

Book Review

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Pharmacogenomics. Edited by Werner Kalow, Urs A. Meyer, and Rachel F. Tyndale. New York: Marcel Dekker, 2001. Pp. 403. \$165.00.

In the early 1960s, when Werner Kalow first published on the “heredity and the response to drugs” (Kalow W [1962] *Pharmacogenetics: Heredity and the Response to Drugs*. W. B. Saunders, Philadelphia), the term “pharmacogenetics” was born. It took another 20 years to identify mutations that are at the core of an individual’s response to a particular drug—findings that coincided with the discovery of a multitude of drug-metabolizing enzymes. This body of work, by the editors of the present volume and by other researchers, merged clinical observations with basic science and led to our current understanding of how mutations, such as SNPs, alter the function of a gene product and thereby moderate drug metabolism.

The sequencing of the human genome and the arrival of new high-throughput technologies made it possible to analyze DNA in an expansive, highly parallel way; today, we are able to analyze multiple genes simultaneously, rather than one at a time. The term “pharmacogenetics” no longer adequately describes such large-scale, often genomewide approaches, and, logically, the use of the term “pharmacogenomics” clearly illustrates this parallel analysis of many genes. However, despite these differences, the terms are often used interchangeably. It is important to note, though, that “pharmacogenomics” widened the meaning to include new abilities, such as the use of genetic markers for association studies and the identification of novel drug targets.

Kalow begins by illustrating the historical aspects of pharmacogenetics through a description of his research regarding a number of fatal outcomes of patients taking the local anesthetic procaine. His conclusions at that time set the stage for the development of individualized, gene-dependent drug therapy, which is described in detail in the ensuing chapters. Today, “personalized medicine” continues to be driven by increasing information and a continuous flow of new knowledge developed from efforts such as the Human Genome Project and the identification of causes of disease and variability in drug response.

Several chapters of *Pharmacogenomics* explore the current status of pharmacogenetics and describe, in detail, allelic variants of genes associated with interindividual variability in drug uptake, transport, and metabolism. Classical, well-studied examples such as cytochrome P450 2D6 (CYP2D6; description of the poor-metabolizer phenotype based on the discovery of polymorphic debrisoquine/sparteine metabolism) are

described, as well as more recent findings about the importance of genetic variants in nuclear receptors (i.e. estrogen and retinoic acid receptors) and drug transporters (i.e. ABC transporters and multidrug-resistance protein).

Unfortunately, another important class of molecules—ion channels—is relegated to a small section within the chapter on receptors. In addition, a table on hepatotoxicity and QT prolongation as two of the most common reasons for withdrawal of drugs from the marketplace appears earlier in the book, making it somewhat out of context. QT prolongation is caused by mutations in genes that control the flux of potassium and sodium ions across the membrane of myocytes. The numerous reports attesting to their great clinical importance and, in particular, the implication of the *HERG* gene as a cause of severe adverse drug reactions call for a more in-depth description of this class of genes.

The authors also address questions related to the presence of genetic variations that confer interindividual differences in drug response and whether these variations are limited to individuals, families, populations, or ethnic groups. Interestingly, the definition of ethnicity is shifting from a limited focus on appearance and geographical location to one using a more scientific approach that considers genetic differences between populations. This new approach is based on two major observations: first, how the frequency of a particular genetic variant differs between populations; and second, how different populations have dissimilar variants. A separate chapter addresses these interethnic differences in drug response and elaborates on these findings through the use of several relevant examples.

Despite the ~100,000 deaths each year, in the United States alone, that can be attributed to adverse drug reactions, pharmacogenetics has not yet made the transition from bench research to clinical applications. Urs A. Meyer, in his chapter on pharmacogenetics from clinical viewpoints ascribes this to a lack of prospective studies to evaluate the impact of genetic information on drug therapy. In addition, the complexity of the tools of the trade (summarized in a later chapter), combined with a lack of education in this area on the part of both physicians and patients, is a likely contributor to the slow acceptance of pharmacogenetics in the clinic. Meyer further summarizes the immediate impact of the genetic background on phenotypes and elaborates on the clinical relevance of pharmacogenetic traits and genetic polymorphisms. Clearly, the message conveyed is that new technologies will open the door to clinical applications for the prediction of interindividual differences in drug efficacy and toxicity on the basis of genetic factors.

Pharmacogenomics includes several chapters on the tools used to tackle the challenges of pharmacogenetics and -gen-

omics research. In addition, a chapter is dedicated to the field of “proteomics,” looking beyond the genome into the dynamics of functional genomics. Although the genome is, with exceptions, identical in each cell, the expression of individual genes is characteristic for each cell type and developmental stage, as well as other cellular differences. Tools to analyze gene expression profiles (the “transcriptome”), such as DNA microarrays, are becoming widely used and are already an established part of the genomics toolbox. However, it has been shown that differences found in protein profiles (the “proteome”) cannot be explained by extrapolating mRNA profiles to the protein level. Other events, such as posttranslational modifications, must contribute to this difference. Because we are most interested in cellular function, we want to know about the form in which the enzyme in front of us appears. These profiles then can provide valuable information on disease-specific proteins, candidate targets, lead-compound identification, and drug toxicity studies. Techniques to identify protein profiles have been developed for quite some time but have only recently matured to the point of being readily available and more or less easy-to-use tools. The chapter summarizes these novel techniques and provides an outlook on the commercial side of proteomic tools.

Bioinformatics has quickly become a major component of pharmacogenomics, providing the ability to design and analyze complex experiments and also to manage the vast amount of information collected in these studies. *Pharmacogenomics* elaborates on two main areas of bioinformatics: the resources

available on the Internet and the use of applied bioinformatics. The very nature of the Web’s open architecture and nearly unlimited flexibility makes it an opportune platform to access and exchange genomic and genetic information. The massive databases maintained by public and private institutions provide a wide range of data-mining capabilities. In *Pharmacogenomics*, the authors list and describe the resources and major databases available on the Web. Despite the difficulty of providing a comprehensive and up-to-date overview of these resources, the authors have done so carefully and with enough depth to provide a valuable guideline for navigating and mining these online resources for relevant genetic and genomic information.

In summary, *Pharmacogenomics* describes the principles of the field and guides interested readers to the relevant sources and original literature, without going into extraneous detail. By touching on all of the important issues, the authors have provided a well-written overview on the state of the art of pharmacogenomics.

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