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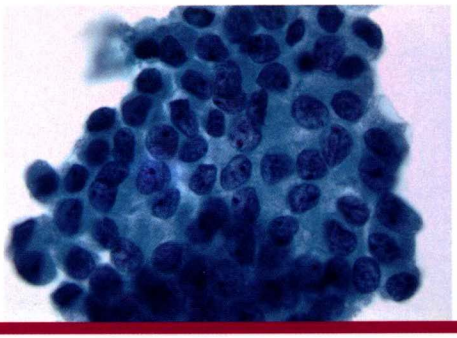

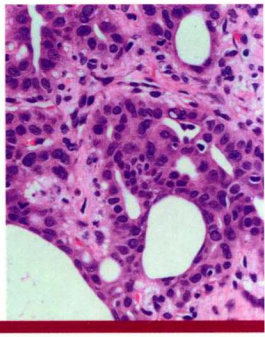

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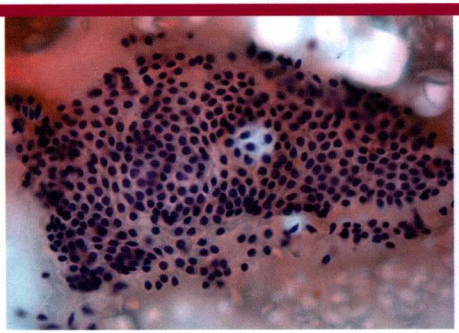

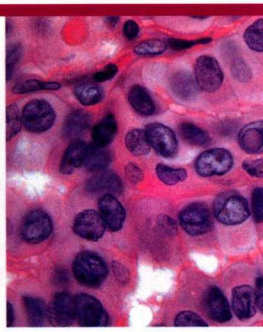

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BIOPSY INTERPRETATION SERIES

BIOPSY INTERPRETATION OF THE THYROID

Second Edition

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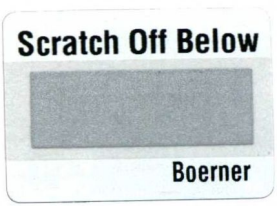

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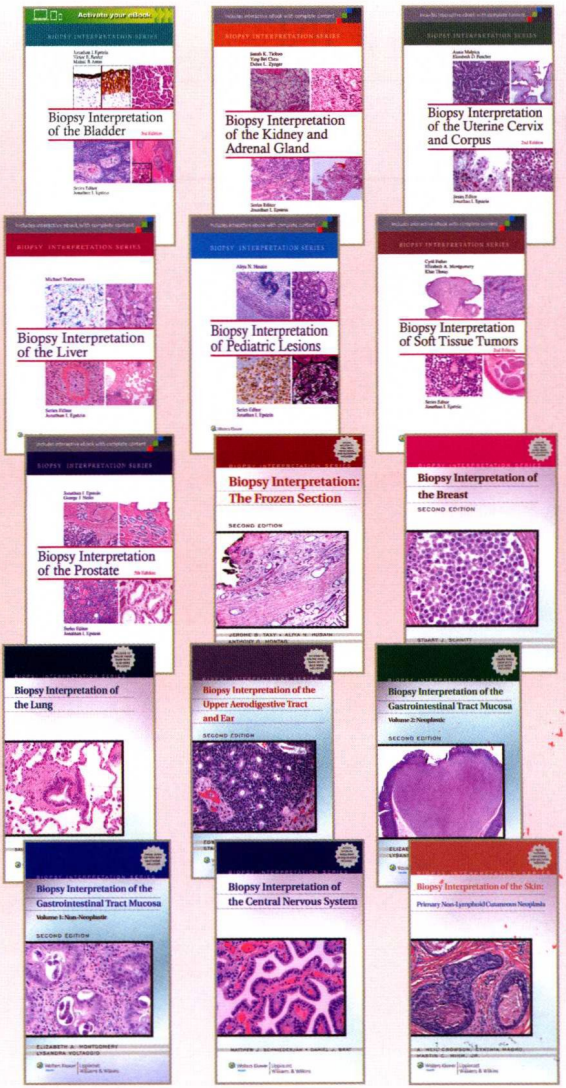

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DEDICATION

This book is dedicated to our teachers, colleagues, students, and particularly the many patients who have taught us about mechanisms of thyroid disease. We thank our families for their support as we pursue the goal of improving thyroid diagnosis for the patients of the future.

