Book Reviews

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Pharmacogenetics. By Wendell W. Weber. New York: Oxford University Press, 1997. Pp. 344. $60.00.

Pharmacogenetics by Wendell W. Weber represents the most recent, most comprehensive book on this rapidly changing subject. "Pharmacogenetics," a term first coined by Friedrich Vogel (Heidelberg) in 1959, is the study of the hereditary basis of the differences in responses to drugs. Werner Kalow (Toronto) and Arno Motulsky (Seattle) are especially to be credited for their public advocacy in this field during the past 4 decades. Ecogenetics is the broader field of interindividual differences in response to all environmental, chemical, and physical agents (e.g., insecticides, compounds formed during combustion, heavy metals, and ultraviolet radiation and x-rays). Weber's book includes some human ecogenetic disorders (e.g., cigarette smoking–induced bronchogenic carcinoma, arylamine-induced bladder cancer, and susceptibility to beryllium toxicity), as well as most of the known pharmacogenetic disorders. It is now clear that each of us has his or her own "individual fingerprint" of unique alleles encoding the so-called drug-metabolizing enzymes (DMEs) and the receptors that regulate these enzymes. After the explosion of molecular biology and human genetics during the past decade, this book therefore provides us with a glimpse of where the field is today, almost 40 years after the term "pharmacogenetics" was first used.

Pharmacogenetics has grown out of Weber's ~30 years of seminars, discussion, and teaching to upper-level undergraduates, graduate students, and other students of the health sciences, at the University of Michigan. I know this well because, on many occasions over the past 20 years, I have been invited by my good friend and colleague to participate in this teaching at Ann Arbor.

The book is divided logically into two parts. Part I ("Pharmacogenetic Concepts") covers the emergence and broad scope of the field, from a historical perspective, whereas part II ("Applications of Pharmacogenetic Concepts") provides the experimental epidemiological evidence and clinical cases for 33 human phenotypes of pharmacogenetic significance.

In part I, the chapters on historical perspective ("Beginnings") and on dose-response relationships and pharmacokinetics ("Human Drug Response") represent an excellent fast-moving introduction to the field. In contrast, chapter 3 ("Heredity") is a bit "user unfriendly" and, in my opinion, may turn off a lot of students because an excess of mathematical equations is listed. Chapter 3 does provide, however, an excellent chronological overview of how pharmacogenetic differences have been studied in fraternal versus identical twins, how monogenic traits were first exploited, and how the consensus that many pharmacogenetic diseases represent multiplex phenotypes caused by two or more genes—that is, that they are polygenic—has now emerged.

The book has some problems in describing basic fundamentals of genetics. In particular, the concept of additive inheritance is covered incorrectly. For example, in table 3-6 (p. 51), at least eight traits listed as "manifesting autosomal recessive inheritance" are in fact inherited additively. Moreover, the text states that "four patterns of inheritance are commonly observed within human families. These are autosomal dominant, autosomal recessive, sex-linked dominant, and sex-linked recessive" (p. 50). There is no mention in the text of *additive* (codominant or gene-dose) *inheritance* until page 136 ("pedigree analysis of ALDH1 in hair root follicles [Goedde et al., 1985] suggests an autosomal codominant mode of inheritance"). Yet, ample data in the subsequent text support numerous examples of autosomal additive inheritance of pharmacogenetic differences (e.g., plasma isoniazid concentrations [fig. 3-7, p. 62]; the inheritance of α1-antitrypsin deficiency [p. 218]; glucocorticoid-induced glaucoma [p. 309]; loss of one or both glutathione-transferase alleles [table 6-18, p. 207]; the paraoxonase [*PON*] gene and PON activities [tables 6-13, p. 179, and 6-14, p. 180]; the *CHE1* gene encoding serum cholinesterase [p. 182]; and thiopurine methyltransferase activity [fig. 6-11, p. 212]). The statement "genetic susceptibility to the insulin-resistant state is a rare trait that is inherited *polygenically*" (p. 255; italics added) is inconsistent with the two paragraphs on the genetic aspects of the insulin-receptor gene, leading me to conclude that Weber had intended this as an example of *polyallelic* inheritance. There are also several distracting examples of vague or nonstandard terms, such as "allelic gene" (p. 185) and "gene loci" (p. 204).

Chapter 4 ("Drugs and Genes") attempts to cover all aspects of James D. Watson's *Molecular Biology of the Gene* and, to me, appears to be unwarranted in a book about pharmacogenetics. For example, do readers of this book really need to know that human chromosome 2 is 277 cM in length (table 4-1, p. 72)? Is an illustration (fig. 4-1, p. 76) of the human mitochondrial "DNA genome" [*sic*] relevant to the subject of this book? That DNA is a helix (fig. 4-2, p. 77), that mRNA is derived from exons after introns have been removed, and that protein is translated from mRNA are facts that are now presented to high-school students. Chapter 4 is the least interesting and least essential part of the book.

