medical management of the seizures fails. Elsewhere in the body, renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis and cardiac rhabdomyomas develop over childhood and adolescence. Cysts may be found at various sites, including the liver, kidneys, and pancreas. Cutaneous lesions include angiofibromas, localized leathery thickenings (shagreen patches), hypopigmented areas (ash-leaf patches), and subungual fibromas.

One tuberous sclerosis locus (*TSC1*) is found on chromosome 9q34, and encodes a protein known as hamartin; the more commonly mutated tuberous sclerosis locus (*TSC2*) is at 16p13.3 and encodes tuberin. These two proteins associate to form a complex that inhibits the kinase mTOR, which is a key regulator of protein synthesis and other aspects of anabolic metabolism. Of note, mTOR controls cell size, and the tumors associated with tuberous sclerosis are remarkable for having voluminous amounts of cytoplasm, particularly giant-cell astrocytomas in the CNS, and cardiac rhabdomyomas. Cortical and subependymal tubers are associated with an intact copy of the wild-type allele, while in subependymal giant-cell astrocytomas there is biallelic loss. Treatment is symptomatic, including anticonvulsant therapy for control of seizures. Treatment of patients with mTOR inhibitors has resulted in some clinical improvement.

MORPHOLOGY

Cortical hamartomas of tuberous sclerosis are firm areas of the cortex that, in contrast to the softer adjacent cortex, have been likened to potatoes, hence the appellation "tubers." These hamartomas are composed of haphazardly arranged neurons that lack the normal laminar organization of neocortex. In addition, some large cells have appearances intermediate between glia and neurons (large vesicular nuclei with nucleoli, resembling neurons, and abundant eosinophilic cytoplasm resembling gemistocytic astrocytes) and often express intermediate filaments of both neuronal (neurofilament) and glial (GFAP) types. Consistent with the preservation of the wild-type allele, these cells usually stain for both tuberin and hamartin. Similar hamartomatous features are present in the subependymal nodules, where the large astrocyte-like cells cluster beneath the ventricular surface. These multiple droplike masses that bulge into the ventricular system gave rise to the term *candle-guttering*. In subependymal areas a tumor unique to tuberous sclerosis, subependymal giant-cell astrocytoma, occurs, which is marked by having very large amounts of eosinophilic cytoplasm.

Von Hippel-Lindau Disease

Individuals with this autosomal dominant disease develop hemangioblastomas of the CNS and cysts involving the pancreas, liver, and kidneys, and have a propensity to develop renal cell carcinoma and pheochromocytoma. Hemangioblastomas are most common in the cerebellum and retina, but may also occur in other locations in the CNS. The disease frequency is 1 in 30,000 to 40,000.

The gene associated with von Hippel-Lindau disease (*VHL*), a tumor suppressor gene, is located on chromosome 3p25.3 and encodes a protein (VHL) that, among its other functions, is a component of a ubiquitin ligase complex that down-regulates hypoxia-induced factor 1 (HIF-1), a transcription factor involved in regulating expression of vascular endothelial growth factor, erythropoietin, and other growth factors. It is the dysregulation of erythropoietin that is responsible for the polycythemia observed in association with hemangioblastomas in about 10% of cases. HIF also regulates the expression of genes that control cellular metabolism and cell growth, activities that likely contribute to tumor formation. Why particular cell types are uniquely susceptible to transformation by HIF hyperactivity, however, remains uncertain.

MORPHOLOGY

Hemangioblastomas are highly vascular neoplasms that occur as a mural nodule associated with a large fluid-filled cyst. The lesion consists of variable proportions of capillary-size or somewhat larger thin-walled vessels and intervening stromal cells of uncertain histogenesis characterized by vacuolated, lightly PAS-positive, lipid-rich cytoplasm. The stromal cells are of uncertain origin but can be demonstrated to express inhibin by immunohistochemistry. These are the cells that show the presence of a second "hit" in the previously normal *VHL* allele, and on this basis they are considered to be the neoplastic element in hemangioblastoma.

Therapy is directed at the symptomatic neoplasms, including resection of the cerebellar hemangioblastomas and laser therapy for retinal hemangioblastomas.

Neurofibromatosis

Two autosomal dominant disorders, NF1 and NF2, are familial tumor syndromes characterized by tumors of the PNS and CNS. NF1 is the more common, with a frequency of 1 in 3,000, and is characterized by neurofibromas of peripheral nerve, gliomas of the optic nerve, pigmented nodules of the iris *(Lisch nodules)*, and cutaneous hyperpigmented macules *(café au lait spots)*. NF2 is most commonly characterized by bilateral schwannomas of the vestibulocochlear nerves (cranial nerve VIII) and multiple meningiomas. Gliomas may also occur in these patients; typically these are ependymomas of the spinal cord. This disorder is much less common than NF1, having a frequency of 1 in 40,000 to 50,000. Both types of neurofibromatosis are discussed in more detail in Chapter 27.

KEY CONCEPTS

Tumors

- Tumors of the CNS may arise from the cells of the coverings (meningiomas), the brain (gliomas, neuronal tumors, choroid plexus tumors), or other CNS cell populations (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (metastases).
- Even low-grade or benign tumors can have poor clinical outcomes, depending on where they occur in the brain.
- Distinct types of tumors affect specific brain regions (e.g., cerebellum for medulloblastoma, an intraventricular location for central neurocytoma) and specific age populations (medulloblastoma and pilocytic astrocytomas in pediatric age groups, and glioblastoma and lymphoma in older patients).