pressure (as in hypotension), small- or large-vessel obstruction, or both.

When blood flow to a portion of the brain is reduced, the survival of the tissue at risk depends on the presence of collateral circulation, the duration of ischemia, and the magnitude and rapidity of the reduction of flow. These factors determine, in turn, the precise anatomic site and size of the lesion and, consequently, the clinical deficit.

The general biochemical changes in cells resulting from ischemia are discussed in Chapter 2. The brain is primarily dependent on oxidative metabolism for generation of ATP, with minimal capacity to use glycolysis or energy substrates other than circulation-delivered glucose. With ischemia, there is depletion of ATP and loss of the membrane potential that is essential for neuronal electrical activity. Accompanying this, there is elevation of cytoplasmic calcium levels, which in turn activates a cascade of enzymatic processes that contribute to cellular injury. In addition to processes shared with ischemia in other parts of the body, the metabolic depletion of energy associated with ischemia can result in inappropriate release of excitatory amino acid neurotransmitters such as glutamate, which can contribute to cell damage by allowing excessive influx of calcium ions through N-methyl-D-aspartate (NMDA)-type glutamate receptors. In the region of transition between necrotic tissue and the normal brain, there is an area of "at-risk" tissue, referred to as the *penumbra*. This region can be rescued from injury in many animal models with a variety of anti-apoptotic interventions, implying that cells in areas of ischemia may die by apoptosis as well.

Global Cerebral Ischemia

Global cerebral ischemia **(diffuse ischemic/hypoxic encephalopathy) occurs when there is a generalized reduction of cerebral perfusion (as in cardiac arrest, shock, and severe hypotension).** The clinical outcome of a severe hypotensive episode that produces *global cerebral ischemia* varies with the severity of the insult. In mild cases, there may be only a transient post-ischemic confusional state followed by complete recovery and no irreversible tissue damage. However, irreversible damage to CNS tissue may occur in some individuals who suffer mild or transient global ischemic insults. There is a hierarchy of sensitivity among CNS cells: neurons are the most sensitive, although glial cells (oligodendrocytes and astrocytes) are also vulnerable. The most sensitive neurons in the brain are in the pyramidal cell layer of the hippocampus (especially area CA1, also referred to as *Sommer sector*), cerebellar Purkinje cells and pyramidal neurons in cerebral cortex. With severe global cerebral ischemia, widespread neuronal death occurs, irrespective of regional vulnerability. Patients who survive this injury often remain in a persistent vegetative state. Other patients meet the current clinical criteria for "brain death," including evidence of irreversible diffuse cortical injury (isoelectric, or "flat," electroencephalogram) and brainstem damage, such as absent reflexes and respiratory drive, and absent cerebral perfusion. When individuals with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes an autolytic process with gradual liquefaction producing the so-called "respirator brain."

Border zone ("watershed") infarcts occur in the regions of the brain or spinal cord that lie at the most distal reaches of the arterial blood supply, the border zones between arterial territories. In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions is at greatest risk. Damage to this region produces a sickle-shaped band of necrosis over the cerebral convexity a few centimeters lateral to the interhemispheric fissure. Border zone infarcts are usually seen after hypotensive episodes.

MORPHOLOGY

In the setting of global ischemia, the brain becomes edematous and swollen, producing widening of the gyri and narrowing of the sulci. The cut surface shows poor demarcation between gray and white matter. The microscopic features of irreversible ischemic injury (infarction) evolve over time. **Early changes,** occurring 12 to 24 hours after the insult, are seen in neurons (red neurons; Figs. 28-13*A* and 28-13*B*) and consist of microvacuolization, then eosinophilia of the neuronal cytoplasm, and later nuclear pyknosis and karyorrhexis. Similar acute changes occur somewhat later in astrocytes and oligodendroglia. After the acute injury, the reaction to tissue damage begins with infiltration by neutrophils (Fig. 28-13*C*). **Subacute changes,** occurring at 24 hours to 2 weeks, include tissue necrosis, influx of macrophages, vascular proliferation, and reactive gliosis (Fig. 28-13*D*). **Repair,** robust after approximately 2 weeks, is characterized by removal of necrotic tissue, loss of normal CNS architecture, and gliosis (Fig. 28-13*E*). In the cerebral neocortex the neuronal loss and gliosis are uneven, with preservation of some layers and destruction of others, producing a pattern of injury termed **pseudolaminar necrosis**.

Focal Cerebral Ischemia

Focal cerebral ischemia follows reduction or cessation of blood flow to a localized area of the brain due to arterial occlusion or hypoperfusion. When the ischemia is sustained, infarction follows in the territory of the compromised vessel. The size, location, and shape of the infarct and the extent of tissue damage that results are influenced by the duration of the ischemia and the adequacy of collateral flow. The major source of collateral flow is the circle of Willis (supplemented by the external carotid-ophthalmic pathway). Partial and inconstant reinforcement is available over the surface of the brain for the distal branches of the anterior, middle, and posterior cerebral arteries through cortical-leptomeningeal anastomoses. In contrast, there is little if any collateral flow for the deep penetrating vessels supplying structures such as the thalamus, basal ganglia, and deep white matter.

Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to embolization from a distant source, in situ thrombosis, or various forms of vasculitides; the basic pathology of these conditions is discussed in Chapters 4 and 11.

- *Embolism* to the brain occurs from a variety of sources. Cardiac mural thrombi are among the most common culprits; myocardial infarct, valvular disease, and atrial fibrillation are important predisposing factors. Next in importance are thromboemboli arising in arteries, most