Lori A. Erickson

Atlas of Endocrine Pathology

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Atlas of Anatomic Pathology

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Series Preface

One Picture is Worth Ten Thousand Words

– Frederick Barnard, 1927

Remarkable progress has been made in anatomic and surgical pathology during the last 10 years. The ability of surgical pathologists to reach a definite diagnosis is now enhanced by immunohistochemical and molecular techniques. Many new clinically important histopathologic entities and variants have been described using these techniques. Established diagnostic entities are more fully defined for virtually every organ system. The emergence of personalized medicine has also created a paradigm shift in surgical pathology. Both promptness and precision are required of modern pathologists. Newer diagnostic tests in anatomic pathology, however, cannot benefit the patient unless the pathologist recognizes the lesion and requests the necessary special studies. An up-to-date Atlas encompassing the full spectrum of benign and malignant lesions, their variants, and evidence-based diagnostic criteria for each organ system is needed. This Atlas is not intended as a comprehensive source of detailed clinical information concerning the entities shown. Clinical and therapeutic guidelines are served admirably by a large number of excellent textbooks. This Atlas, however, is intended as a "first knowledge base" in the quest for definitive and efficient diagnosis of both usual and unusual diseases.

The *Atlas of Anatomic Pathology* is presented to the reader as a quick reference guide for diagnosis and classification of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions organized by organ systems. Normal and variations of "normal" histology are illustrated for each organ. The Atlas focuses on visual diagnostic criteria and differential diagnosis. The organization is intended to provide quick access to images and confirmatory tests for each specific organ or site. The Atlas adopts the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms.

This book Series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. It is also a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. We hope that our trainees, students, and readers at all levels of expertise will learn, understand, and gain insight into the pathophysiology of disease processes through this comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. We hope that the new Series will serve as a virtual pathology museum for the edification of our readers.

Indianapolis, IN, USA

Liang Cheng, MD

Preface

The *Atlas of Endocrine Pathology* provides a comprehensive compendium of photomicrographs of common and uncommon entities in endocrine pathology. Histologic features of normal features, reactive conditions, hyperplasia, and tumors are included. The most helpful diagnostic features are illustrated to provide direction and clues to the diagnosis of endocrine tumors. The photomicrographs highlight the most pertinent diagnostic features in problematic diagnoses in endocrine pathology. This Atlas serves as a learning tool for those becoming familiar with the diverse entities encountered in endocrine pathology and a reference for practicing pathologists faced with challenging diagnoses in endocrine pathology.

Rochester, MN, USA — Lori A. Erickson, MD

Contents

Thyroid Histology

1

The thyroid gland weighs 15–25 g and is composed of two lobes joined by the isthmus, with approximately 40 % of people having a pyramidal lobe [1]. The thyroid is composed of lobules, each of which is composed of 20–40 follicles. Each follicle is surrounded by a basement membrane and lined by follicular cells. Colloid is present in the lumen of the follicles. The presence of calcium oxalate crystals in the colloid is a helpful feature differentiating it from parathyroid. Thyrocytes also may be distinguished from parathyroid cells by reactivity to thyroid transcription factor 1 (TTF1) and thyroglobulin and the absence of parathyroid hormone and the neuroendocrine markers chromogranin and synaptophysin in thyrocytes. C cells are calcitonin-producing cells in the thyroid. They are present in interfollicular areas but are difficult to identify in normal thyroid tissue with hematoxylin and eosin (H&E) alone. The immunohistochemical stains calcitonin, chromogranin, synaptophysin, somatostatin, calcitonin gene-related peptide, and bombesin will highlight these neuroendocrine cells of the thyroid. Thyroid follicular cells produce thyroxine (T4) and triiodothyronine (T3), and C cells produce calcitonin. C cells migrate from the neural crest to the ultimobranchial bodies, which are derived from branchial pouch complexes IV and V and develop in the first five to seven fetal weeks [2, 3]. C cells have clear cytoplasm and oval to round nuclei; they are positive for calcitonin, chromogranin, synaptophysin, calcitonin, calcitonin gene-related peptide, somatostatin, and bombesin [4]. Calcitonin mRNA has been localized in C cells by in situ hybridization studies [5]. Calcitonin is present in both 280-nm type I and 130-nm type II secretory granules; it is produced by C cells. Calcitonin interacts with bone, kidney, and the gastrointestinal tract to lower serum calcium [6]. Thyroid follicular cells and tumors are immunopositive for thyroglobulin, TTF1, and keratin. Thyroid C cells and tumors are immunopositive for calcitonin, chromogranin, synaptophysin, keratin (Cam5.2), and TTF1, although the intensity of TTF1 immunostaining often is less than in follicular thyroid cells and tumors. Interesting histologic features occasionally may be recognized in thyroid tissue, including solid cell nests, fatty metaplasia, radiation changes, drugs such as minocycline and amiodarone, and palpation thyroiditis. Thyroid tissue also may occur ectopically, and tumors may develop in this tissue.

L.A. Erickson, *Atlas of Endocrine Pathology*, Atlas of Anatomic Pathology,
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Normal Thyroid