PREFACE

The thyroid gland is the site of frequent and common pathological processes that result in clinical manifestations. Because of its location in the anterior neck, pathological processes that result in glandular enlargement create masses that can be palpable or even visually conspicuous. The functional effects of hormone hyper- or hyposecretion create clinical scenarios that prompt investigation. The increasing application of ultrasound as a noninvasive, office-based, low-risk technique has increased the prevalence of clinically detected thyroid lesions, and patients with thyroid disorders undergo biopsy as a mainstay of diagnosis. While thyroid pathology is common, its interpretation is one of the most controversial in pathology. Nevertheless, the accurate evaluation of thyroid specimens is critical to the management of patients with thyroid disorders.

This book provides an approach to the interpretation of thyroid biopsies based on the patterns of thyroid lesions. In different practices, cytologic and histologic biopsies are performed; each has advantages and disadvantages that are reviewed. The text includes discussions of normal structure and function, the various techniques that are used to obtain, process and interpret biopsies, as well as the diagnostic criteria that are applied to the various pathological disorders of the thyroid. We review the application of ancillary tools including histologic stains, immunohistochemical localization of antigens, flow cytometric studies to classify cell types and determine ploidy, and molecular diagnostics to identify gene mutations and rearrangements. The indications and applications of these various techniques are discussed.

We hope that the reader will find this book to be a practical and accessible educational tool to guide the practicing diagnostic pathologist through the interpretation of biopsies of the thyroid that can be challenging and complex.

CONTENTS

1

INTRODUCTION

The thyroid gland is a butterfly-shaped gland in the anterior inferior neck. It is readily palpable and even visible in the slender patient. It is a source of common pathology. The most common problems that develop in the thyroid include:

- Hypothyroidism
- Hyperthyroidism
- Thyroiditis
- Goiter
- Thyroid nodules

An estimated 27 million Americans have thyroid disease, and more than half are undiagnosed. Women are at the greatest risk, developing thyroid problems seven times more often than men. A woman faces as high as a one-in-five chance of developing thyroid problems during her lifetime, a risk that increases with age and for those with a family history of thyroid problems [1,2].

The majority of patients with hypo- or hyperthyroidism have functional disease that is not the subject of biopsy. These patients are diagnosed with biochemical tests and treated accordingly. However, knowledge of the functional status of the thyroid is critical to the correct interpretation of biopsies, since the changes that underlie the functional alterations impact on the structure of the gland.

The majority of biopsies are used to classify nodules in the gland. These may arise in the setting of nodular goiter or thyroiditis, or they may be solitary neoplasms.

Thyroid nodules are extremely common in the general population [3]. The prevalence varies in different populations and with the methods used to detect nodules. Nodules increase in incidence with age; they are more common in women and in populations with iodine deficiency. It has been estimated that 2% to 6% of the population has a nodule identified on palpation, and variable rates from 19% to 67% have a lesion that is found with ultrasound [4,5]. Autopsy studies report thyroid nodules in up to 65% of cases [4]. Multiple nodules are more common than solitary nodules, and the incidence of malignancy may be lower in patients with multiple nodules than in solitary nodules, but

this appears to be true only outside the United States and in areas of iodine deficiency [6].

The incidence of thyroid cancer has increased substantially in many countries during the past two decades [7–9]. Indeed, several studies have shown that up to one-third of thyroid glands at autopsy contain an incidental papillary microcarcinoma [10,11]; however, most of these lesions are and will remain asymptomatic and therefore do not require aggressive management. The increase in incidence has not been associated with a concomitant increase in mortality, proving this point. The implementation of cancer screening in South Korea provided evidence that overdiagnosis of thyroid cancer due to aggressive ultrasonographic screening is a cause for concern [12]. Therefore, the role of biopsy should be clearly identified as of relevance for clinically significant pathology.

