Changes in the lipoprotein plasma profile of an individual can potentially influence drug disposition and drug activity (67).

Like AAG, changes in albumin plasma concentrations can also affect drug distribution and response. Hypoalbuminemia can occur in elderly patients and those with renal failure. A decrease in the concentration of plasma albumin will increase drug free fraction (f_u) which increases V. Phenytoin is a useful example (68). Patients with hypoalbuminemia will have an increased f_u of phenytoin which can potentially result in toxicity (renal failure will further complicate this as uremia increases f_u of phenytoin even more).

A recent review by Benet and Hoener (69) demonstrated that protein binding changes caused by drug–drug and disease drug interactions are rarely of clinical importance. Except in rare cases (e.g., a compound with a high extraction ratio and narrow therapeutic range), an increase in f_u will result in increased drug clearance. Consequently, clinical exposure of a patient to the drug will be unaffected. Nevertheless, protein binding measurements are important during drug development for several reasons. First, interspecies differences in f_u will affect allometric predictions of pharmacokinetic parameters (clearance, volume of distribution). Second, knowledge of drug protein binding (f_u) is necessary for establishing a suitable first dose in humans. Third, therapeutic drug monitoring typically involves measuring total drug concentrations. For a highly protein-bound compound with a narrow therapeutic range (e.g., phenytoin), this can result in erroneous dosing adjustments for patients with elevated f_u. In the phenytoin example described above, patients with reduced protein binding of phenytoin (e.g., secondary to hypoalbuminemia) tend to have lower total drug concentrations (i.e., below the established therapeutic range), which are often misinterpreted. In this case, attempts should be made to extrapolate observed drug concentrations to "normal binding" conditions in order to avoid unnecessary increases in dose (69).

In addition to plasma proteins, other components of the blood may influence drug disposition. Specifically, the erythrocytes are a potentially important distribution site for medications. The erythrocytes play an important role in the transport and disposition kinetics of medications (e.g., carbonic anhydrase inhibitors) in the blood (70,71). However, the erythrocytes are often regarded as an insignificant compartment of drug distribution. For those compounds that accumulate in the erythrocytes to an appreciable extent, characterization of different kinetic events occurring within the erythrocyte can provide significant insight into drug disposition (72).

5. MECHANISMS OF SMALL MOLECULE METABOLISM

Clearance is the most important determinant of drug disposition, and it is the parameter used to establish suitable doses of medications. Drug