1 Introduction: An Overview of the Role of Metabolism in Drug Toxicity

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Up until the 1960s, the metabolism of drugs and other chemicals was primarily associated with detoxication processes. In fact, the first major monograph on the metabolism of drugs and other chemicals was written by R. Tecwyn Williams and appeared in 1947 under the title *Detoxication Mechanisms–The Metabolism of Drugs and Allied Organic Chemicals* [1]. This landmark book in the field of drug metabolism was followed by others that were widely used as texts and reference guides, which highlighted the basic enzyme systems involved in drug metabolism and the chemical structural groups affected. *Fundamentals of Drug Metabolism and Drug Disposition* by La Du *et al*. [2] and a two-part series entitled *Drug Metabolism: Chemical and Biochemical Aspects* and *Concepts in Drug Metabolism, Part B* by Bernard Testa and Peter Jenner are now classics in the field [3,4].

Since the 1980s, essentially every monograph in the area of drug metabolism has incorporated concepts of reactive metabolites and drug toxicity, and drug interactions and drug toxicity [5–8]. Some monographs have been primarily devoted to these concepts because in several instances, metabolism-based toxicities have caused human morbidity and mortality and limit the development and use of drugs and other chemicals that otherwise may be very beneficial [9]. Some of the earliest work on the characterization of reactive metabolites as mediators of toxicity were carried out in the 1950s during the investigations on mechanisms of chemical carcinogenesis by the Millers (see Ref. 10 for a review of this early work). Meanwhile, in approximately the same time period, the first case reports of drug interactions that caused drug toxicities appeared (see Ref. 11 for a proceedings report of these early cases).

Reactive metabolite-based drug toxicities came to the forefront with the now classic series of papers published in the late 1970s by researchers led by Jerry Mitchell, Jim Gillette, and B. B. Brodie in the Laboratory of Chemical Pharmacology of the National Heart, Lung, and Blood Institute at the NIH on the bioactivation of the widely used analgesic/antipyretic drug, acetaminophen, to a reactive metabolite that caused hepatotoxicity [12–15]. Thousands of research papers, many book chapters and reviews, and even a book have since been published on the mechanism of liver injury caused by this drug (for more recent reviews, see Refs 16–19). Several other examples of reactive metabolite formation from drugs leading to toxic effects in animals

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and humans soon followed, and biological reactive intermediates have been the subject of numerous symposia and symposia proceedings. One of the most recent of these provided data showing that drug toxicity is now responsible for approximately one-third of the terminations of drug candidates in development and that over 70% of those cases were related to drug metabolism [20].

Although reports of drug interactions leading to toxicities have appeared since the early 1950s [21], drug interactions did not receive serious attention until the publication of *Drug Interactions: Clinical Significance of Drug Interactions and Drug Effects on Clinical Laboratory Results* by Hansten in 1971 [22]. The public did not really take note until the discovery in the early 1990s that inhibition of cytochrome P450 3A4 caused cardiac toxicity and death in patients taking the antihistamine, terfenadine [23–25]. This resulted in the issuance of new guidelines in 1997 by the FDA and other regulatory agencies worldwide, stipulating the need for *in vitro* drug interaction studies as part of the safety assessment of new drugs. Since then, books have been published on mechanisms of drug interactions [7].

The chapters in this volume of this encyclopedia represent an update on the multiplicity of chemical and biological factors that are involved in both reactive metabolites and their role in drug toxicities and in drug interactions. Box 1.1 is a brief synopsis of some of the major factors that are discussed. Drug structure plays a significant role, in that it determines the structures of metabolites that can be formed by a cadre of enzymes that can catalyze a wide variety of reactions on organic chemicals. The chapters titled ***Bioactivation I: Bioactivation by Cytochrome* P450*s***, ***Bioactivation II: Phase I (Non-*P450*)***, ***Bioactivation by Phase-II-Enzyme-Catalyzed Conjugation of Xenobiotics***, ***Safety Testing of Drug Metabolites: A Practical Approach for the Implementation of the MIST Guidance in PKDM***, ***In Vitro Toxicity Screening in Early Drug Discovery: Importance of Metabolism and Reactive Metabolites*** describe the mechanisms of formation of drug metabolites with a focus on bioactivation mechanisms and the various enzymes that catalyze the reactions. The chapter titled ***Stereochemical Elements Associated with Drug Metabolism and Toxicity*** describes specific examples where the stereochemistry of a drug and its metabolites play a significant role in drug toxicities and drug interactions. It is important for the reader to understand that all drug-metabolizing enzymes can form products that can cause toxicities depending on the drug structure, which when coupled to the particular reaction catalyzed, defines the structure of the metabolite.

BOX 1.1 SEVERAL IMPORTANT DETERMINANTS OF DRUG TOXICITIES.

Chemical structure of a drug and its metabolites

Dose of the drug

Rates of toxic metabolite formation vs. detoxification

(Dependent on concentrations of enzymes and cofactors, which in turn are affected by genetics, gut microflora, diet, and other drugs as inducers, inhibitors, etc.)

Immune recognition of macromolecular adducts of a drug or its metabolites

Efficiency of macromolecular repair mechanisms

BOX 1.2 A LIST OF SUBSTRUCTURES FOUND IN DRUGS THAT HAVE BEEN MOST COMMONLY ASSOCIATED WITH THE FORMATION OF REACTIVE METABOLITES THAT HAVE CAUSED TOXICITIES.