The differential diagnosis of the thyroid nodule includes numerous entities, nonneoplastic and neoplastic and benign and malignant [13–16]. The pathologist has an important role to play in their evaluation through biopsy. But, what exactly constitutes a "biopsy" of the thyroid? Historically, this consisted of a lobectomy or hemithyroidectomy. Certainly, a number of lobectomies and hemithyroidectomies are required for definitive classification of a thyroid nodule of clinical suspicion. However, fine needle aspiration (FNA) and needle core biopsy have taken prominent roles in the preoperative assessment of thyroid lesions prior to surgical resection. Therefore, our discussion will attempt to explore the pathological findings seen in each of these samples: FNA, needle core biopsy, and surgical resection specimens.

While some of these entities are readily diagnosed based on specific features seen in a routine slide stained with conventional dyes, the morphologic evaluation of many of these lesions is fraught with controversy and diagnostic criteria are highly variable from pathologist to pathologist [17]. Nevertheless, histology remains the gold standard against which we measure outcomes of cytology, intraoperative consultations, molecular and other studies, and it represents the basis on which we determine patient management and the efficacy of various therapies. Unfortunately, no current morphologic criteria provide adequate information to predict outcome for many follicular nodules of thyroid. However, the diagnosis of most other lesions is accurate and plays an important role in determining appropriate management and outcome.

Advances in our understanding of the molecular basis of thyroid cancer allows more accurate characterization of specific subtypes of neoplasia and malignancy [18], and this information is being applied to material obtained at FNA biopsy [19,20]. This should further enhance the usefulness of this technique and better guide the management of patients with a thyroid nodule. The new knowledge has also provided novel targets for therapy and predictive genetic screens for patients with genetic predisposition to certain endocrine neoplasia syndromes.

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2

THE NORMAL THYROID

The normal adult thyroid gland weighs 16 to 25 g and is composed of two lateral lobes and an isthmus (Fig. 2.1). Because it derives from an evagination of the base of the tongue and migrates down the anterior neck, there is usually a thin remnant of the track of descent known as the pyramidal lobe at the superior end of the isthmus [1]. In the normal mature gland, each lobe has a pointed superior pole and a blunt, rounded inferior pole. Each lobe measures approximately 4 cm in the superoinferior plane, 2.5 cm in the mediolateral plane, and 2 cm in the anteroposterior plane [2]. The isthmus is more variable in size; it usually measures from 1 to 2 cm mediolaterally but can vary from 0.5 to 2 cm in the superoinferior plane. There are usually several small lymph nodes around the isthmus. The dominant node is known as the "delphian node" because of its prophetic role in patients with thyroid cancer.

Lobules of thyroid parenchyma are composed of follicles. The lobulation is subtle, but the fibroconnective tissue that define the lobules is important to recognize (Fig. 2.2, e-Figs. 2.1 and 2.2), since they are lost in neoplastic proliferations and they can be accentuated in inflammatory lesions.

The follicles of the normal gland are lined by follicular epithelial cells that are heterogeneous. They are mainly cuboidal cells (Fig. 2.3, e-Fig. 2.3), the most active are columnar cells with basal nuclei, and some follicles have areas of flat attenuated epithelium. The follicular cells maintain adhesion to the basement membrane surrounding the follicle. The follicles contain thyroglobulin that is usually stored as pale and homogeneous colloid. Colloid often retracts from the surrounding tissue during fixation, but when it is being actively resorbed for thyroid hormone synthesis, the proteolytic cleavage induced by the resorbing cell causes a peculiar scalloping effect (Fig. 2.4, e-Fig. 2.4).

