CHAPTER 1

Introduction: Pharmacogenomics and Pharmacogenetics—A Historical Look

LEARNING OUTCOMES:

At the end of the chapter, you should be able to:

1. Identify and discuss significant historical findings as they relate to pharmacogenomic and pharmacogenetic issues in current contemporary pharmacy practice.

2. Identify and discuss the specific mechanisms by which genetic differences might account for differences in therapeutic effectiveness or toxicity as applied to patient care.

3. Discuss the two aspects of "personalized medicine."

For nearly a generation, it has been understood that some of the differences in how individuals respond to drugs are inherited and therefore, at least in part, genetic. Recent technological advances in genetics now allow pharmacists and other health care professionals to explain and anticipate some of this genetic variation in drug response. The rapidly emerging science of **pharmacogenomics** has the ultimate goal of identifying the many underlying genetic factors that play a role in the efficacy or toxicity of all drugs.

Pharmacogenomics is one of the most rapidly growing fields of biomedical science and is becoming integral to all aspects of drug discovery, design, and development. The science of pharmacogenomics represents the union of three fields of genetics—molecular, population, and quantitative genetics. Although it is not yet clear whether this pharmacogenomic revolution will have widespread clinical relevance, there is no doubt that in the future, health care professionals in general, and pharmacists in particular, will require significant understanding of genetics and genomics.

1.1 Genetics and Pharmacogenetics: A Brief History

Individuals have always differed in how they respond to drugs. The ways in which patients respond to a particular drug is too often unpredictable; responses range from little or no therapeutic benefit to harmful adverse drug reactions.[1,2] This lack of predictability in patient response results in substantial costs to contemporary health care systems. Many factors, including age, gender, drug interactions, and concomitant diseases and therapies, have long been known to affect treatment efficacy or toxicity (Figure 1-1). In addition, drug response may be enhanced or altered by drugs that a patient may be taking concurrently.[3]

Recently, the advent of molecular genetics and the dramatic development of genomic technologies have made it possible to consider the effect of a patient's underlying genetic makeup on drug response. This is true despite the massive complexity of the human **genome**, which has more than three billion gene-encoding "letters." However, neither the term **pharmacogenetics** nor the field it represents are recent phenomena (Figure 1-2). The term itself was coined in 1959 by Vogel, a German geneticist, 94 years after an Augustinian priest, Gregor Johann

Pharmacogenomics:
The study of the genome-wide role of human variation in drug response. Pharmacogenomics is a broad term that includes pharmacogenetic effects. Pharmacogenomics also includes the application of genomic technologies in drug discovery, disposition, and function.

Genome:
The genome of an organism encompasses all the genetic material in the cell. In humans, this includes the 3 billion base pairs contained in the chromosomes in the nucleus and the approximately 16,000 base pairs of the mitochondrion.

Pharmacogenetics:
The study of the role of genetic variation in determining individual drug response. Generally, pharmacogenetics has been limited to the effects of one or a few genes.

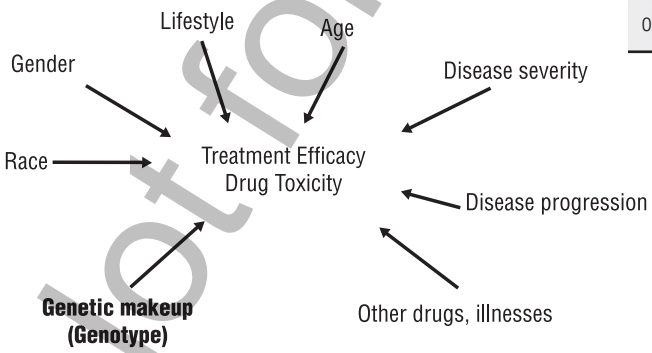

Figure 1-1. Many factors, working alone or in concert, determine how any given individual will respond to a drug. With the advent of genomic technologies and knowledge, it is becoming possible to assess the role an individual's genetic makeup or genotype plays in this response.

