loss-of-function mutations in the *TSC1* or *TSC2* tumor suppressor genes. Tuberous sclerosis is characterized by lesions of the cerebral cortex that produce epilepsy and mental retardation, a variety of skin abnormalities, and unusual benign tumors at other sites, such as the heart (Chapters 12 and 28). The clinical importance of angiomyolipoma is due largely to their susceptibility to spontaneous hemorrhage.

Oncocytoma

This is an epithelial neoplasm composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli. It is thought to arise from the intercalated cells of collecting ducts, and accounts for approximately 5% to 15% of renal neoplasms. Ultrastructurally the eosinophilic cells have numerous mitochondria. In gross appearance, the tumors are tan or mahogany brown, relatively homogeneous, and usually well encapsulated with a central scar in one-third of cases. However, they may achieve a large size (up to 12 cm in diameter). There are some familial cases in which these tumors are multicentric rather than solitary.

Malignant Neoplasms

Renal Cell Carcinoma

Renal cell carcinomas represent about 3% of all newly diagnosed cancers in the United States and account for 85% of renal cancers in adults. There are approximately 65,000 new cases per year and 13,000 deaths from the disease. The tumors occur most often in older individuals, usually in the sixth and seventh decades of life, and show a 2:1 male preponderance.

Epidemiology. Tobacco is the most significant risk factor. Cigarette smokers have double the incidence of renal cell carcinoma, and pipe and cigar smokers are also more susceptible. An international study has identified additional risk factors, including obesity (particularly in women); hypertension; unopposed estrogen therapy; and exposure to asbestos, petroleum products, and heavy metals. There is also an increased risk in patients with end-stage renal disease, chronic kidney disease, acquired cystic disease (see earlier) and tuberous sclerosis.

Most renal cancer is sporadic, but unusual forms of autosomal dominant familial cancers occur, usually in younger individuals. Although they account for only 4% of renal cancers, familial variants have been instructive in understanding renal carcinogenesis.

- *Von Hippel-Lindau (VHL) syndrome:* Half to two thirds of individuals with VHL (nearly all, if they live long enough) (Chapter 28) develop renal cysts and bilateral, often multiple, renal cell carcinomas. *Current studies implicate the VHL gene in the development of both familial and sporadic clear cell carcinomas.*
- *Hereditary leiomyomatosis and renal cell cancer syndrome:* This autosomal dominant disease is caused by mutations of the *FH* gene, which expresses fumarate hydratase, and is characterized by cutaneous and uterine leiomyomata and an aggressive type of papillary carcinoma with increased propensity for metastatic spread.
- *Hereditary papillary carcinoma*. This autosomal dominant form is manifested by multiple bilateral tumors with papillary histology. These tumors show a series of cytogenetic abnormalities and, as will be described, mutations in the *MET* proto-oncogene.
- *Birt-Hogg-Dubé syndrome:* The autosomal dominant inheritance pattern of this disease is due to mutations involving the *BHD* gene, which expresses folliculin. The syndrome features a constellation of skin (fibrofolliculomas, trichodiscomas, and acrochordons), pulmonary (cysts or blebs), and renal tumors with a wide range of histologic subtypes.

Classification of renal cell carcinoma: histology, cytogenetics, and genetics. The classification of renal cell carcinoma is based on correlative cytogenetic, genetic, and histologic studies of both familial and sporadic tumors. The major types of tumor are as follows (Fig. 20-50):

- *Clear cell carcinoma.* This is the most common type, accounting for 70% to 80% of renal cell cancers. The tumors are made up of cells with clear or granular cytoplasm and are *nonpapillary*. They can be familial, but in most cases (95%) are sporadic. In 98% of these tumors, whether familial, sporadic, or associated with VHL syndrome, there is loss of sequences on the short arm of chromosome 3. The deleted region harbors the *VHL* gene (3p25.3). A second nondeleted allele of the *VHL* gene shows somatic mutations or hypermethylation-induced inactivation in up to 80% of clear cell cancers, indicating that the *VHL* gene acts as a tumor suppressor gene in both sporadic and familial cancers (Chapter 7). The *VHL* gene encodes a protein that is part of a ubiquitin ligase complex involved in targeting other proteins for degradation. Important among the targets of the VHL protein is the transcription factor hypoxia-inducible factor-1 (HIF-1). When *VHL* is inactive, HIF-1 levels remain high, even under normoxic conditions, causing inappropriate expression of a number of genes that are turned on by HIF. These include genes that promote angiogenesis, such as VEGF, and genes that stimulate cell growth, such as insulin-like growth factor-1 (IGF-1). In addition, HIF collaborates in complex ways with the oncogenic factor MYC to "reprogram" cellular metabolism in a way that favors growth. Deep sequencing of renal carcinoma genomes has revealed frequent mutations in a number of genes that regulate histone modifications, indicating that dysregulation of the epigenome also has an important role in clear cell carcinoma.
- *Papillary carcinoma* accounts for 10% to 15% of renal cancers. It is characterized by a papillary growth pattern and also occurs in both familial and sporadic forms. These tumors are not associated with 3p deletions. The most common cytogenetic abnormalities are trisomies 7 and 17 and loss of Y in male patients in the sporadic form, and trisomy 7 in the familial form. The gene on chromosome 7 for the familial form has been mapped to *MET*, a proto-oncogene that encodes the tyrosine kinase receptor for *hepatocyte growth factor*. *MET* is also mutated in a small proportion of sporadic papillary carcinomas. Described in Chapter 3, hepatocyte growth factor (also called *scatter factor*) mediates growth, cell