Scattered within this parenchyma at the junction of the upper third and lower two-thirds of each lateral lobe are the C cells that produce calcitonin [3,4]. These cells were initially described by Karl Hürthle in 1904 [5], although his name has come to be associated with something completely different, oncocytic follicular cells. C cells are so called because they have clear cytoplasm and because they make calcitonin. These neuroendocrine cells are difficult to recognize on routine sections stained with hematoxylin and eosin (e-Fig. 2.5) but are readily identified by calcitonin immunohistochemistry (Fig. 2.5, e-Fig. 2.6). They are usually isolated as single cells within

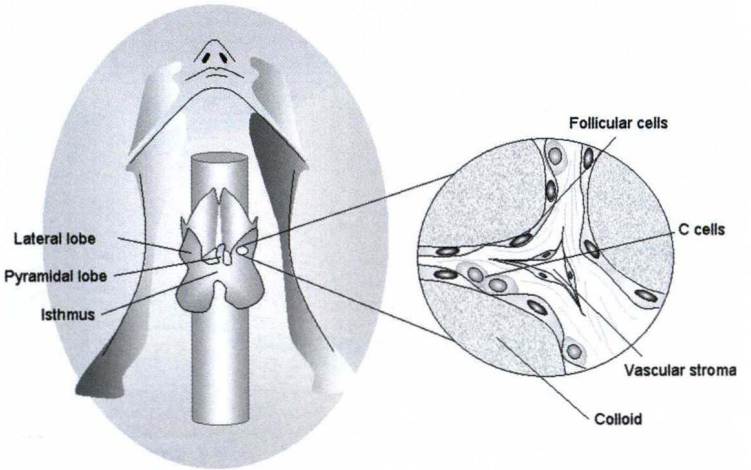

FIGURE 2.1 **The normal thyroid gland.** The normal gland is composed of a left and right lobe connected by an isthmus from which a variably sized pyramidal lobe may take origin. The gland itself is subdivided into ill-defined lobules by a fine fibrovascular stroma (*inset* and Fig. 2.2). Microscopically, the lobules are composed of follicles filled with colloid and lined by a single layer of follicular epithelial cells (*inset*). C cells (or parafollicular cells) are difficult to identify on routine hematoxylin and eosin staining but lie adjacent to the basement membrane of follicles in the middle third of the right and left lobes (see Fig. 2.5).

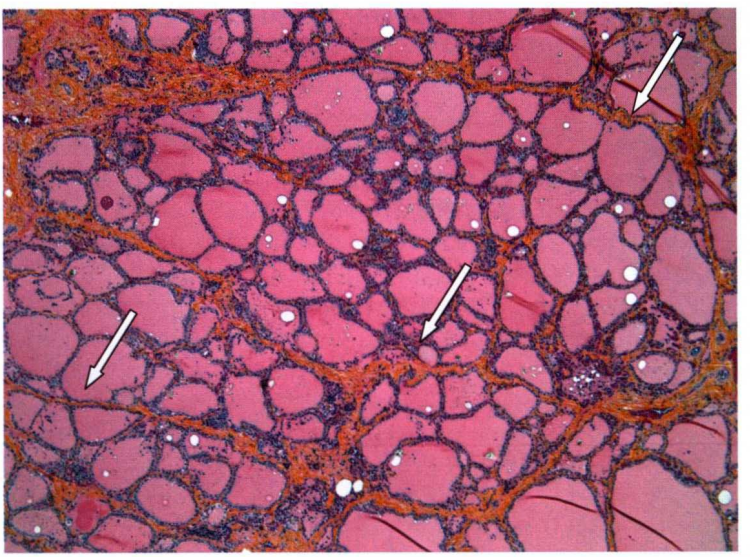

FIGURE 2.2 **Normal lobular architecture of the thyroid gland.** The normal thyroid gland is divided into lobules composed of variably sized follicles separated by delicate bands of fibrovascular tissue (*white arrows*). These fibrovascular septae are lost in neoplastic proliferations and are frequently exaggerated in inflammatory lesions (hematoxylin, phloxine, and saffron stain).