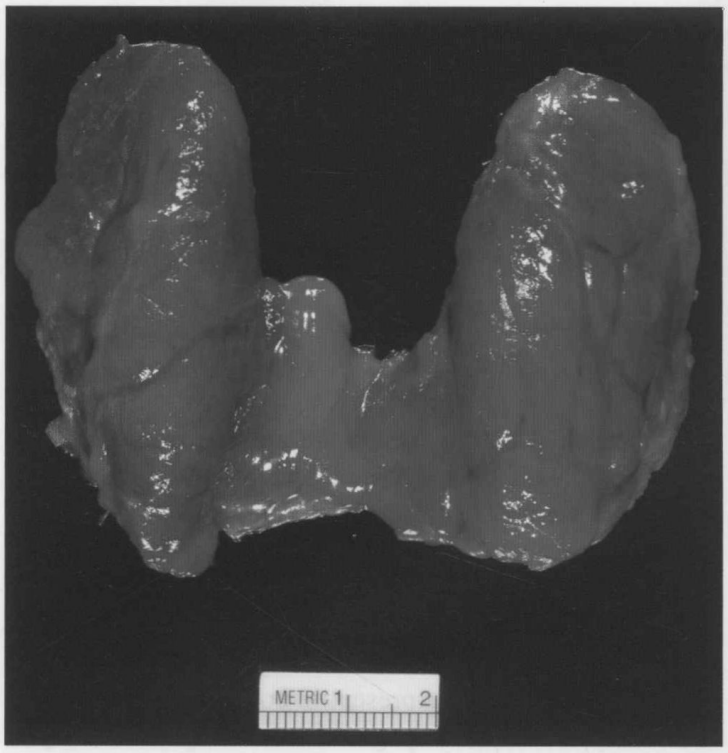

Fig. 1.1 Normal thyroid. Gross image of a normal thyroid gland showing the bilobed gland joined by the isthmus in the center. The isthmus lies anterior to the trachea and inferior to the cricoid cartilage. The thyroid is in front of the larynx and trachea. The thyroid descends with the thyroglossal duct into the neck and expands after the thyroglossal duct atrophies. The pyramidal lobe, present in approximately 40 % of people, is a vestige of the thyroglossal duct. The anlage is visible in the pharynx in association with the heart by day 17 of fetal life [7, 8]. Follicles develop from 9 to 12 fetal weeks, and well-developed colloid follicles are seen at 14 weeks' gestation [7, 8]

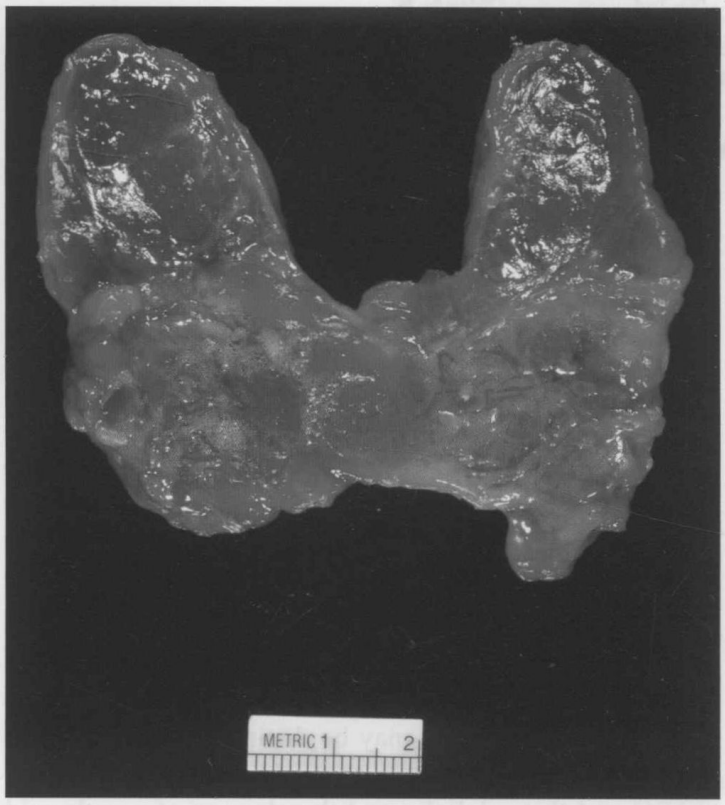

Fig. 1.2 Normal thyroid. Gross image of a cut section of a normal thyroid gland, showing the bilobed gland joined by the isthmus in the center. Normal thyroid glands in adults weigh 15–25 g and may vary with constitutional factors, age, sex, size of the individual, and functional status. The thyroid may be larger in women and may change with hormonal effects such as pregnancy and the menstrual cycle [9, 10]. An enlarged thyroid gland is referred to as a goiter

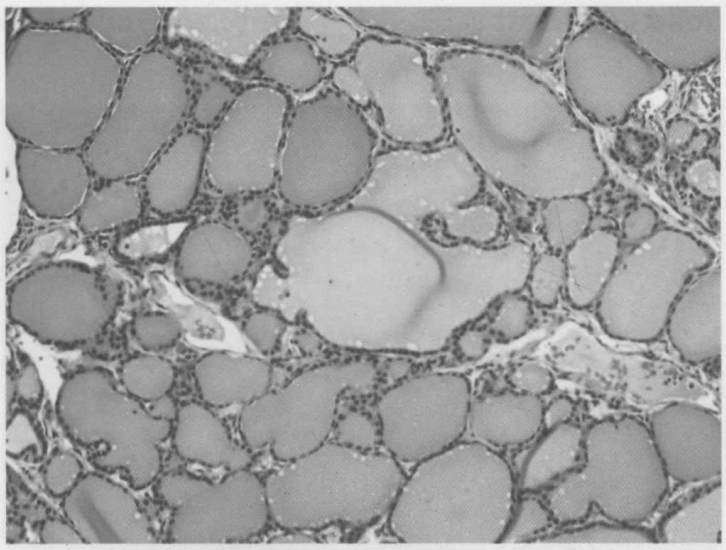

Fig. 1.3 Normal thyroid. The thyroid gland is made up of lobules of 20–40 follicles. The follicles have an average size of 200 μm (range of 50–500 μm) and have colloid in their lumens, which is made up mostly of thyroglobulin. Calcium oxalate crystals are present in normal colloid and allow a distinction from colloid-like material in parathyroid tissue that lacks calcium oxalate [11]. Normal thyroid tissue may be present in soft tissues next to the thyroid as ectopic thyroid tissue [12]. The follicular cells have round nuclei with a diffuse chromatin pattern and amphophilic to eosinophilic cytoplasm. Thyroglobulin mRNA has been identified in follicular cells by in situ hybridization studies [13]. Follicular cells are positive for the immunohistochemical markers thyroglobulin, keratin, and TTF1

