necrosis of the cortex, predominantly involving deep layers. The hippocampus is also vulnerable to glucose depletion and may show a marked loss of pyramidal neurons in Sommer sector (area CA1) of the hippocampus. Purkinje cells of the cerebellum are also sensitive to hypoglycemia, although to a lesser extent than to hypoxia. If the level and duration of hypoglycemia are of sufficient severity, there may be widespread injury to many areas of the brain.

Hyperglycemia

Hyperglycemia, most commonly associated with inadequately controlled diabetes mellitus and associated with either ketoacidosis or hyperosmolar coma, does not elicit significant morphologic changes in the brain. The affected individual becomes dehydrated and develops confusion, stupor, and eventually coma. The fluid depletion must be corrected gradually; otherwise, severe cerebral edema may follow.

Hepatic Encephalopathy

The encephalopathy found in the setting of impaired liver function is accompanied by a glial response within the CNS. Critical mediators appear to include elevated ammonia levels as well as proinflammatory cytokines. Astrocytes with enlarged nuclei and minimal reactive cytoplasm, known as Alzheimer type II cells, appear in the cerebral cortex and basal ganglia and other subcortical gray matter regions.

Toxic Disorders

Cellular and tissue injury from toxic agents is discussed in Chapter 9. Aspects of several important toxic disorders that are of unique neurologic importance are discussed here.

Carbon Monoxide

Many of the pathologic findings that follow acute carbon monoxide exposure are the result of impaired oxygen-carrying capacity of hemoglobin. There can also be local effects from the interaction of CO with the heme of cytochrome C oxidase, inhibiting electron transport in the mitochondria. Selective injury of the neurons of layers III and V of the cerebral cortex, Sommer sector of the hippocampus, and Purkinje cells is characteristic. Bilateral necrosis of the globus pallidus may also occur; it is more common in carbon monoxide-induced hypoxia than in hypoxia from other causes. Demyelination of white matter tracts may be a later event.

Methanol

Methanol toxicity preferentially affects the retina, where degeneration of retinal ganglion cells may cause blindness. Selective bilateral necrosis of the putamen and focal white-matter necrosis also occur when the exposure is severe. Formate and other metabolites of methanol appear to contribute to toxicity through disruption of oxidative phosphorylation and through nonenzymatic protein modification. Methanol toxicity occurs by ingestion of illicit liquor (moonshine) contaminated with methanol or when it is used as a substitute for ethanol.

Ethanol

Experience tells us that the effects of acute ethanol intoxication are reversible, but chronic alcohol abuse is associated with a variety of neurologic sequelae, including Wernicke-Korsakoff syndrome from thiamine deficiency (see earlier). The toxic effects of chronic alcohol intake may be either direct or secondary to nutritional deficits. Cerebellar dysfunction occurs in about 1% of chronic alcoholics, associated with a clinical syndrome of truncal ataxia, unsteady gait, and nystagmus. The histologic changes are atrophy and loss of granule cells predominantly in the anterior vermis (Fig. 28-45). In advanced cases there is loss of Purkinje cells and proliferation of the adjacent astrocytes *(Bergmann gliosis)* between the depleted granular cell layer and the molecular layer of the cerebellum. The fetal alcohol syndrome is discussed in Chapter 10.

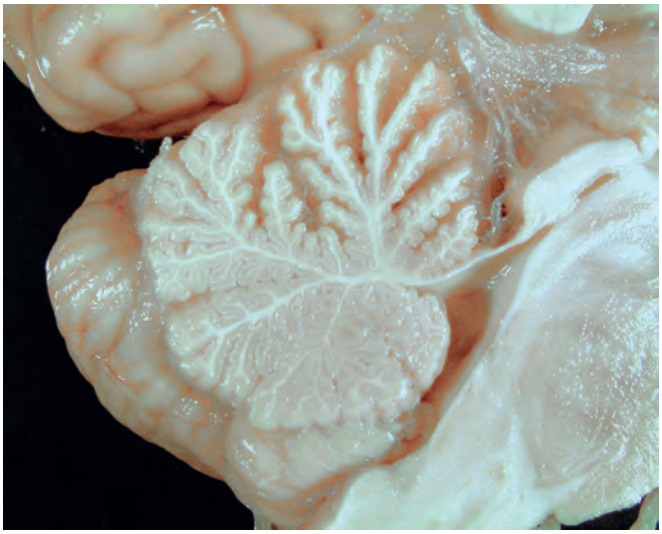

Figure 28-45 Alcoholic cerebellar degeneration. The anterior portion of the vermis (upper portion of figure) is atrophic with widened spaces between the folia.

Radiation

Exposure of the brain to radiation can occur accidentally or as part of therapeutic regimens for brain tumors. As discussed in Chapter 9, exposure to very high doses of radiation (>10 Gy) can cause intractable nausea, confusion, convulsions, and rapid onset of coma, followed by death. Delayed effects of radiation can also present with rapidly evolving symptoms, including headaches, nausea, vomiting, and papilledema that may appear months to years after irradiation.

The pathologic findings consist of large areas of coagulative necrosis, primarily in white matter, with all tissue elements within the area undergoing necrosis. This is accompanied by marked edema in the surrounding tissue, along with vascular fibrinoid necrosis and eventual sclerosis. The combination of radiation and methotrexate, administered either concurrently or sequentially, can act synergistically to cause tissue injury. While similar in appearance to that caused by radiation alone, these lesions are often adjacent to the lateral ventricles but may be distributed throughout the white matter or in the brainstem. Axons and cell bodies in the vicinity of the lesions undergo dystrophic mineralization, and there is adjacent gliosis. Radiation can also induce tumors, which usually develop years after radiation therapy and include sarcomas, gliomas, and meningiomas.