Pharmacogenomics		Genetics
	1859	Darwin publishes *On the Origin of Species*
	1865	Gregor Mendel's work published
	1869	Miescher isolates DNA
	1900	Rediscovery of Mendel's work by Carl Correns, Erich von Tschermak-Seysenegg, and Hugo DeVries
Chemical Individuality—"individuals do not conform to rigid standards of metabolism", Garrod.	1902	Bateson coins the term genetics and discovers linkage; also coins epistasis
	1910	Morgan's description of sex-linkage in *Drosophila melanogaster*; chromosomal basis of inheritance
Garrod's *Inborn Factors in Diseases* —first link between genetics and pharmacology—postulated a mutation in gene for enzyme responsible for metabolism	1931	
Snyder—PTC and "taste blindness" in 800 families	1932	
	1941	Beadle & Tatum—one gene, one enzyme (biochemical genetics and medicine)
	1944	Avery, MacCloed, and McCarty—DNA may be the stuff
Alving et al.—acute hemolytic response to primaquine in African American soldiers	1952	Hershey and Chase—DNA is the stuff
	1953	Watson and Crick's molecular model for DNA
Kalow and genetics of serum cholinesterase, first to show heritable variant enzyme and drug sensitivity Motulsky—*Drug reactions, enzyme, and biochemical genetics*	1957	
Vogel proposes the term *Pharmacogenetics*	1959	
Kalow publishes first monograph in pharmacogenetics	1962	
	1966	Genetic code described
	1970	Isolation of first restriction enzyme
Smith—Debrisoquine and CYP2D6	1977	DNA sequencing
	1985	Polymerase chain reaction
First cloning of "pharmacogenetic	1988	Human Genome Project
gene", CYP2D6, Gonzalez et al.		
	2000	First draft Human Genome

Figure 1-2. Genetic timeline showing the correspondence among discoveries in the pharmaceutical sciences and genetics. With our better understanding of genetics and the molecular biology of drug action, these two seemingly disparate fields are beginning to merge and hasten the advance of both.

Mendel, first described the laws that govern the inheritance of simple traits in pea plants. *Pharmacogenetics* has traditionally been defined as the study of the influence of a single gene on drug response. *Pharmacogenomics*, a more recent term, is often used interchangeably with *pharmacogenetics*, though the former is

a broader term that includes not only the effects of a single gene but also the genome-wide influence on drug response, efficacy, and toxicity. The field of pharmacogenomics also includes the application of genomic technologies to identify networks of genes that affect drug efficacy and toxicity, ascertain new therapeutic drug targets, and optimize current pharmacotherapeutic treatments. It is this latter area of pharmacogenomics that is having an enormous, though largely unreported, impact on the pharmaceutical and biomedical sciences.

Mutation:
A change in the DNA sequence of the genome. Mutations occurring in the germ line are potentially heritable. Changes in DNA sequence are of two basic types: single-nucleotide polymorphisms (SNPs) or insertion/deletions (indels) that can be from one to millions of nucleotides in size.

Autosomal:
Genes or loci that reside on any chromosome other than the sex chromosomes (i.e., the X and Y chromosomes).

Recessive:
A property of one of two alleles. An allele is said to be recessive when its phenotype is masked or unseen when in combination with another allele. The other allele is said to be dominant. Recessive alleles need not be rare in a population or deleterious to the individual.

Perhaps the first link between genetics and pharmacology was made by Sir Archibald Garrod, who postulated in his book *Inborn Errors of Metabolism*[4] that a **mutation** in a gene coding for an enzyme may be responsible for human differences in the metabolism of drugs and environmental chemicals. The first large-scale study documenting human variation in response to a chemical was conducted by L. H. Snyder.[5] Snyder investigated over 750 families and showed that "taste blindness," the inability of some individuals to taste the chemical phenylthiocarbamide, was inherited as an **autosomal-recessive** trait.