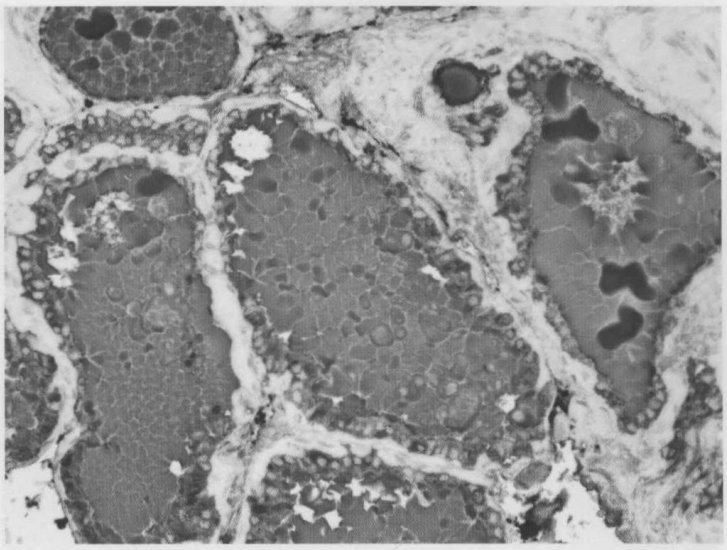

Fig. 1.5 Normal thyroid. Immunopositivity for thyroglobulin is present in thyroid tissues and folliculogenic thyroid tumors. The thyrocytes stain with thyroglobulin, as does the colloid. Medullary thyroid tumors are negative for thyroglobulin. Thyroglobulin is helpful in identifying tissues and tumors as thyroid and differentiating them from tumors from other sites

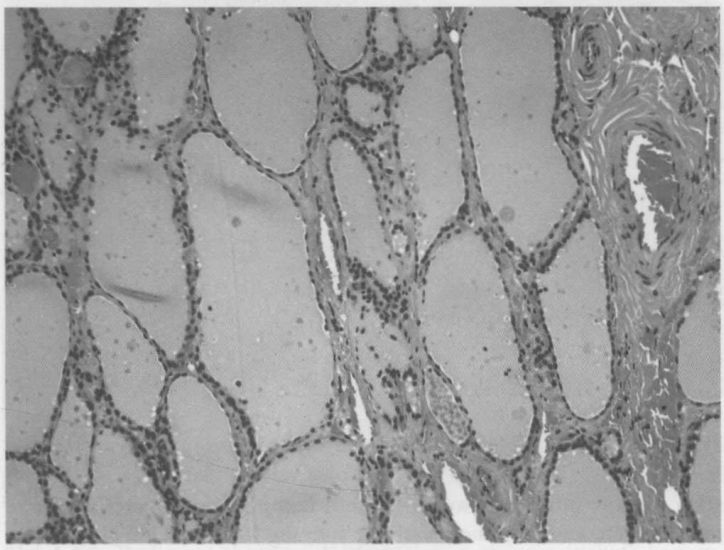

Fig. 1.4 Normal thyroid. Thyroid follicles are present with a central lumen containing colloid. Thyroid follicular cells are polygonal, with central nuclei and round nuclei with diffuse chromatin and moderate amounts of amphophilic to eosinophilic cytoplasm. The follicular cells produce thyroxine (T4) and triiodothyronine (T3) from exogenous iodine, which is oxidized and catalyzed by thyroid peroxidase. Thyroid-stimulating hormone (TSH) regulates the release of thyroglobulin, stored as colloid, endocytosed, and hydrolyzed with release of T3 and T4. Thyroglobulin breakdown and release of T3 and T4 are inhibited by iodine by inhibiting TSH stimulation of thyroid adenylate cyclase

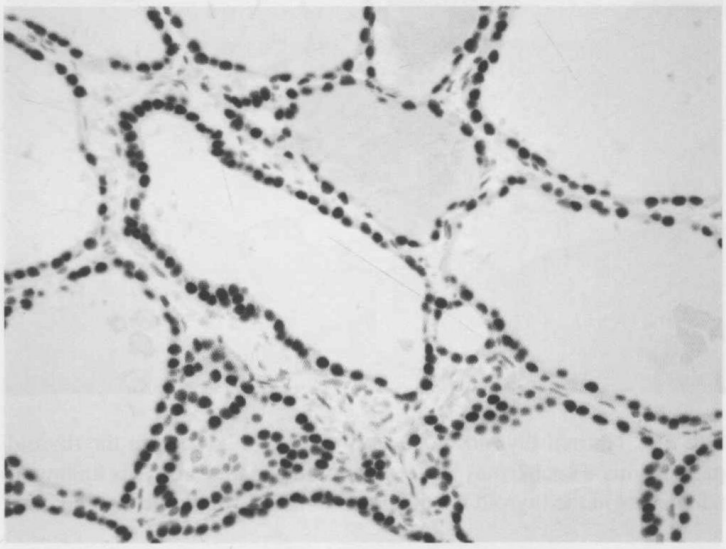

Fig. 1.6 Normal thyroid. Thyroid follicular cells are immunopositive for TTF1, which is helpful in differentiating thyroid from parathyroid and other tissues. TTF1 is not specific for thyroid follicular cells or folliculogenic tumors as it also stains, although with less intensity, medullary thyroid carcinoma. TTF1 also stains most adenocarcinomas of the lung and papillary adenocarcinoma of the sinuses. High-grade neuroendocrine tumors from the lung and some other sites may stain from TTF1. Thus, this marker is not specific for thyroid, although it is very helpful in determining the differentiation or primary site of difficult tumors, particularly when used as part of a panel of immunostains

