

# 3.2

## CLINICAL APPLICATION

### THE BLOOD-BRAIN BARRIER

**Perhaps nowhere else in the body are cells attached as firmly and closely as they are in the 400-mile network of capillaries in the brain. They form a “blood-brain barrier” that tightly controls which substances can enter and leave the brain. The walls of these microscopic blood vessels are a single cell thick. A century ago, bacteriologist Paul Ehrlich showed the existence of the blood-brain barrier by injecting a dye intravenously. The brain failed to take up the dye, indicating that its blood vessels did not allow the molecules to leave and enter the brain’s nervous tissue.**

Studies in 1969 using the electron microscope revealed that in the brain, capillary cell membranes overlap to form a barrier of tight junctions. Unlike the cells forming capillary walls elsewhere in the body, which are pocked with vesicles and windowlike portals called clefts, the cells comprising the blood-brain barrier have few vesicles and no clefts. Star-shaped brain

cells called astrocytes contribute to this barrier as well.

The blood-brain barrier shields delicate brain tissue from toxins in the bloodstream and from biochemical fluctuations that could be overwhelming if the brain had to continually respond to them. It also allows selective drug delivery—for example some antihistamines do not cause drowsiness because they cannot breach the blood-brain barrier. But all this protection has a limitation—the brain cannot take up many therapeutic drugs that must penetrate to be effective.

By studying the types of molecules embedded in the membranes of the cells forming the barrier, researchers can deliver drugs into the brain. They can tag drugs to substances that can cross the barrier, design drugs to fit natural receptors in the barrier, or inject substances that temporarily relax the tight junctions forming the barrier. Drugs that can cross the blood-brain barrier could be used to treat Alzheimer disease,

Parkinson disease, brain tumors, and AIDS-related brain infections.

A malfunctioning blood-brain barrier can threaten health. During the Persian Gulf War in 1991, response of the barrier to stress in soldiers caused illness. Many troops were given a drug to protect against the effects of nerve gas on peripheral nerves—those outside the brain and spinal cord. The drug, based on its chemistry, was not expected to cross the blood-brain barrier. However, 213 Israeli soldiers treated with the drug developed brain-based symptoms, including nervousness, insomnia, headaches, drowsiness, and inability to pay attention and to do simple calculations. Further reports from soldiers, and experiments on mice, revealed that under stressful conditions, the blood-brain barrier can temporarily loosen, admitting a drug that it would normally keep out. The blood-brain barrier, then, is not a fixed boundary, but rather a dynamic structure that can change in response to a changing environment. ■