remaining life. Metastases to the epidural or subdural space can cause spinal cord compression, which requires emergency treatment.

MORPHOLOGY

Intraparenchymal metastases form sharply demarcated masses, often at the junction of gray and white matter, usually surrounded by a zone of edema. The boundary between tumor and brain parenchyma is usually well-defined microscopically; melanoma does not always follow this rule and individual cells may invade the brain. Nodules of tumor, often with central areas of necrosis, are surrounded by reactive gliosis. Meningeal carcinomatosis, with tumor nodules studding the surface of the brain, spinal cord, and intradural nerve roots, is most commonly associated with carcinoma of the lung and the breast.

Paraneoplastic Syndromes

In addition to the direct and localized effects produced by metastases, patients with diverse tumors develop *paraneoplastic syndromes* that involve the peripheral and/or central nervous systems, sometimes even preceding the clinical recognition of the malignant neoplasm. A variety of clinical paraneoplastic syndromes have been described. An underlying mechanism of these syndromes appears to be the development of an immune response against tumor antigens that cross-react with antigens in the central or peripheral nervous systems. Certain malignancies are typically associated with a particular clinical syndrome. The circulating antibodies and target antigens are in the process of being defined in some of the clinical syndromes. Illustrative examples of these are described below:

- *Subacute cerebellar degeneration* is associated with destruction of Purkinje cells, gliosis, and a mild chronic inflammatory cell infiltrate. One group of these patients has a circulating PCA-1 antibody (anti-Yo) that recognizes cerebellar Purkinje cells; this antibody occurs predominantly in women with ovarian, uterine, or breast carcinoma.
- *Limbic encephalitis* is characterized by subacute dementia and marked by perivascular inflammatory cuffs, microglial nodules, some neuronal loss, and gliosis, most evident in the anterior and medial portions of the temporal lobe; the microscopic picture resembles that of an infectious process. A comparable process involving the brainstem can be seen in isolation or together with limbic system involvement. Some of these patients have a circulating ANNA-1 antibody (anti-Hu) that recognizes neuronal nuclei in the central and peripheral nervous systems; ANNA-1 is most commonly associated with small cell carcinoma of the lung. Another group of these patients has a circulating antibody that recognizes the NMDA receptor and cross-reacts with hippocampal neurons. Originally identified in women with ovarian teratomas, the same clinical syndrome is now also recognized in a small proportion of patients with sporadic encephalitis. A third group of patients has a circulating VGKC-complex antibody that recognizes the voltage-gated potassium channel; the presence of this antibody may be associated with peripheral neuropathy as well. It is important to note that in many cases of limbic encephalitis, the syndrome appears before any malignancy is suspected and as such triggers the search for a tumor elsewhere in the body.
- *Eye movement disorders*, most commonly opsoclonus, may be found, often in association with other evidence of cerebellar and brainstem dysfunction. In children this is most commonly associated with neuroblastoma and is often accompanied by myoclonus.

The peripheral nervous system can also be affected:

- *Subacute sensory neuropathy* may be found in association with limbic encephalitis or in isolation. It is marked by loss of sensory neurons from dorsal root ganglia, in association with lymphocytic inflammation.
- *Lambert-Eaton myasthenic syndrome* is caused by antibodies against the voltage-gated calcium channel in the presynaptic elements of the neuromuscular junction. This can be seen in the absence of malignancy as well.

For some paraneoplastic syndromes, there is evidence that immunotherapy (removal of circulating antibodies and immunosuppression) and tumor removal result in clinical improvement. In general, those clinical syndromes with plasma membrane-reactive antibodies (e.g., VGKC and NMDAR) respond to immunotherapy better than those associated with intracellular antigens (e.g., ANNA-1 and PCA-1).

Familial Tumor Syndromes

A number of inherited diseases are associated with the occurrence of tumors (Chapter 7). In several of these, tumors of the nervous system are a prominent aspect of the disease and these are discussed below. Other syndromes include tumors of the CNS as part of their spectrum, but the bulk of disease burden lies elsewhere.

- *Cowden syndrome:* Dysplastic gangliogliocytoma of the cerebellum (Lhermitte-Duclos disease), caused by mutations in *PTEN* resulting in PI3K/AKT signaling pathway activity (Chapter 7)
- *Li-Fraumeni syndrome:* Medulloblastomas, caused by mutations in *TP53* (Chapter 7)
- *Turcot syndrome:* Medulloblastoma or glioblastoma, caused by mutations in *APC* or mismatch repair genes (as for familial colon cancer; Chapter 17)
- *Gorlin syndrome:* Medulloblastoma, caused by mutations in the *PTCH* gene resulting in up-regulation of sonic hedgehog signaling pathways (Chapter 25).

Tuberous Sclerosis Complex

Tuberous sclerosis is an autosomal dominant syndrome occurring at a frequency of approximately 1 in 6000 births. It is characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues; the most frequent clinical manifestations are seizures, autism, and mental retardation. Hamartomas within the CNS take the form of cortical tubers and subependymal nodules; subependymal giant-cell astrocytomas are low grade neoplasms that appear to develop from the hamartomatous nodules in the same location. Cortical tubers are often epileptogenic, and surgical resection can be beneficial when