Book Reviews

Drug Metabolism. Chemical and Enzymatic Aspects. By Jack P. Utrecht and William Trager. Informa Healthcare USA, New York. 2007. v + 173 pp. 18.5 × 26.5 cm. ISBN 978-0-84937595-8. $229.95.

According to the preface of this book, most idiosyncratic adverse drug reactions are due to chemically reactive metabolites, and an important goal of drug design and development is to avoid these problems by a better understanding of chemical structural features that lead to such metabolites. The two North American authors, both academic chemists in these areas, have as a further objective a presentation useful not only to chemists but also to the biologists who work with them.

The first of eight general topics in the volume is an introduction in which the importance of genetic polymorphism among some enzymes important to drug metabolism is emphasized. This is followed by a pair of background chapters, each of about a dozen pages. The first, for nonchemists, emphasizes prediction of aqueous solubility, prediction of charge from pK_a data, structural factors that affect absorption, distribution, and excretion, and hints for understanding chemical mechanisms. The second, for chemists, considers basic aspects of pharmacokinetics, drug transporters, enzyme kinetics, and deuterium isotope effects. Chapter 4, the longest (about 40%) of the text, first reviews the classes of oxidative enzymes: cytochrome P450 isoforms, peroxidases, flavin monooxygenases, alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidase, xanthine oxidase, and aldehyde oxidase. The various oxidation pathways, such as alkane oxidation and oxidation adjacent to a heteroatom, are then discussed. The four chapters following present reductive pathways, hydrolytic pathways, conjugation pathways, and the formation of reactive metabolites. An abundance of clear structural formulas illustrates the foregoing discussions, which are documented by 5−160 citations.

There are occasional errors in the text: conversion to metabolites in the liver is stated to occur "before the drug even enters the blood stream" (p 1), and the formula for thianaphthene and its sulfoxide are labeled "thiophene" and "thiophene *S*-oxide" (p 158). A more serious shortcoming of the book is the failure to connect, where possible, the various isolated drug structures, chemical mechanisms, enzymes, pathways, and host responses into a more integrated understanding that would help to achieve, in some part, the goal of avoiding reactive metabolites as proposed in the preface. The N-deethylation of phenacetin by CYP1A2 to form the widely used drug acetaminophen (APAP) is shown on p 42. The importance of CYP2D6 and its genetic polymorphism in drug metabolism, which can lead to ultrarapid, extensive, and poor metabolizers, is found on pp 47 and 49. The induction of CYP2E1 by ethanol is described on p 50. The formation of *N*-acetyl-*p*-benzoquinone imine (NAPQI) from APAP is mentioned on pp 87−88. The reactivity, hepatotoxicity, and detoxication of NAPQI by glutathione is outlined on p 154. Thus, the complex causes of APAP toxicity are scattered over the whole book, and they cannot be accessed from the relatively brief seven-page index.

This unreasonably expensive book ($1.33 per page) is also available as a softcover textbook edition ($99.95). It is noted that a 700-page two-volume set ($130) by Testa and Krämer, covering the biochemistry of drug metabolism, is due to appear shortly.

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Biosimulation in Drug Development. Edited by M. Bertau, E. Mosekilde, and H. V. Westerhoff. Wiley-VCH, Weinheim, Germany. 2008. xxviii + 512 pp. 17 × 25 cm. ISBN 978-3-527-31699-1. $200.

The drug development process is fraught with uncertainty despite an abundance of data. To reduce the failure rate of new drugs and appropriately channel resources, the pharmaceutical industry must weigh the available data in the context of our overall knowledge about physiology, pathophysiology, and molecular mechanisms of disease. This is an enormously complex task, and this book describes a new tool called biosimulation that may help.

Biosimulation is the process of mathematically modeling the salient features of a physiological system and simulating the system dynamics to better understand how it functions and how it will respond to an intervention. The book introduces a wide range of activities in the field and its application to help understand disease mechanisms and their treatment. Many of the authors are members of the EU BioSim Network of Excellence whose objective is to demonstrate how biosimulation can lead to a more rational drug development process, improved treatment procedures, and reduced animal experimentation. The 18-chapter book is divided into four parts. Part 1 provides an introduction to biosimulation with examples ranging from highly applied research in pharmacokinetics and pharmacodynamics (Chapter 1) to more academic topics like modeling electrical bursting behavior of pancreatic β cells (Chapter 2). Chapter 3 describes kinetic modeling of various drug metabolism pathways in yeast as a model organism.

Part 2 is devoted to simulating cells and tissues and includes a chapter on intestinal absorption and transport processes with particular emphasis on using such models to help make the transition from in vitro data to making in vivo predictions (Chapter 4). Chapter 6 provides a very nice overview of the complex, multiorgan control system regulating blood glucose levels that is central to understanding the pathophysiology of diabetes. Chapter 9 provides an overview of a relatively mature application of biosimulation to help understand and treat cardiac arrhythmia.

Part 3 addresses the technologies for simulating drug action and effect. Chapter 10 presents a cell cycle model coupled to a circadian rhythm to simulate how the periodic timing of anticancer drug delivery may lead to different degrees of cytotoxicity. Chapters 11 and 12 illustrate the use of biosimulation to help understand basic physiological processes such as the role of calcium channel kinetics and clustering in the

exocytosis process in pancreatic beta cells (Chapter 11) and kidney pressure and flow regulation (Chapter 12).

Part 4 focuses on applications of biosimulation at various stages of drug development. Chapter 15 discusses kinetic models at the cellular level and methods for simplifying such models to aid in their analysis and simulation. The chapter is targeted toward integrating kinetic models in the context of systems biology approaches that are likely most useful at the target identification phase. Chapter 16 uses biosimulation to help understand various mechanisms underlying the high interindividual variability of drug absorption, distribution, metabolism, and elimination. Chapter 17 presents a broad perspective of various kinds of modeling approaches in the context of the different stages of clinical drug development. The final chapter discusses the potential impact of biosimulation for the ethical use of experimental animals and humans in the process of drug development. This book will be useful to anyone interested in a broad overview of biosimulation methods and selected applications. While several chapters are clearly focused on the drug development process, some contributions are more theoretical and are targeted toward providing insights into basic physiology. Overall, the book would be an excellent addition to libraries and would serve as a good introduction to a wide range of activities in the field.

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