longer affects the body and can be effectively removed. The liver, kidneys, and intestines metabolize drugs. The liver does most of the work of drug metabolism by means of its enzymes.

This biotransformation may actually determine the route of administration because metabolism may transform the medication into a useless form too quickly. For example, insulin given by mouth is virtually useless; stomach acid breaks down insulin to an inactive form before it can be absorbed into the bloodstream.

In some instances, a drug's metabolite is the desired medication; therefore, the drug is administered in its inactive form to become activated through metabolism. This category of drugs is known as *prodrugs*. An example of a prodrug is fosamprenavir (Lexiva) used in the fight against HIV.

Like absorption, drug metabolism can be affected by the patient's age, genetics, disease state, and other factors. For example, blood flow to the liver is decreased in the elderly and therefore metabolism is slower. Genetics, which determine how much of certain enzymes that we each have, also determine how fast we metabolize a medication. Specific diseases, such as those that affect the liver, may cause slower metabolism. In all of these situations, medications may build up in the body to toxic levels as the patient may continue to receive more and more doses of the medication with it not being broken down into harmless metabolites.

CRITICAL THINKING

David M. is a chronic alcoholic. How could that damage affect the way his body metabolizes drugs?

Excretion

Once a medication has acted in the body, it is excreted. This process occurs mainly through the kidneys, although some medications are released as a gas by the lungs, and a few are excreted through bile. Saliva and sweat glands excrete a small amount of drugs, and some medications are excreted through breast milk.

Excretion is necessary because it ensures that drugs and their transformed products are removed and do not build up in the body (called *cumulation*). If buildup occurs, the patient may become very ill. For example, if morphine is not excreted because a patient has decreased kidney or liver function, the buildup may cause diminished or absent respiration. Even seemingly harmless medications such as acetaminophen (Tylenol) or ibuprofen (e.g., Advil, Motrin) can cause a cumulative effect and damage the liver or kidneys. Aspirin can cause bleeding problems.

Excretion is an important factor to consider because of the specific time frame needed for exposure to a drug. A medication may not produce the desired effect if it is left in the system too long. A prime example of this is methotrexate (e.g. Rheumatrex, Trexall, Otrexup) when used in high does for certain types of cancer including leukemia. Methotrexate starves the cancer cell of folic acid; however, if the drug is left in the system too long it causes a lack of folic acid in all of the body's healthy cells too. Therefore, leucovorin is used as an antidote or rescue drug to stop methotrexate's effects at a specified interval after it is administered. Conversely, if a medication is metabolized too quickly, it may not have time to affect the body before its metabolites are excreted. Scientists work very hard to discover and develop medications in the correct format and strength to provide precise treatment before these drugs are metabolized and excreted.

ISSUES AFFECTING THE DRUG CYCLE

Therapeutic level, potency, and interactions with other medications affect the drug cycle. The therapeutic level of a medication refers to the point at which the drug has the optimum desired effect. Too little medication renders it less than effective; too much can be **toxic,** or poisonous, to the patient. The prescriber therefore routinely orders drugs at the lowest dose possible to obtain therapeutic levels. To be sure the drug level is in the therapeutic range, a patient's blood levels may need to be monitored. In addition, if a prescriber orders a drug with known toxic effects, the patient must be monitored for toxicity. An example is gentamicin (e.g., Garamycin, Cidomycin), which is known to be both nephrotoxic (toxic to the kidneys) and ototoxic (toxic to the ears). Thus, kidney function and hearing would be monitored closely in a patient taking this drug.