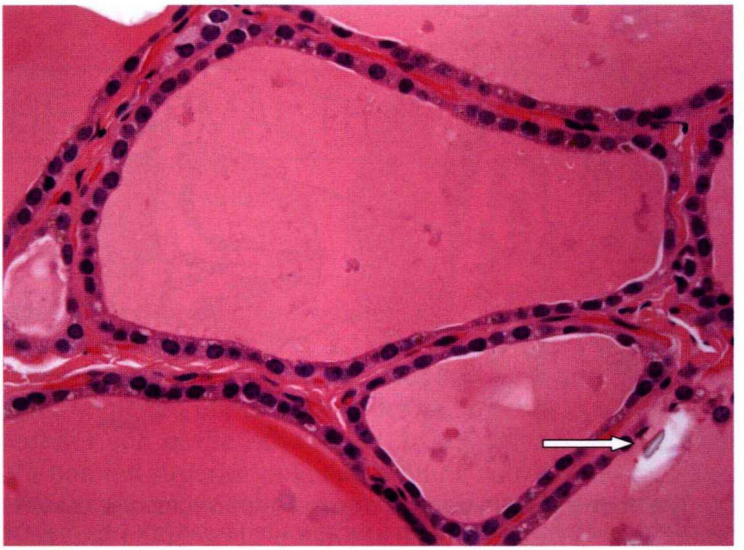

FIGURE 2.3 **Normal follicular histology.** The normal follicular epithelium presents as a single layer of cells closely apposed to their basement membrane with a central pool of colloid. The epithelium may have a variety of appearances. Commonly, the epithelium is seen as cuboidal cells as in this illustration, but when active, the epithelial cells are columnar with basally oriented nuclei; when atrophic, they are flattened, attenuated epithelium. Notice the presence of calcium oxalate crystals within the colloid (*white arrow*) (hematoxylin and eosin stain).

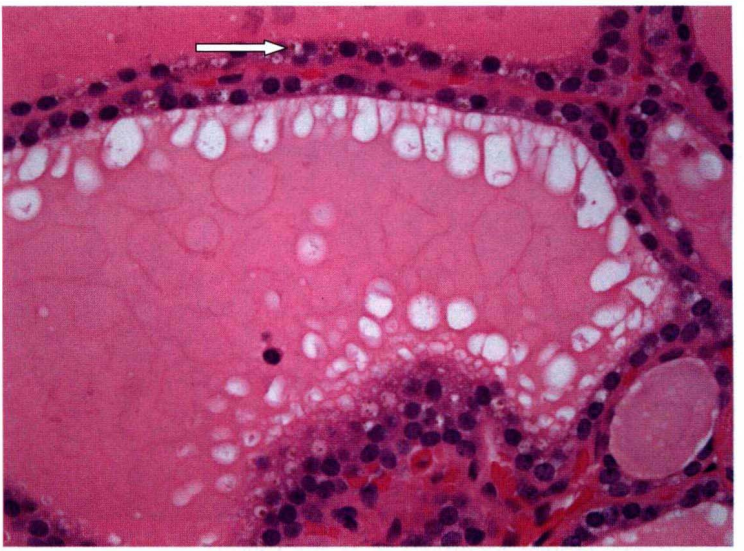

FIGURE 2.4 **Scalloping of colloid.** Proteolytic cleavage of the colloid by resorbing epithelial cells generates a peculiar scalloped effect on the adjacent colloid. Notice the presence of lipofuscin in the cytoplasm of a number of the epithelial cells (*white arrow*) (hematoxylin and eosin stain).

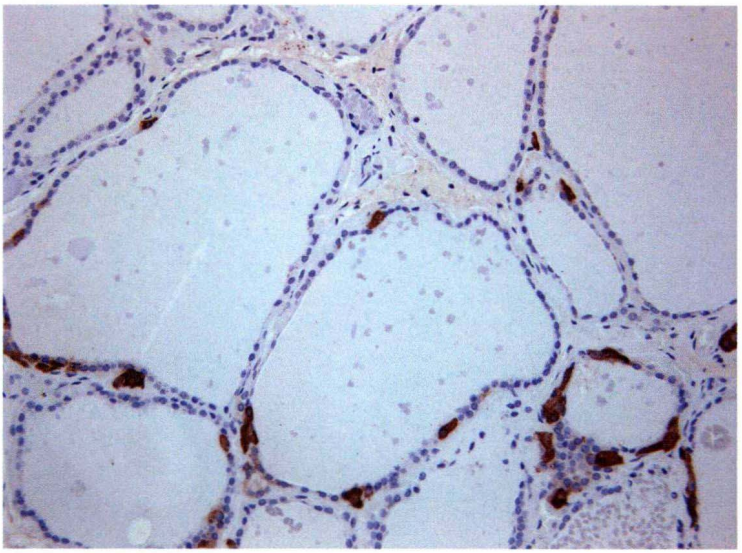

FIGURE 2.5 **C cells (parafollicular cells) in the normal thyroid gland.** The C cells of the normal thyroid are difficult to appreciate on routine staining. In this immunohistochemical stain for calcitonin, the C cells are highlighted, and their position adjacent to the basement membrane of the follicles becomes apparent (calcitonin stain).

the basement membrane of a follicle, but they may form small cluster of two or three cells. They are not usually found in the isthmus or lower poles of the lobes.

