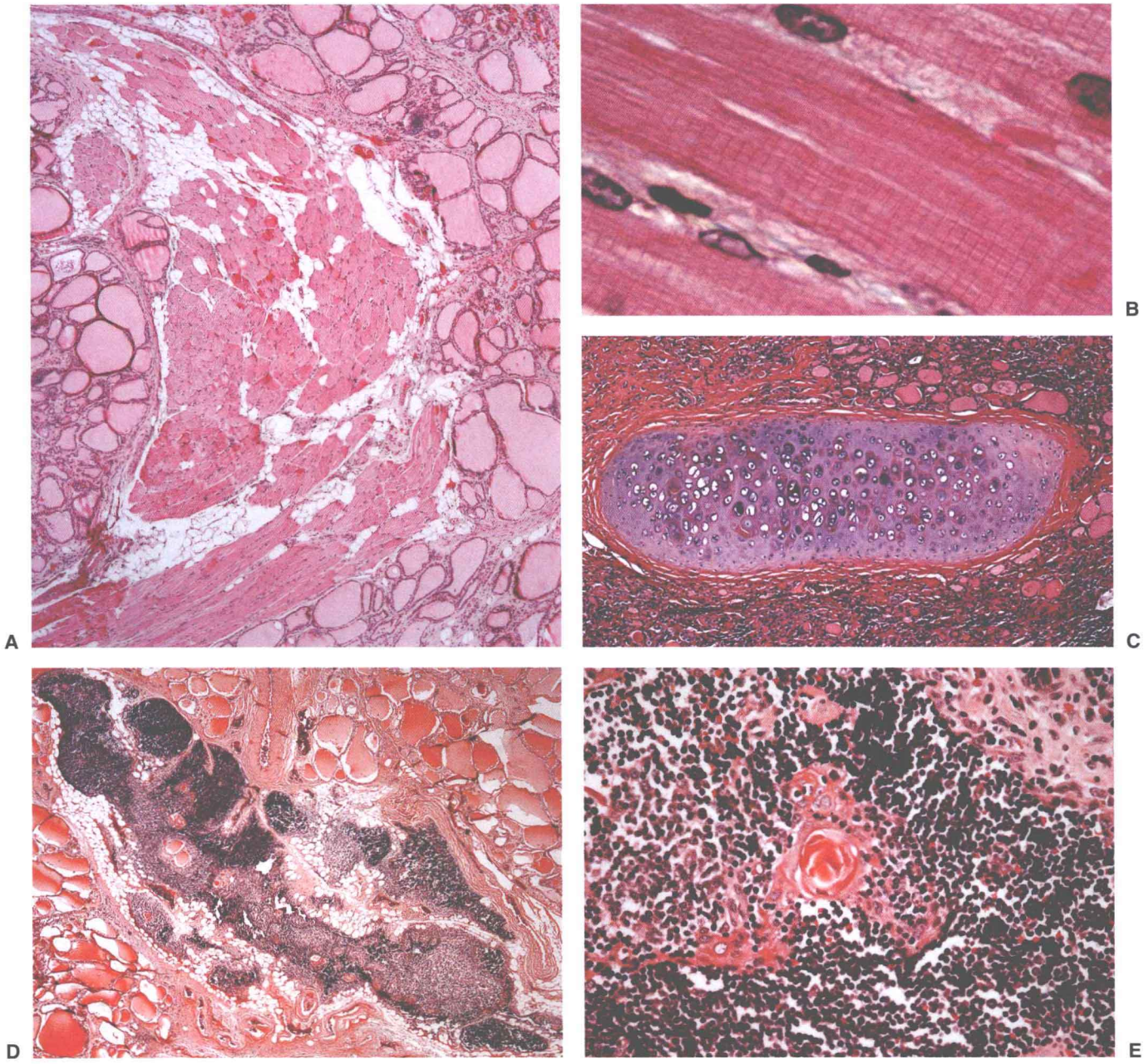



**FIGURE 1.13. Heterologous tissues within thyroid. (A)** Focus of adipose tissue and skeletal muscle. **(B)** High-power view of skeletal muscle. **(C)** Focus of intrathyroidal cartilage. **(D, E)** Intrathyroidal thymic tissue. High-power view shows Hassall corpuscle **(E)**.

of hyperplasia and neoplastic transformation. If true, the risk of neoplastic transformation must be quite low given the relatively high frequency of solid cell nests and rarity of mucoepidermoid carcinomas of the thyroid.

## Heterologous Tissues within Thyroid

A number of tissues typically found external to the thyroid can be found within the substance of the gland. These include adipose, skeletal muscle, parathyroidal, thymic, salivary, and cartilaginous tissue (Fig. 1.13). These heterologous tissues are sometimes in proximity to solid cell nests and may represent remnants of a pharyngeal pouch component.[14,51]

## REFERENCES

1. Warton T. *Adenographia (Translated from the Latin by Stephen Freer).* Oxford: Clarendon Press; 1996.
2. Braun EM, Windisch G, Wolf G, et al. The pyramidal lobe: clinical anatomy and its importance in thyroid surgery. *Surg Radiol Anat* 2007;29:21–27.
3. Gravante G, Delogu D, Rizzello A, et al. The Zuckerkandl tubercle. *Am J Surg* 2007;193:484–485.
4. Hegedus L, Perrild H, Poulsen LR, et al. The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. *J Clin Endocrinol Metab* 1983;56:260–263.
5. Pankow BG, Michalak J, McGee MK. Adult human thyroid weight. *Health Phys* 1985;49:1097–1103.
6. de la Grandmaison GL, Clairand I, Durigon M. Organ weight in 684 adult autopsies: new tables for a Caucasoid population. *Forensic Sci Int* 2001; 119:149–154.