One of the first documented "pharmacogenetic stories" was isoniazid, first synthesized in 1912, which became the first line of treatment for tuberculosis in the 1950s. Isoniazid is metabolized in the liver via **acetylation**, and elimination for the metabolite is primarily renal. As isoniazid increased in clinical usage, it was quickly noted that some patients reported peripheral neuropathies, specifically numbness in the arms or legs, often accompanied by pain. These complications were attributed to the interaction of the drug with pyridoxine, or vitamin B_6—specifically, the depletion of vitamin B_6. By 1954, the complications were found to be specifically associated with patients exhibiting deficiencies of a specific enzyme, N-acetyltransferase.[6] Patients with genetic deficiencies of N-acetyltransferase-2 exhibited a low ability to degrade isoniazid to acetylisoniazid and were termed "slow acetylators." Ultimately it was found that approximately 50% of African Americans and Caucasians are slow acetylators, whereas rapid acetylators are more common

among Asians. Fast acetylators have been identified with drug half-lives that are two to four times shorter than those seen in slow acetylators, and these differences have had clinical consequences for a number of important drugs other than isoniazid, including procainamide, hydralazine, phenelzine, and salicylazosulfapyridine.[7]

Acetylation:
A reaction that introduces an acetyl functional group into a chemical compound. Most proteins are modified by acetylation.

Polymorphic:
A gene or locus is polymorphic if there are differences among individuals in its DNA sequence or length. Generally, the specific difference must have a frequency of 5% in the population to be considered polymorphic.

Homozygous:
A locus or individual is said to be homozygous if the two alleles present are identical. Heterozygous individuals carry different alleles at the locus of interest.

An interesting case of interactions among genes, drugs, and ethnic origins was noted during World War II. The commonly used antimalarial drug primaquine was found to cause hemolytic disease in an unusually high number of African American soldiers. After the war, work done in the Alving laboratory at the University of Chicago showed that a poor response occurred in patients with glucose 6-phosphate dehydrogenase deficiency.[8,9] The gene for glucose 6-phosphate dehydrogenase is found on the X chromosome and is one of the most **polymorphic** in humans. The deficiency was found to be more common among Americans of African, Mediterranean, and Asian descent and presumably reached higher frequencies in these populations because it provided some resistance to malaria. The frequency of these low-activity alleles of glucose 6-phosphate dehydrogenase is highest among populations where malaria is prevalent. In this case, the gene placing patients at risk is not part of the drug's metabolizing pathway, nor is it the immediate target of the drug. This example provides a hint of the complexity of the many gene–gene interactions that are now familiar to scientists. Individuals with this genetic defect are also prone to hemolytic events due to other causes, such as infections and ingestion of fava beans (favism).

Another early example of genetic differences in drug biotransformation was elucidated by Kalow and colleagues, who in 1957 demonstrated that prolonged apnea in response to the muscle relaxant succinylcholine was due to inherited structural differences in the enzyme pseudocholinesterase.[10] This work was the first to demonstrate a link between heritable differences in an enzyme structure and drug response in patients. Recently, Lockridge has shown that this enzyme variant is due to a substitution of the nucleotide at position 209, which results in a change in amino acids from aspartic acid to glycine.[11] Approximately one in 3,500 Caucasians are **homozygous** for atypical forms of this gene.[12]

By the late 1950s, enough "pharmacogenetic cases" existed that the American Medical Association invited the geneticist Arno Motulsky to summarize the known findings in a paper titled "Drug Reactions, Enzymes, and Biochemical Genetics."[13] It was two years later that Vogel coined the term *pharmacogenetics*.[14] The field of pharmacogenetics had begun, and by 1962, Kalow had published the first book in the field.[15]

Perhaps the most studied genetic polymorphism in a drug-metabolizing enzyme, cytochrome P450 2D6 (CYP2D6) results in an abnormal and extended drop in blood pressure in response to the no-longer-used antihypertensive debrisoquine. Work has shown that subjects can be readily grouped into two classes, "poor metabolizers" and "extensive metabolizers."[16] Poor metabolizers are deficient or lacking in this enzyme. They have also been found to have lower urinary concentrations of metabolite and higher plasma concentrations of parent drug than do normal individuals or extensive metabolizers. Another drug, the anti-arrhythmic spartein, is also metabolized by CYP2D6 and produces a similar response.[17]