Chapter 5 ("Experimental Models") represents a return to excellence. There is an outstanding description of the development of congenic mouse lines and their relevance to pharmacogenetics (a subject near and dear to Weber and to me). There is one important typo (p. 117): in the book, "*formyl-*

acetoacetate hydrolase" (italics added) should have been written as *fumaryl*acetoacetate hydrolase (encoded by the *FAH* gene). The chapter ends with the most recent concepts on how to generate knockout and other transgenic mouse lines and on how to use "quantitative trait linkage (QTL) mapping" in the elucidation of pharmacogenetic disorders. These discussions are absolutely first-rate.

Part II of the book is almost twice as long as part I. Each chapter and section in part II is followed by short exercises designed to demonstrate a pharmacogenetic principle or to illustrate the application of concepts and techniques to pharmacological problems; these exercises are drawn almost entirely from observations (taken from the original literature) representing authentic clinical situations.

On the whole, part II is excellent. It is a bit disappointing, however, that, although the P450 cytochromes are discussed at some length (pp. 131–133 and elsewhere), there are no references citing the well-developed *CYP* gene–superfamily nomenclature system or the continuously updated Website (http://drnelson.utmem.edu/homepage.html) on this subject. It also is unfortunate that the *CYP2D6* alleles "A, B, C, D, L," et cetera (p. 169) are described in this book published in 1997, because a recommended standardized nomenclature system for all the human *CYP2D6* alleles was reported in early 1996 and has already become widely accepted. Furthermore, it would have been helpful to the student reader to learn that aldosterone synthase and steroid 11-β-hydroxylase (under "Glucocorticoid-Remediable Aldosteronism," pp. 222–225) are in fact P450 cytochromes encoded by the *CYP11B2* and *CYP11B1* genes, respectively.

It always has been debatable as to where to draw the line regarding inclusion or exclusion of a human disease as a pharmacogenetic defect. For example, if pyridoxine-responsive anemia, fructose intolerance, and lactose intolerance are included as "pharmacogenetic disorders," then why not acatalasemia, ceruloplasmin deficiency (Wilson disease), and Na^+-sensitive hypertension? Likewise, cystic fibrosis, vasopressin resistance, retinoic acid resistance/acute promyelocytic leukemia, and thrombophilia are included in the book, whereas other disorders (e.g., the CYP2A6-mediated coumarin 7-hydroxylase, NAD(P)H:quinone oxidoreductase, and microsomal epoxide hydrolase polymorphisms) are not included.

Last, I believe that the textbook could have been improved if the reader had been given the opportunity to ponder why, on an evolutionary basis, these human pharmacogenetic polymorphisms might have occurred in the first place (see Nebert 1997 and the references therein). It is now very clear that DMEs and the DME receptors that control the levels of DMEs first evolved for critical life functions (e.g., cell division, sporulation, mating, homeostasis, electrolyte balance, differentiation, apoptosis, and neuroendocrine functions); then, in animals, DMEs more recently expanded to include the role of detoxification of dietary products, evolving plant metabolites and, of course, drugs. Hence, the high allelic frequencies seen for many DME genes, among individuals within any one ethnic group, might represent the evolution of *balanced polymorphisms* that we presently cannot appreciate, such as improved rates of implantation, prenatal growth and development, postnatal health in response to dietary selective pressures, or even resistance to bacterial or viral infections. Allelic frequencies in DME genes that differ among ethnic groups also might reflect differences in diet that have evolved over thousands of years.

Two recent examples of clinical diseases correlated with mutations in a DME gene (encoding enzymes that have been commonly ascribed only to metabolizing drugs and other foreign chemicals) further underscore the tenet that DMEs often modulate critical life processes. Mutations and deletions in the microsomal aldehyde-dehydrogenase gene called "fatty-aldehyde dehydrogenase" (*FALDH*) have been shown to be the cause of Sjögren-Larsson syndrome, which is characterized by mental retardation, spasticity, and ichthyosis, indicating the importance of this enzyme in neurocutaneous homeostasis. Mutations in the *CYP1B1* gene appear to be responsible for primary congenital glaucoma (buphthalmos), implying that failure of the CYP1B1 enzyme to metabolize a specific endogenous substrate leads to this affliction. Perhaps this subject (i.e., the real reason for the existence of DME genes and these clinical polymorphisms) could have been used to replace the naive chapter 4 of part I, or it could have been used as a third, conclusion section.

All in all, however, this book is a worthwhile addition to the shelves of all colleagues in the field. *Pharmacogenetics* should serve, for the next several years, as an invaluable resource for helping to teach upper-level undergraduates, graduate students, and other students of such health sciences as medicine, pharmacy, and nursing.

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Reference

Nebert DW (1997) Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? Am J Hum Genet 60:265–271

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Oxford Medical Databases, version 2.0. By Robin Winter and Michael Baraitser. Oxford: Oxford University Press, 1996. £395.00 each.

The *London Dysmorphology Database* has been my favorite syndromology search program for many years, but I have never found it particularly easy to use. When I have been away from it for a few weeks, I always seem to forget exactly which key to push to make it do what I want. I was, therefore, anxious to tear open the shrink-wrap on this new Windows® implementation to see if my old friend was now friendlier.

The version of *Oxford Medical Databases* (*OMD*) that I