Drugs that contain or can be metabolized to the following structures may cause toxic effects via the formation of reactive metabolites:

- Hydrazines and hydrazides
- Arylacetic or aryl-propionic acids
- Thiophene, furan, or pyrrole
- Anilines or anilides
- Quinone and quinone imines
- Medium chain fatty acids
- Halogenated hydrocarbons and some halogenated aromatics
- Nitroaromatics
- Moieties that can form reactive α,β-unsaturated enal-like structures
- Thiols, thiono compounds, and thiazolidinediones

The major chemical substructures found in drugs that have caused overt tissue injury in the past are listed in Box 1.2. For the most part, these structures are metabolized to reactive electrophiles that interact with tissue nucleophiles (primarily proteins) to form covalent adducts, a topic of considerable interest at present that is discussed in detail in the chapter titled ***Covalent Drug–Protein Adducts: An Exploration of Their Role in Drug-Induced Liver and General Organ Toxicity***. In some cases, these electrophilic species can also lead to oxidation of tissue macromolecules, and in a few cases, radical metabolites can be formed that can react with oxygen to form toxic oxygen products (Fig. 1.1).

It is well known that there are a host of factors that influence not only the enzymes involved in the metabolism of drugs but also the disposition of these metabolites and their ultimate effect on our biological system. Genetics and gene regulation play a very significant role in the rates of reactive metabolite formation, in their disposition as described in the chapter on ***Genetics of Drug Disposition***, and in the response of the cell/tissue/organism to the effects of the metabolites. The first work in the area of pharmacogenetics was published over 50 years ago [26], and now, genome-wide association studies are helping to define the role of particular genes involved in drug toxicities (for discussions, see Refs 27 and 28). The advancing field of toxicogenomics is discussed in the chapter titled ***The Application of Preclinical Toxicogenomics for Predicting and Understanding Drug-Induced Toxicity and Metabolism***, and the influence of genetics and gene regulation on drug interactions and drug metabolism is the topic of the chapters titled ***Clinical Implications of CYP Induction-Mediated Drug–Drug Interactions***, and ***Regulation of Drug Metabolizing Enzymes and Transporters in Infection, Inflammation, and Cancer***. Additional work in proteomics and metabolomics/metabonomics is extending our understanding of the effects of drugs and

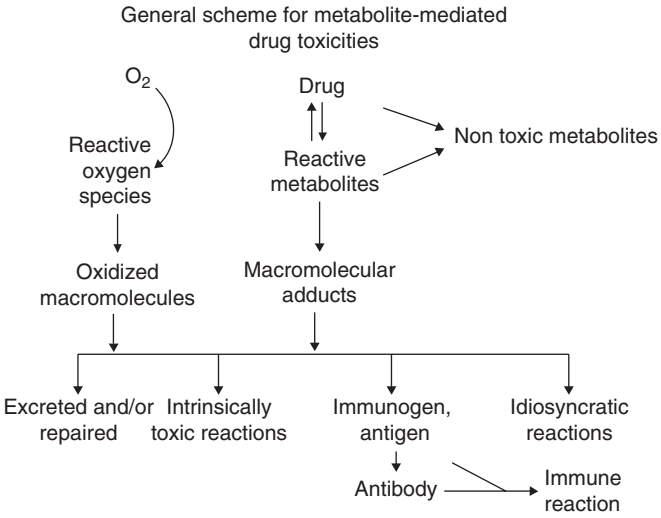

Figure 1.1 A simplified scheme for general mechanisms of drug metabolite-mediated drug toxicities.

drug metabolites at the cellular and whole body levels, thereby providing additional insights on phenotypic variations in drug metabolism, drug toxicities, and drug interactions. Proteomics in drug toxicities is the subject of the chapter titled ***Proteomics in Drug Discovery and Development***, and metabolomics/metabonomics is the subject of the chapter titled ***Metabonomics in Understanding Drug Metabolism and Toxicology***.

Finally, there are a host of other factors that can affect either the metabolism of drugs or the response of our biological system to the metabolites formed (Box 1.1). The dose of a drug (or any chemical substance) was recognized as a very important factor in as early as the 1500s when Paracelsus stated, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy." Thus, the lower the dose of a drug, the lower the amounts of toxic metabolites that can be generated. In most instances, this translates to a decreased risk for toxicity. However, many toxic effects of drugs occur in only a small percentage of individuals who take the drug. These idiosyncratic drug reactions are not yet very predictable, and several factors, such as inflammatory episodes, may leave an individual at more risk to an idiosyncratic drug reaction. This is the subject of the chapters titled ***Idiosyncratic Drug Reactions*** and ***Animal Models of Idiosyncratic, Drug-Induced Liver Injury: Emphasis on the Inflammatory Stress Hypothesis***. Other factors such as drugs acting as inhibitors of drug metabolizing enzymes (see chapter titled ***Drug–Drug Interactions 1: Inhibition***) age and diet (see chapters titled ***Age-Dependent Expression of Human Drug-Metabolizing Enzymes*** and ***Phytochemical Modulators of Human Drug Metabolism: Drug Interactions with Fruits, Vegetables, and Botanical Dietary Supplements***) can also play a significant role in drug metabolism-related drug toxicities.

In summary, our knowledge of drug-mediated toxicities and the role that drug metabolites play in those toxicities has increased dramatically over the last 50 years. Advances in systems biology approaches to better define the most important factors in drug-metabolism-based toxicities should identify new biomarkers that can provide early signals of potential drug toxicities and lead to improvements in drug safety.

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