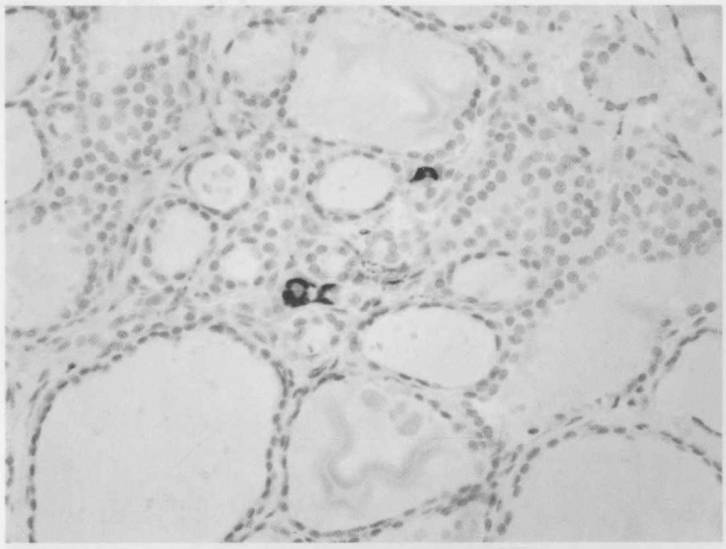

Fig. 1.7 Normal thyroid. This chromogranin immunostain highlights scattered C cells in interfollicular areas in normal thyroid. C cells of the thyroid are difficult to identify in normal thyroid tissue with H&E staining. C cells have clear cytoplasm and oval to round nuclei. They are positive for calcitonin, chromogranin, synaptophysin, calcitonin, calcitonin gene-related peptide, somatostatin, and bombesin [4]

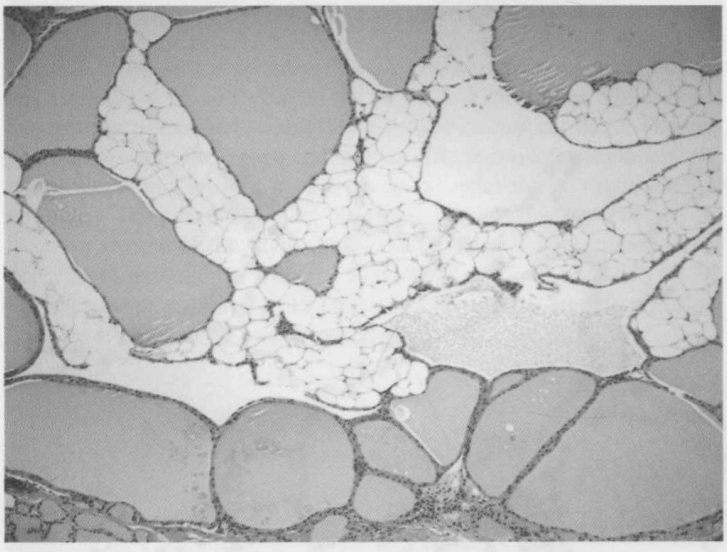

Fig. 1.8 Normal thyroid. Foci of fat cells can be seen in the thyroid parenchyma. Fat also may be seen in thyroid neoplasms. This finding of adipocytes in the thyroid is not known to be of pathologic significance

Solid Cell Nests

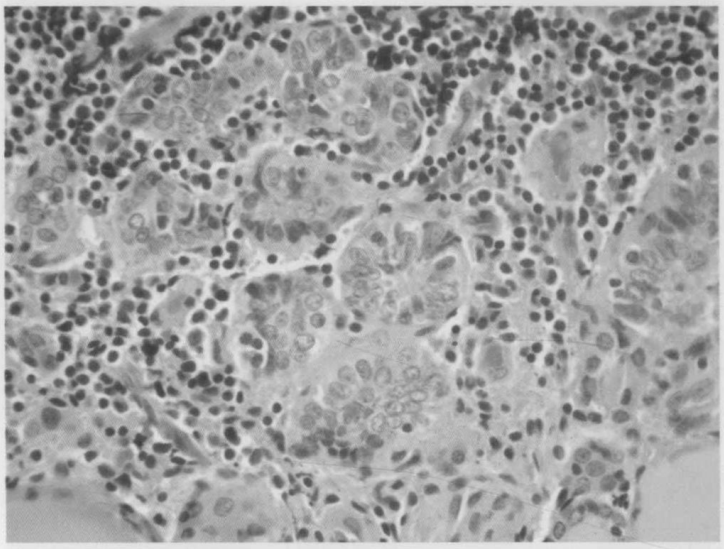

Fig. 1.9 Solid cell nests. Solid cell nests are small nests of oval cells with fine chromatin identified in 3 % of thyroid glands. They are thought to be ultimobranchial body rests [14]

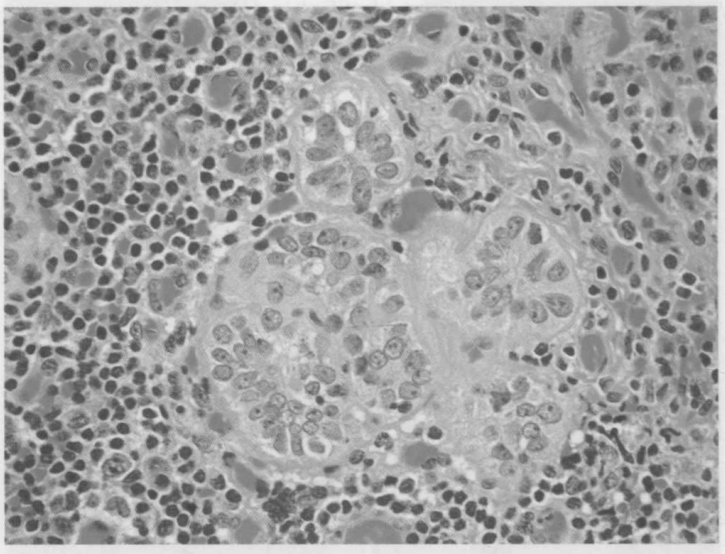

Fig. 1.10 Solid cell nests. Solid cell nests may be mistaken for papillary thyroid carcinomas (PTCs) and for squamous metaplasia. They stain for low molecular weight keratin and polyclonal carcinoembryonic antigen, and may show variable staining for calcitonin [15]

