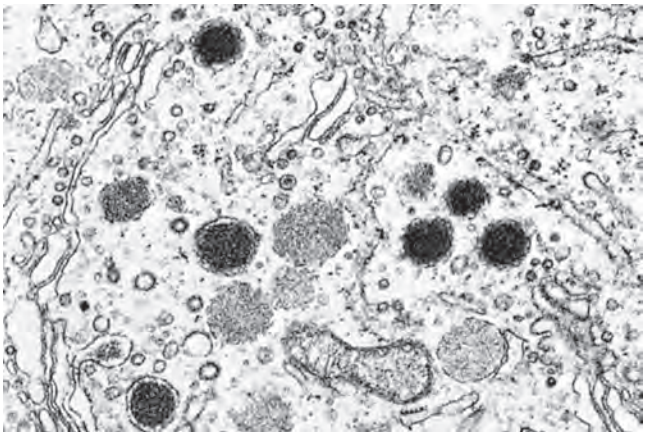

Figure 24-23 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory granules that are the sites of storage of calcitonin and other peptides.

parathyroid glands). Medullary carcinomas arising in the context of MEN-2B are generally more aggressive and metastasize more frequently than those occurring in patients with sporadic tumors, MEN-2A, or FMTC. As will be discussed later, asymptomatic MEN-2 patients carrying germline *RET* mutations are offered prophylactic thyroidectomy as early as possible to prevent the otherwise inevitable development of medullary carcinomas, the major risk factor for poor outcome in these individuals. Sometimes the only histologic finding in the resected thyroid of asymptomatic carriers is the presence of C-cell hyperplasia or small (<1 cm) "micromedullary" carcinomas. Several small-molecule inhibitors of RET tyrosine kinase have recently been developed, and are being tested in individuals with medullary carcinomas.

KEY CONCEPTS

Thyroid Neoplasms

- Most thyroid neoplasms manifest as *solitary thyroid nodules*; only 1% of all thyroid nodules are neoplastic.
- *Follicular adenomas* are the most common benign neoplasms, while papillary carcinoma is the most common malignancy.
- Multiple genetic pathways are involved in *thyroid carcinogenesis.* Some of the genetic abnormalities that are fairly unique to thyroid cancers include *PAX8/PPARG* fusion genes or mutations that activate RAS or PI-3K (in follicular carcinomas), chromosomal rearrangements involving the *RET* oncogene or mutations in *BRAF* (in papillary carcinomas), and mutations of *RET* (in medullary carcinomas).
- *Follicular adenomas and carcinomas* both are composed of well-differentiated follicular epithelial cells; the latter are distinguished by evidence of capsular and/or vascular invasion.
- *Papillary carcinomas* are recognized based on nuclear features (ground-glass nuclei, pseudoinclusions) even in the absence of papillae. Psammoma bodies are a characteristic feature of papillary cancers; these neoplasms often metastasize by way of lymphatics, but the prognosis is excellent.
- *Anaplastic carcinomas* are thought to arise by dedifferentiation of more differentiated neoplasms. They are highly aggressive, uniformly lethal cancers.
- *Medullary cancers* are neoplasms arising from the parafollicular C cells and can occur in either sporadic (70%) or familial (30%) settings. Multicentricity and C cell hyperplasia are features of familial cases. Amyloid deposits are a characteristic histologic finding.

Congenital Anomalies

Thyroglossal duct cyst is the most common clinically significant congenital anomaly of the thyroid. A sinus tract may persist as a vestige of the tubular development of the thyroid gland. Parts of this tube may be obliterated, leaving small segments to form cysts. These occur at any age and might not become evident until adult life. Mucinous, clear secretions may collect within the cysts to form either spherical masses or fusiform swellings, rarely over 2 to 3 cm in diameter, that present in the midline of the neck anterior to the trachea. Segments of the duct and cysts that occur high in the neck are lined by stratified squamous epithelium resembling the covering of the posterior portion of the tongue in the region of the foramen cecum. Anomalies that occur in the lower neck more proximal to the thyroid gland are lined by epithelium resembling the thyroidal acinar epithelium. Characteristically, subjacent to the lining epithelium, there is an intense lymphocytic infiltrate. Superimposed infection may convert these lesions into abscess cavities, and rarely, they give rise to cancers.

PARATHYROID GLANDS

The four parathyroid glands are composed of two cell types: chief cells and oxyphil cells. Chief cells predominate; they are are polygonal, 12 to 20 μm in diameter, and have central, round, uniform nuclei and light to dark pink cytoplasm. Sometimes these cells take on a *water-clear* appearance due to the presence of large amounts of cytoplasmic glycogen. In addition, they have secretory granules containing *parathyroid hormone (PTH)*. *Oxyphil cells* and transitional oxyphils are found throughout the normal parathyroid, either singly or in small clusters. They are slightly larger than the chief cells, have acidophilic cytoplasm, and are tightly packed with mitochondria. Glycogen granules are also present in these cells, but secretory granules are sparse or absent. In early infancy and childhood, the parathyroid glands are composed almost entirely of solid sheets of chief cells. The amount of stromal fat increases up to age 25, reaching a maximum of approximately 30% of the gland, and then plateaus.

The function of the parathyroid glands is to regulate calcium homeostasis. The activity of the parathyroid