In considering a compound's ability to distribute throughout the body and the impact of permeability, it is important to realize that biological barriers are not uniform. The plasma membranes of the cells lining the GI tract are substantially different from those of the pancreas, which are different still from the cell membrane that surrounds the various types of neuronal cells. A compound with a high degree of permeability through the GI tract may still experience distribution issues as a result of poor permeability through cellular barriers encountered between the GI tract and the intended target.

Of course, compounds designed to modulate targets that circulate in the bloodstream do not need to exit the systemic circulation, so permeability beyond the GI tract is not an issue with respect to reaching the biomolecular target. However, a compound's permeability through other tissue types can still play an indirect role. As will be discussed later in this chapter, extraction of compounds by the liver and kidneys can lead to metabolism and excretion. Rates of metabolism by liver enzymes will be impacted by a compound's ability to enter liver cells (liver cell permeability), while excretion rates will be controlled in part by a compound's ability to permeate through the cellular barriers within the kidney. In other words, a compound's liver metabolism and renal excretion will depend in part on its ability to be distributed into these organs.

Distribution of potential drug compounds into the brain is a special case worthy of further elaboration. Compounds that impact the CNS account for a substantial portion of the drug market, and yet they are perhaps the most difficult to identify, as therapeutic action requires that compounds pass through the blood–brain barrier. This protective layer consists of a single monolayer of cells that line the inner surface of the capillaries that run throughout the brain, providing it with nutrients and oxygen, and removing cellular waste products. The endothelial cells of the BBB are packed together tightly (Figure 6.20), preventing

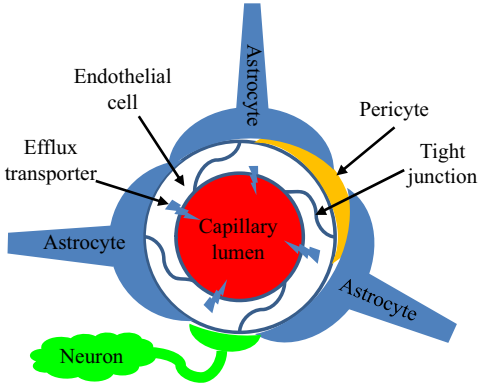

FIGURE 6.20 The blood–brain barrier consists of a monolayer of tightly packed endothelial cells that prevent paracellular transport and endocytosis. Passive diffusion is the main route of entry into the brain and abundant transporter proteins further slow entry of xenobiotics.