Radiation Changes

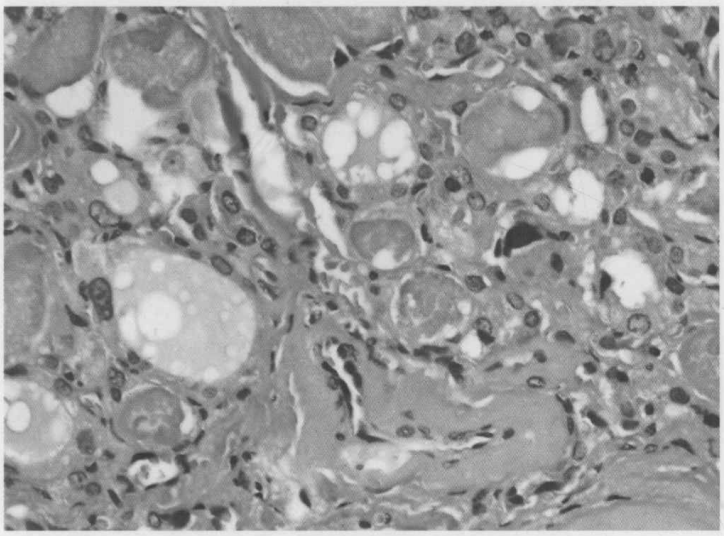

Fig. 1.11 Radiation changes. Radiation to the thyroid, neck, or tonsils may affect the thyroid. The effects depend on the dose and isotope [16–18]. Historical irradiation of the tonsils was associated with nodular hyperplasia of the thyroid. Radiation for acne also was associated with thyroid carcinoma [19]. More extensive irradiation, as with lymphoma treatment, is associated with increased cellularity, increased nodular size, fibrosis, chronic thyroiditis, and cytologic atypia [16]

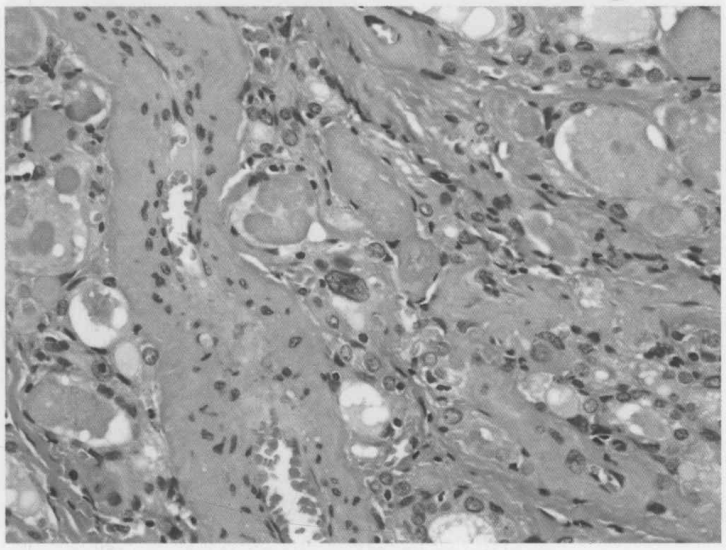

Fig. 1.12 Radiation changes. Acute radiation changes include hemorrhage, neutrophilic infiltration, necrosis, and follicular disruption [18]. Radiation may be associated with cytologic atypia, pleomorphism, and an increased incidence of thyroid carcinoma, predominantly PTCs [20, 21]. The latency may vary from decades to a short latency, as in childhood cancers after the Chernobyl accident [17, 22]. It is speculated that dietary iodine levels may have implications in radiation-associated thyroid carcinogenesis, and iodine deficiency might increase incidence, reduce latency, and influence tumor morphology and aggressiveness [23]

Minocycline and Amiodarone Thyroid

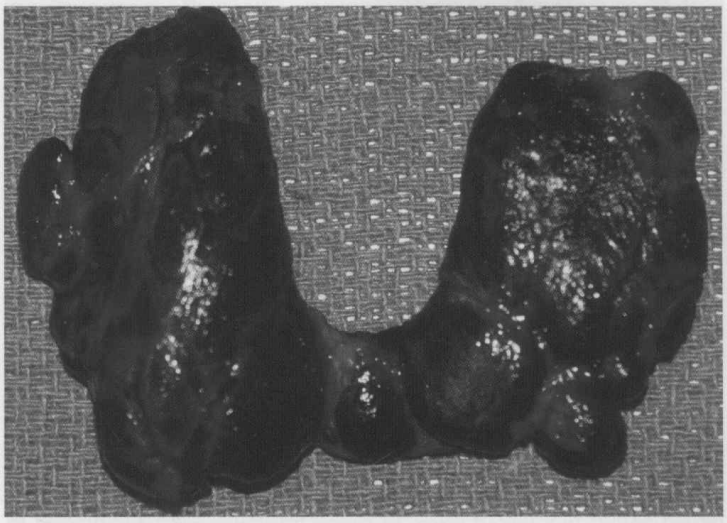

Fig. 1.13 Minocycline thyroid. Drugs may have various effects on the thyroid. Minocycline is a tetracycline antibiotic that produces a black pigment in the thyroid, which may be related to its interaction with thyroid peroxidase [24]. Minocycline pigmentation also may affect the skin, sclera, teeth, bone, heart valves, oral mucosa, and atherosclerotic plaques [25–30]. The antithyroid compounds thiocyanate (both in its chemical form and in cabbage and turnips) and perchlorate can inhibit thyroid iodine transport, whereas propothiouracil, methimazole, phenylbutazone, and lithium can inhibit binding reactions and thyroid hormone release [4, 31]

