Factors Affecting Metabolism

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Multiple pathways generally compete for metabolism of any particular compound. Thus, the relative amounts of each metabolite formed may be somewhat or even quite different from one species to another, one gender to the other, one age group to another, among otherwise apparently similar individuals, and even from one time point to another in a single individual. Furthermore, the proportion of each metabolite formed *in vivo* may be different than the proportion formed *in vitro*. Major influences causing these differences are availability of relevant enzyme systems, availability of relevant cofactors, presence of modulators, and transport properties of the parent and/or metabolites. Thus, in general, *in vitro* metabolism provides examples of the *possible* biotransformations of a particular agent, whereas *in vivo* metabolism is limited by the specific conditions of availability of enzyme, cofactor, modulators, and transport.

Investigation of the differences in metabolism among species, age groups, genders, polymorphic enzymes, and presence of modulators is applicable to both drug development and drug therapy. In development, knowledge of these differences in metabolism helps to correlate pharmacokinetic (PK), toxicology, and structure–effect studies from animal models to humans. During development and therapy, knowledge of these individual differences in metabolism helps to predict and understand differences in drug response and adverse effects. Because metabolism is an important criterion determining the rate of clearance of most drugs, differences in clearance can cause significant difference in individual dose–response and incidence of adverse effects. This is especially important for drugs with a *narrow therapeutic window*, that is, those having a small difference between minimum plasma concentration needed to reach a therapeutic effect and maximum plasma concentration to prevent adverse effects.

The major influences affecting metabolism can be categorized into genetic, environmental, and physiological factors, although the distinction between the categories is confounded by the fact that environmental and physiological factors can modify genetic susceptibilities. *Environmental factors* are thought of as temporal factors, with varying consequences according to their concentration over time. Environmental factors are usually limited to exogenous "small" molecules such as other drugs, compounds

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