tumor development from thyroid hormone perturbations. The underlying mechanisms for these different sensitivities between rats and humans are not yet clear, although human UGT1A1 and 1A9 are inducible (137).

5.6.3. Identification of CYP Enzymes Involved in Drug Metabolism

In addition to enzyme inhibition and induction studies, successful prediction of metabolic drug interactions from in vitro data also requires identification of the human CYP isozymes responsible for the metabolism of the test drug, particularly when other compounds can inhibit the metabolism of the test drug (117). However, if a drug is metabolized by more than one CYP isoform, then the metabolism of the test drug may be compensated even if one CYP isoform is inhibited. Therefore, the relative contribution (by determination of kinetic parameters) of the metabolic pathways by different isozymes should be determined. There are three main approaches utilized in CYP isozyme identification in human liver microsomes (117,138,139): (I) metabolism using cDNA expressed enzymes; (II) effect of specific chemical inhibitors or antibodies of CYP isoforms, on the metabolism of the test drug; (III) correlation analysis with specific probe substrate metabolism using a panel of human liver microsomes pooled from 10 to 15 subjects.

6. MECHANISMS OF SMALL MOLECULE EXCRETION

6.1. Renal Excretion

The kidney is the primary organ responsible for the excretion of medications and their biotransformation products from the body. Detailed reviews of renal drug excretion mechanisms are available in the literature (140,141). The major processes involved in the renal elimination of drugs are glomerular filtration, active tubular secretion, intrarenal metabolism, and passive reabsorption. The combined effect of the first two processes is the extraction of drug from the blood into the urine. The last process, reabsorption, involves the movement of drug back into the blood from the primitive urine. Thus, the renal excretion rate of a compound is the net result of these individual mechanisms.

6.1.1. Glomerular Filtration

Urine formation begins with glomerular filtration. The glomerular filtrate normally contains no cells, is essentially protein-free, and contains most inorganic ions and low-molecular weight organic solutes (glucose and amino acids, for example) in virtually the same concentrations as in the plasma. The quantity of drug that is filtered by the kidney parallels the concentration of unbound drug in the plasma. Overall, the rate of filtration is the product of unbound plasma concentration and glomerular filtration rate (GFR) (142).