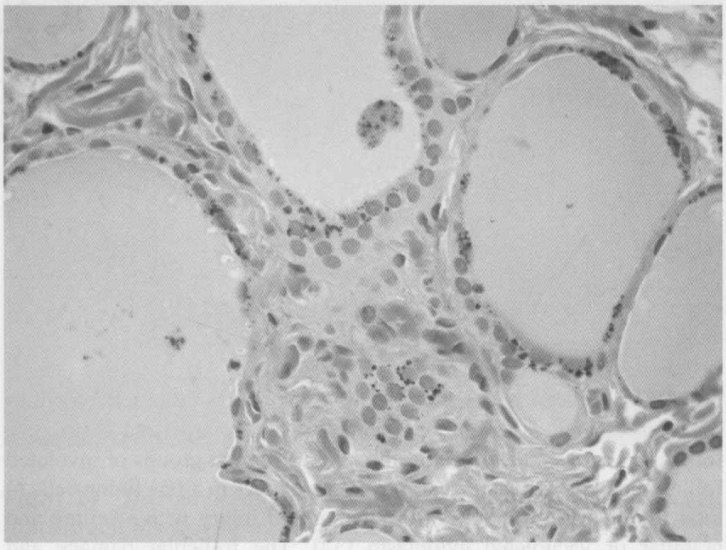

Fig. 1.14 Minocycline thyroid. Minocycline pigment in the colloid and localized within the cytoplasm of thyroid follicular epithelial cells. Lipofuscin and hemosiderin also may localize in the cytoplasm but are light brown and brown yellow, respectively. Minocycline is dark brown/black

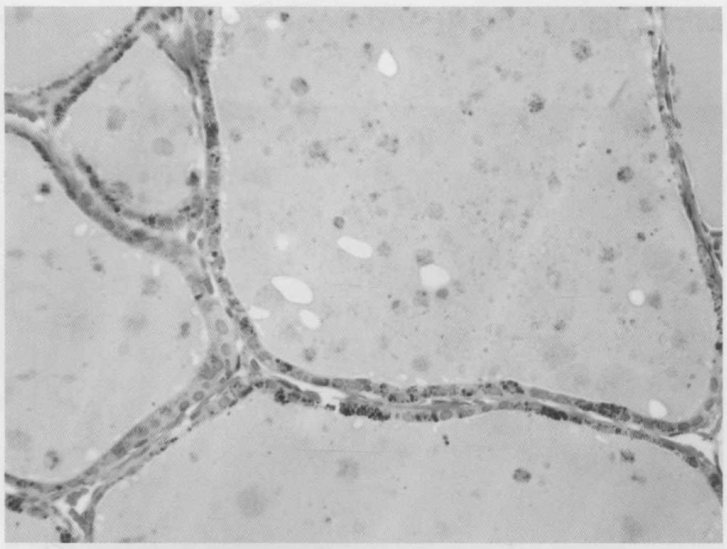

Fig. 1.15 Minocycline thyroid. Minocycline is present in the follicular lumen and as pigmented granules in the follicular cells. In addition to pigments, other substances, such as calcium oxalate crystals, may be seen in colloid and are highlighted with polarization. Crystals are not specific for a particular disorder but are helpful in separating thyroid from parathyroid, which lacks calcium oxalate crystals

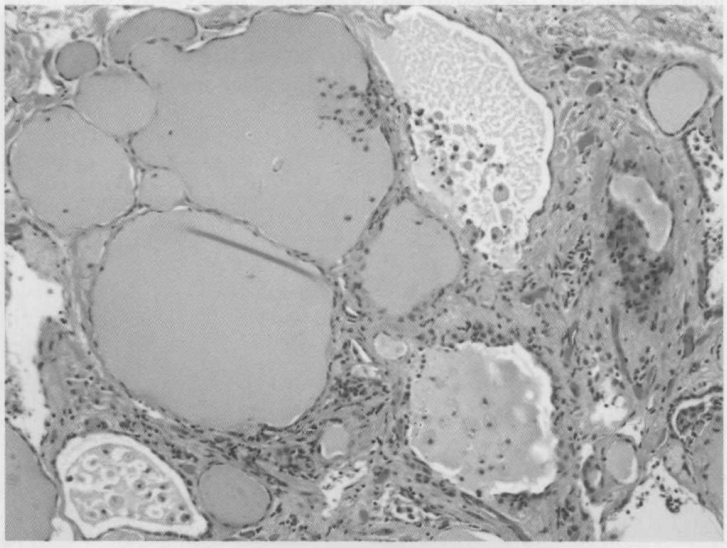

Fig. 1.16 Amiodarone thyroid. Histologic features of amiodarone thyroid disease include involutional changes, degenerative and destructive follicular lesions, and zones of fibrosis [32]. Small groups of involuted follicles may have damage varying from changes in a few lining cells to total follicular destruction and follicular cell injury with swelling and granular or vacuolated cytoplasm [32]. The follicular damage and release of hormones may contribute to the associated thyrotoxicosis [32]

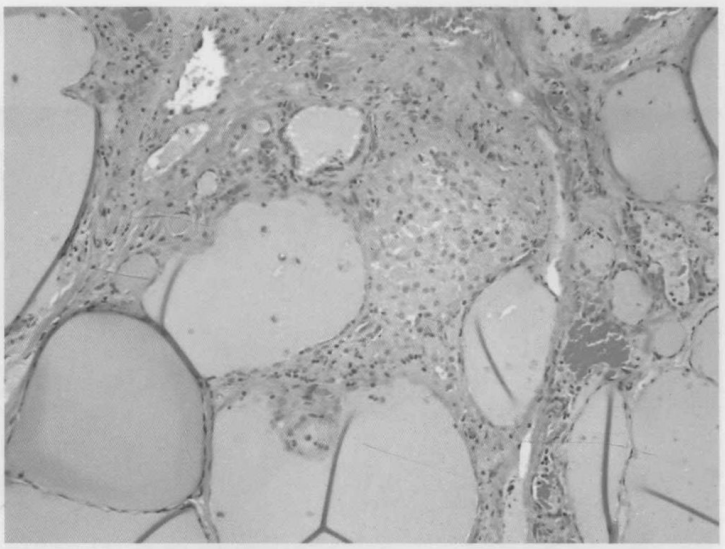

Fig. 1.17 Amiodarone thyroid. Amiodarone is a class III antiarrhythmic agent associated with changes in thyroid function tests due to inhibition of 5′-deiodinase, resulting in decreased T3 generation from T4 with an associated increase in reverse T3 [33]. Amiodarone is associated with amiodarone-induced thyrotoxicosis related to excess iodine-induced thyroid hormone synthesis in an abnormal thyroid or is the result of destructive thyroiditis [33]. Amiodarone-induced hypothyroidism is thought to result from escape from the acute Wolff-Chaikoff effect, from defects in thyroid hormonogenesis, or from concomitant Hashimoto thyroiditis [33]