Also found at the junction of the upper pole and lower two-thirds of each lobe are other vestigial remnants of the ultimobranchial body, known as "solid cell nests" or "ultimobranchial body rests" (Fig. 2.6, e-Figs. 2.7 and 2.8) [6–10]. These solid nests and cords are composed of polygonal, epidermoid, or transitional cells with focal cystic areas that may contain eosinophilic material. Occasionally, there is evidence of mucin production. They can be confused with papillary microcarcinomas, and their importance is in recognition to avoid a false diagnosis of malignancy.

Other structures that can be found in the thyroid include parathyroid glands and tissue, normal thymus, salivary gland remnants, and occasional teratomatous elements such as cartilage. The gland is richly vascularized but only weakly innervated, mainly around vascular channels, with the exception of the recurrent laryngeal nerve that is embedded in the posterior surface of the gland.

The subject of the thyroid capsule is an important one that rarely receives attention. Surgeons often refer to the thyroid capsule when dissecting the gland, and reference is made to invasion of the thyroid capsule in discussions of thyroid malignancies. However, there is no anatomical structure that could be construed as a capsule of the gland [11]. Indeed, the parenchyma of the thyroid gland contains fibroconnective tissue that

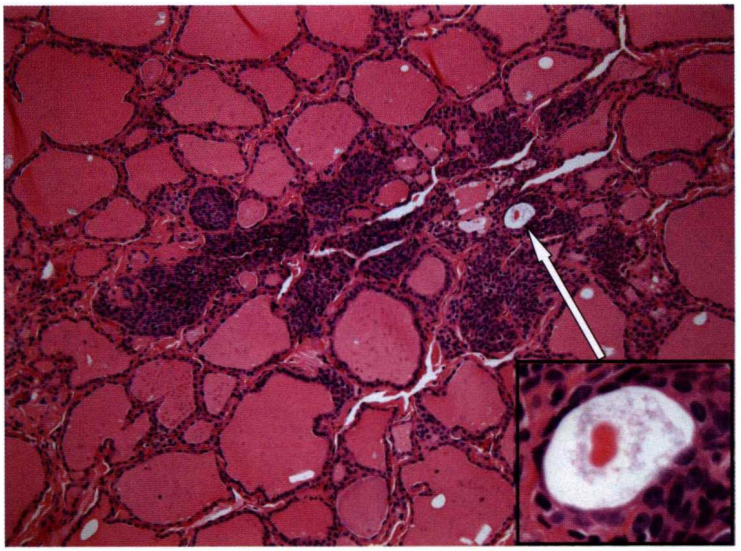

FIGURE 2.6 **Solid cell nests.** Solid cell nests represent vestigial remnants of the ultimobranchial body. The cells frequently display a squamoid or transitional morphology with focal cyst formation containing eosinophilic material (*white arrow* with *inset*). They may exhibit mucin production. It is important to distinguish these structures from microcarcinomas (hematoxylin and eosin stain).

delineated lobules, and there is often fat within the gland; the stroma contains nerves, and the recurrent laryngeal nerve penetrates into the substance of the gland. In addition, as evidenced by the pathology of sporadic nodular goiter, there are usually many embryological rests of thyroid tissue throughout the soft tissue of the neck outside the main body of the gland, and often along the path of descent from the base of tongue to the mediastinum [12]. These are not surrounded by a capsule and are usually separate from the gland itself, disproving the hypothesis of a "thyroid capsule." These anatomical features are important to recognize when defining the limits of growth that are implicated in "extrathyroidal extension" of thyroid carcinomas.

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