Extending the half-life of a compound is often the focus of drug discovery programs, but it is important to keep the end goal of a program in mind as a program progresses. While it may be useful to develop a pain medication that is slowly eliminated from the body in order to allow once a day dosing for 24 h relief, the same is not true of a medication designed to cure insomnia. A potential insomnia treatment that last for 24 h could prevent the patient from waking up after the standard 8 h of sleep. While people suffering from insomnia might need to catch up on a significant amount of sleep, it is unlikely that they would want to accomplish this by sleeping for 24 h after taking a sleeping pill. The end goal of a program must be kept in mind when considering the elimination of a compound from systemic circulation.

Metabolism

As soon as a compound enters the body, the various mechanisms in place designed to protect the body from xenobiotics begin to process the foreign material. The biological barriers to the entry into the circulatory system of an orally delivered material, the walls of the intestines and the stomach, are the first line of defense. When a compound has been absorbed in the GI tract, it moves directly into the portal vein, which transports the compound to the liver (Figure 6.24). While metabolic processing of

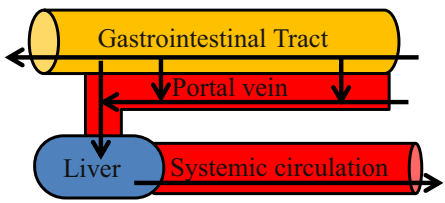

FIGURE 6.24 Upon absorption in the GI tract, compounds enter the portal vein, which delivers them to the liver. The metabolic machinery of the liver acts as an additional barrier between xenobiotics and the systemic circulation.

compounds can occur in a variety of different places, the vast majority of drug metabolism occurs in the liver. This organ is specifically designed to chemically modify a wide range of compounds in order to enhance their elimination through the kidney. In order for an orally delivered material to move beyond the liver and exert an influence on bodily function, some fraction of the material must survive the presystemic metabolism of the liver. This is also referred to as "first-pass metabolism" as it is the first time the drug moves through the liver. Compounds that exit the liver enter the systemic circulation and move through the body, but they are continuously exposed to the liver with each cycle through the circulatory system, providing repeated opportunities for metabolic processing. Each pass through the liver will decrease the concentration of the compound, and this in turn will have a direct impact on properties such as bioavailability,