Palpation Thyroiditis

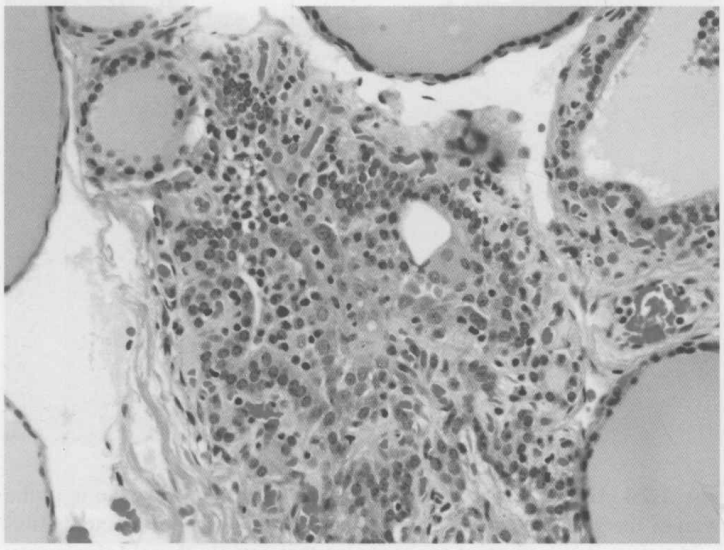

Fig. 1.18 Palpation thyroiditis. Multiple foci of small groups or single follicles are disrupted and associated with a mixed inflammatory infiltrate with prominent histiocytes, appearing as multiple small granulomatous foci in this case of palpation thyroiditis. Palpation thyroiditis is a common finding in surgically resected thyroids from palpation of the thyroid gland

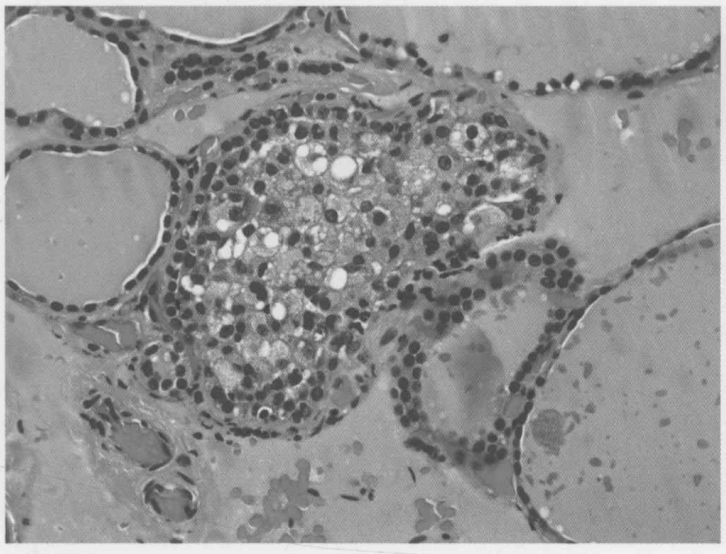

Fig. 1.19 Palpation thyroiditis. Palpation thyroiditis with disrupted follicles with mixed inflammatory infiltrate forming a small granulomatous focus. Palpation folliculitis is believed to be caused by traumatic rupture of isolated thyroid follicles as a result of palpation of the gland [34]

Thyroid Needle-Biopsy Site

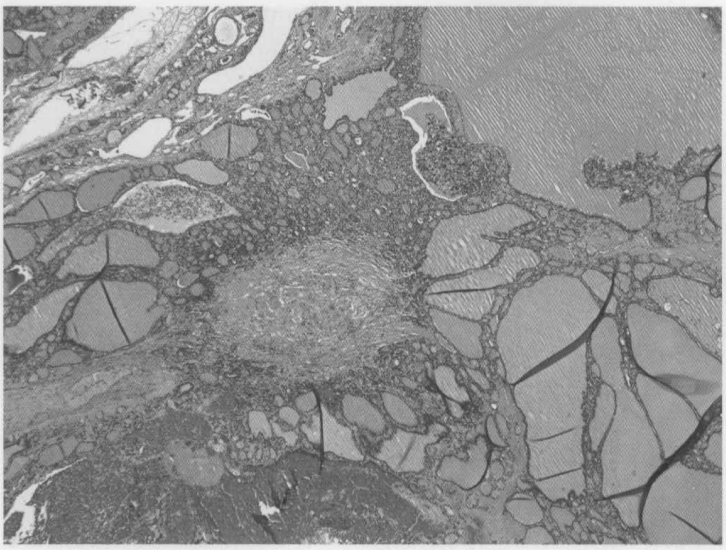

Fig. 1.20 Thyroid needle-biopsy site. Shown is an area of fibrosis where prior fine-needle aspiration was performed. Needle-biopsy sites are not an uncommon finding in the thyroid. The fibrosis in these cases may entrap follicular cells and be mistaken for infiltrative growth. Inflammation and hemosiderin in these fibrous foci are helpful in identification