This work has become significant for two reasons (see Kalow 2004 for an excellent historical review[18]). First, this polymorphism is fairly common, having allele frequencies of 5% to 10% among Caucasians in Europe and North America, and thus is likely to be clinically important. Second, CYP2D6 is known to metabolize many clinically important drugs, including β-adrenergic–blocking agents, antidepressants, and anti-arrhythmics. CYP2D6 was the first pharmacogenetically relevant gene to be cloned and sequenced and to have its "poor metabolizer" alleles characterized.[19] Recently, many more genetic variants have been identified and shown to have effects ranging from low or no enzyme activity to individuals with multiple copies of the gene. Interestingly, the frequency of the multicopy CYP2D6 gene was 29% in one Ethiopian study,[20] a likely indication of the geographic origin of this mutation.

With the near completion of the sequencing of the human genome in 2000, the broader impact of the field of pharmacogenomics has grown at an increasing rate. The list of pharmacologically relevant genes has greatly increased to include not only those encoding traditional drug-metabolizing enzymes but also genes coding for drug transporters, as well as the many genes coding for the targets of drug action. Pharmacogenetic data are now routine components of new drug investigations and applications. Pharmacogenetic information is included in required drug labeling for new drugs as appropriate based on required clinical testing. The U.S. Food and Drug Administration has recently approved genetic tests for a number of medications. The role of genetics in pharmacy and pharmacy practice has a long history, and there is little doubt that genomics has and will continue to have a significant impact on the science and practice of pharmacy.

1.2 The Role of Pharmacogenomics in Pharmacy and Pharmacy Practice

Genomics is changing the nature of medicine and health care. The ability of genomic technologies to generate data has far outpaced researchers' abilities to assimilate the information. In as little as 20 years, sequencing rates have increased from efforts requiring two days to garner 500 base pairs of DNA sequence to automated systems generating millions of base pairs of sequence in a single day. The once unimaginable idea that individuals could have their entire genome sequenced at a cost similar to that of routine medical tests is now anticipated in the very near future. It's been estimated that the cost of determining an individual's genome sequence is decreasing by a factor of 2 with each year; thus the cost of determining the entire genome sequence for an individual at birth will be feasible, though likely unnecessary. Similarly, many thousands of human genetic polymorphisms for genes encoding drug-metabolizing enzymes can now be assayed on a single DNA "chip." These same genomic technologies enable the assessment of gene expression for thousands of genes from as little as a few cells, allowing for the very precise measurement of gene expression for specific tissues within an organ or tumor. These technologies are revolutionizing research in all the life sciences.

1.2.1 Personalized Medicine: Two Perspectives

It is now becoming possible to examine and ultimately comprehend the nature of disease and drug action at the molecular level. This information will certainly be the foundation of humankind's ultimate understanding of the nature of human health and disease. New molecular diagnostic tools will allow health care professionals to characterize human disease into ever finer distinctions and categorizations. Personalized medicine will come to mean not just the right drug for the right individual, but the right drug for the specific disease type afflicting the specific individual. This "individualization" of disease will allow for many more specific and successful therapeutic interventions than are now possible.

The speed at which technologies have become available and the ease with which they are conducted make the challenge not so much determining a patient's genetic makeup or specific disease state as deciphering the massive amount of data presented. The field of bioinformatics has grown in parallel to genomics as a means to address the computational complexity associated with increasing genetic information. Similarly, the greatest challenge to the translation of genomics and pharmacogenomics from "bench to bedside" is the education of pharmacists and other health care professionals. This educational deficit has been noted both within the curricula of schools of pharmacy[21] and among practicing pharmacists.[22] The need is particularly acute because the science of pharmacogenomics is really a combination of three information-rich areas of genetics (Figure 1-3):

