- **Myoclonic epilepsy and ragged red fibers (MERRF)** is a maternally transmitted disease in which affected individuals have myoclonus, a seizure disorder, and evidence of a myopathy. The myopathy is often characterized by ragged red fibers on muscle biopsy (Chapter 27). Ataxia, associated with neuronal loss from the cerebellar system (including the inferior olive in the medulla, cerebellar cortex, and deep nuclei), is also a common component. Most cases of MERRF are associated with mutations in tRNAs other that the specific tRNA mutation associated with MELAS.
- **Leigh syndrome** is a disease of infancy characterized by lactic acidemia, arrest of psychomotor development, feeding problems, seizures, extraocular palsies, and weakness with hypotonia. Death usually occurs within 1 to 2 years. On histologic examination there are multifocal regions of destruction of brain tissue associated with a spongiform appearance and proliferation of blood vessels. Brainstem nuclei, thalamus, and hypothalamus are typically involved, usually in a symmetric manner. A wide spectrum of mutations has been identified as causing Leigh syndrome, including both nuclear and mitochondrial DNA mutations involving components of oxidative phosphorylation complexes and proteins involved in the assembly the electron transport chain.

KEY CONCEPTS

Genetic Metabolic Diseases

- Mutations that disrupt metabolic or synthetic pathways can affect the nervous system. These pathways can involve general cellular processes or those that are relatively specific to the nervous system.
- Diseases with earlier onset are typically more severe in the degree of damage and pace of illness.
- Neuronal storage diseases are commonly autosomal recessive disorders. The characteristic finding is usually accumulation of material within neurons, along with evidence of neuronal death. Seizures are common components of the clinical presentation, along with loss of cognitive function.
- Leukodystrophies are also typically autosomal recessive, with disruption of the synthesis or turnover of myelin components. Motor dysfunction, including spasticity, hypertonia or hypotonia and ataxia are common aspects of the clinical presentation.
- Mitochondrial encephalomyopathies are a pleiotropic set of disorders that involves neurons as well as tissues outside of the nervous system. These can be associated with mutations in the nuclear as well as the mitochondrial genome.

Toxic and Acquired Metabolic Diseases

Toxic and acquired metabolic diseases are relatively common causes of neurologic illnesses. These diseases are discussed in Chapter 9; only aspects that are relevant to CNS pathology are presented here.

Vitamin Deficiencies

Thiamine (Vitamin B_1) Deficiency

Wernicke encephalopathy is caused by thiamine deficiency and is characterized by the acute appearance of a combination of psychotic symptoms and ophthalmoplegia. The acute symptoms are reversible when treated with thiamine. However, if unrecognized and untreated, they may be followed by a prolonged and largely irreversible condition, called *Korsakoff syndrome,* that is characterized clinically by disturbances of short term memory and confabulation. The syndrome is particularly common in the setting of chronic alcoholism, but it may also be encountered in individuals with thiamine deficiency resulting from gastric disorders, including carcinoma, chronic gastritis, or persistent vomiting.

MORPHOLOGY

Wernicke encephalopathy is characterized by foci of hemorrhage and necrosis in the mamillary bodies and the walls of the third and fourth ventricles. Early lesions show dilated capillaries with prominent endothelial cells. Subsequently, the capillaries become leaky, producing hemorrhagic areas. With time, there is infiltration of macrophages and development of a cystic space with hemosiderin-laden macrophages. These chronic lesions predominate in individuals with Korsakoff syndrome. Lesions in the dorsomedial nucleus of the thalamus seem to be the best correlate of the memory disturbance and confabulation.

Vitamin B_{12} Deficiency

Subacute combined degeneration of the spinal cord is caused by deficiency of vitamin B_{12} resulting in degeneration of both ascending and descending spinal tracts. The lesions are caused by a defect in myelin formation; the mechanism of this defect is not known. Symptoms may present over a few weeks, initially with bilaterally symmetrical numbness, tingling, and slight ataxia in the lower extremities, but may progress to include spastic weakness of the lower extremities. Complete paraplegia may occur, usually only later in the course. With prompt vitamin replacement therapy, clinical improvement occurs; however, once complete paraplegia has developed, recovery is poor. On microscopic examination, there is swelling of myelin layers, producing vacuoles, in the affected tracts; with time, axons degenerate as well. In the early stages of the disease the mid-thoracic level of the spinal cord is affected, from where the process may extend proximally and distally.

Neurologic Sequelae of Metabolic Disturbances

Hypoglycemia

Since the brain requires glucose and oxygen for its energy production, the cellular effects of diminished glucose resemble those of oxygen deprivation, described earlier. Some regions of the brain are more sensitive to hypoglycemia than are others. Glucose deprivation initially leads to selective injury to large pyramidal neurons of the cerebral cortex, which, if severe, may result in pseudolaminar