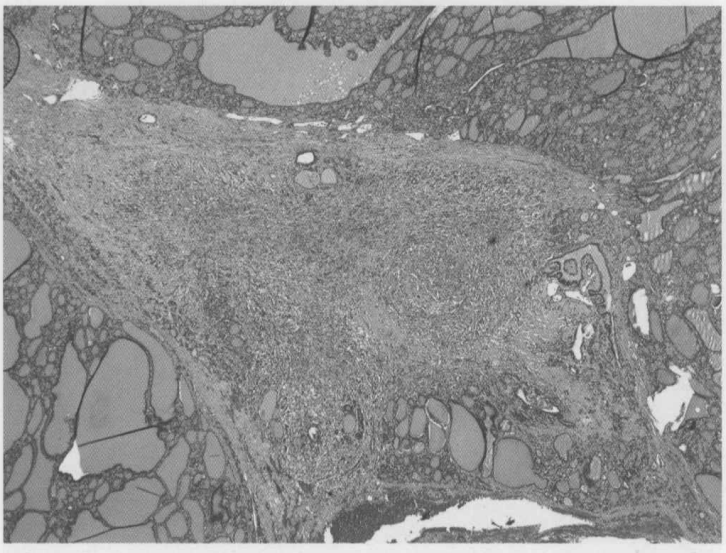

Fig. 1.21 Thyroid needle biopsy site. Inflamed focus with associated fibrosis and histiocytic reaction in a fine-needle aspiration site. Cells associated with inflammation may have cytologic clearing and irregularity and should not be mistaken for PTC. Also, in follicular neoplasms, identifying the perpendicular and linear appearance of the needle-biopsy site with associated inflammation and hemosiderin prevents misinterpretation of capsular invasion

Ectopic Thyroid Tissue

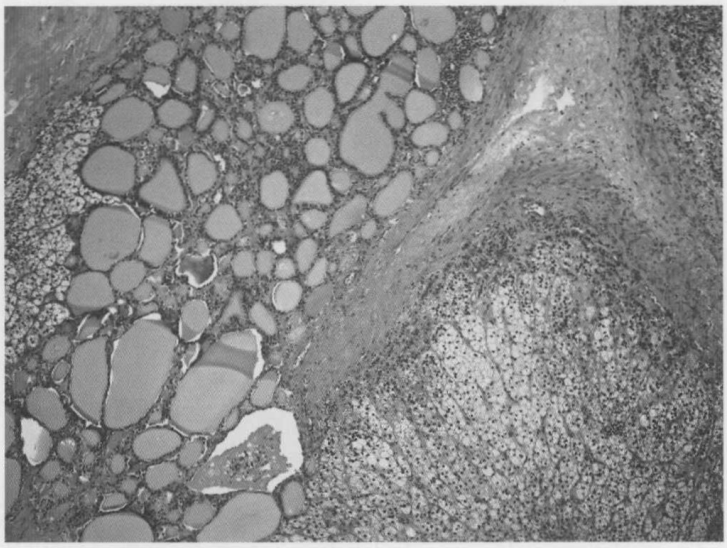

Fig. 1.22 Ectopic thyroid tissue. This is an unusual example of ectopic thyroid tissue in the adrenal gland. Ectopic thyroid tissue has been reported from a variety of sites; however, historic reference to ectopic thyroid tissue involving lymph nodes now is thought most likely to represent metastatic PTC, particularly if lateral to the jugular vein [35–37]

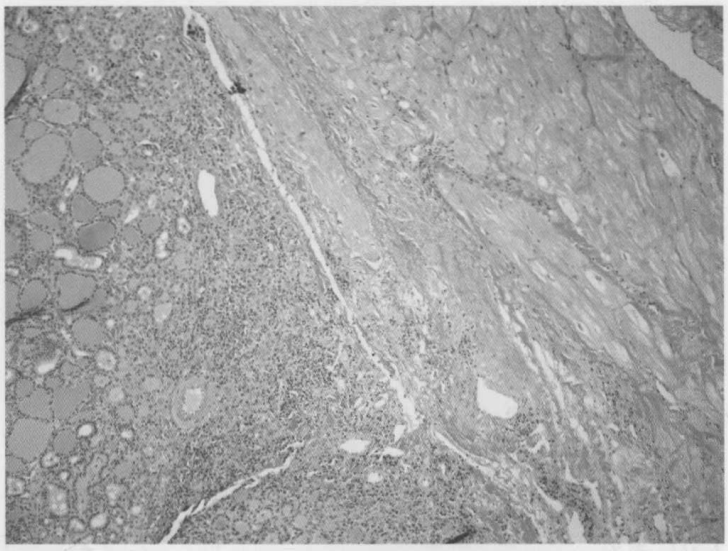

Fig. 1.23 Ectopic thyroid tissue. This ectopic thyroid tissue in the heart was identified along the left ventricular outflow tract. Ectopic thyroid tissue has been reported along the thyroglossal tract and in unusual locations such as the heart and pericardium, chest wall, porta hepatis, and vagina [38–40]

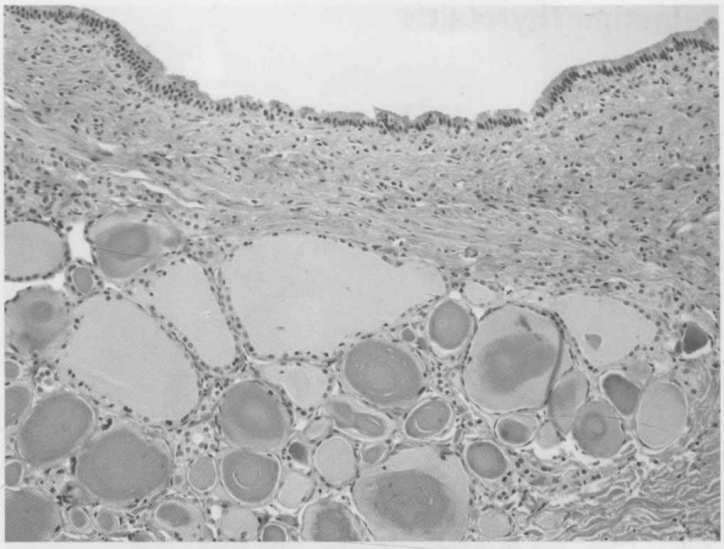

Fig. 1.24 Ectopic thyroid tissue. This ectopic thyroid tissue is in the wall of the gallbladder. Although this is a rare location for ectopic thyroid tissue, it is important to recognize that ectopic thyroid tissue may occur in unusual locations and not to mistake it for another tissue type of a metastasis