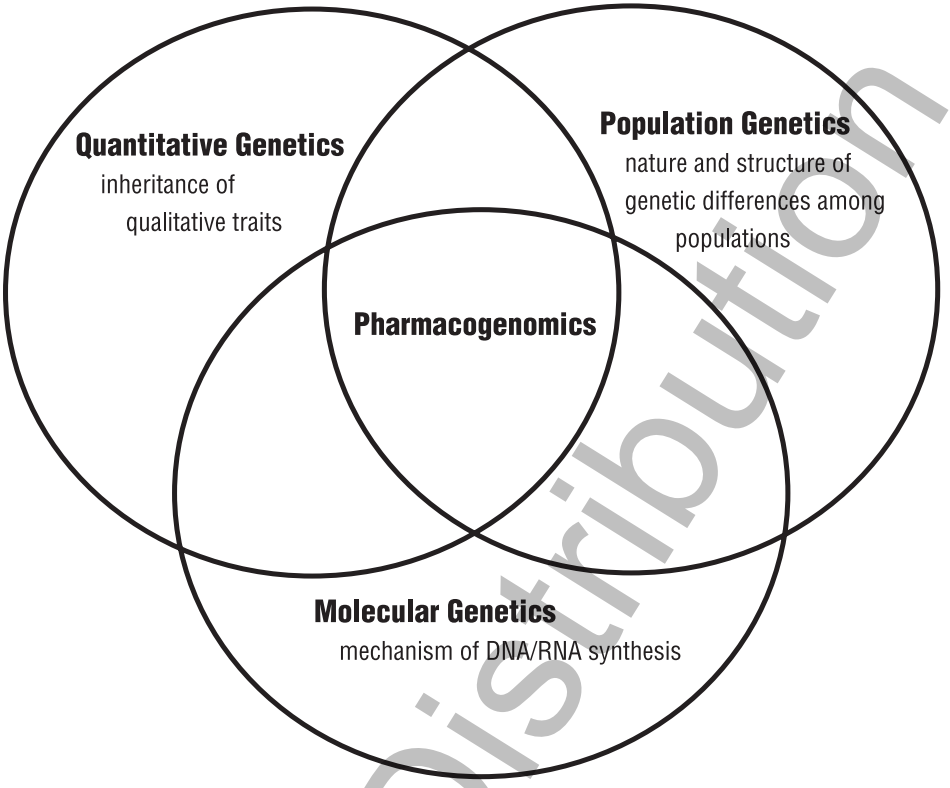

Figure 1-3. The field of pharmacogenomics/pharmacogenetics represents the intersection of three distinct disciplines in genetics. Ultimately, any "genomic" understanding of how a patient responds to a drug will be a function of the molecular mechanisms that underlie the cellular response (molecular genetics), the interaction between the patient's many genes and a multitude of environmental factors (quantitative genetics), and the variation in genetic background among human populations (population genetics).

- Molecular genetics—the study of the mechanisms of DNA and RNA synthesis, including gene regulation.
- Population genetics—the study of the nature, structure, and maintenance of genetic variation among populations.
- Quantitative genetics—the study of the inheritance of continuous or qualitative traits.

The future practice of pharmacy and medicine will require of its practitioners a basic understanding of genetic and genomic principles in order to realize the advancements that genomics offers.

QUESTIONS

1. What is a genome of an organism, and how does it relate to contemporary patient care?

2. Discuss the difference between the terms *pharmacogenetics* and *pharmacogenomics* as it relates to contemporary pharmacy practice and health care.

3. Identify specific types of polymorphisms that could affect the efficacy or toxicity of a specific drug.

4. Identify the significant findings made by the following individuals as they relate to differences in patients' response to drugs or disease:

   a. Sir Archibald Garrod
   b. L. H. Snyder
   c. A. S. Alving
   d. A. Motulsky
   e. W. Kalow
   f. R. L. Smith
   g. F. Vogel

5. Define "personalized medicine" and its significance in patient care.

6. Pharmacogenomics is the integration of what three genetic areas?

7. What genetic polymorphism is fairly common with respect to drug biotransformation, and what is the clinical significance in pharmacy practice?

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