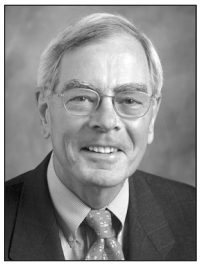

Michael J. Dunn, MD

Dean's Corner

Efforts in pharmacogenetics will help patients get right amount of right drug

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Physicians know that some patients respond better to one drug than another, despite the drugs having identical mechanisms of action. They also know that a beneficial drug can be either harmful or useless if the dose is too high or too low. From these simple observations, the surprisingly mature field of pharmacogenetics originated.

Since at least the 1950s, this information has been documented and to some extent utilized to make clinical decisions, but with the advent of the Humane Genome Project, pharmacogenetics has raced to the forefront of medicine as researchers elucidate the substantial role of genes in the body's interaction with drugs. As we recognize the vast potential of this knowledge to improve outcomes, the Medical College of Wisconsin has faculty physicians and scientists dedicated to answering key questions that will make drug development and use safer and more effective.

In practical application, pharmacogenetics uses a genetic assessment to predict a patient's response to a pharmaceutical treatment. For the patient, it individualizes treatment to the extent that optimal therapy may be achieved more quickly and toxicity may be avoided. The most dramatic influence may be for those drugs that have a narrow therapeutic window—the distance in drug concentration between what is therapeutic and what is toxic. When drugs have a wide therapeutic window, refining the dose is not as important. When the window is narrow, precise dosing is crucial.

The anticoagulant warfarin is an apt example and one in which pharmacogenetics has changed the way the drug is prescribed. While the drug is not new, recent research into the 2 genes that account for the majority of the variation seen in human response to the drug has resulted in algorithms physicians can use. These algorithms take into account the patient's gender, age, body mass, and the genetics of 2 different gene loci: 1 for the enzyme that is involved in metabolism of the drug (CYP2C9) and 1 for the target (VKORC1), the enzyme that gets blocked by warfarin. The result is a recommended starting dose optimized for that patient.

Chemotherapy drugs also have a narrow therapeutic window, so pharmacogenetics is helping patients avoid toxicity from drugs such as thiopurine methyltransferase (TPMT). People who are homozygous for the variant in the gene that handles TPMT have a much greater risk of adverse outcomes.

Such variants underscore the importance of a pharmacogenetic approach to patient care. Researchers have discovered that many of the genetic variants that affect drug response and drug disposition in the body are relatively common. Some exist in 40%—50% of the population. Now, the challenge is to build on the plethora of knowledge that is the foundation of the field. In many cases, we know which enzymes handle which drugs, we are aware of the polymorphisms that contribute to varied response, and we generally know how much of an impact these variations have. By working to expand the science, we facilitate the development of tools or other resources that physicians can use.

Ron Hines, PhD, and Gail McCarver, MD, are among the most active Medical College of Wisconsin investigators in pharmacogenetics. Dr Hines is professor and Dr McCarver is associate professor of Pediatrics and of Pharmacology/Toxicology. They are Pediatric Co-section Chiefs of Clinical Pharmacology, Pharmacogenetics and Teratology, and they conduct much of their work within the Children's Research Institute.

Pharmacogenetics in the pediatric population has distinctive elements, particularly in that different genes turn on (and off) at different times in human development. Some genes may turn on prior to birth. Others may turn off at birth. Even more may be silent until a child is 1 or 2 years old. The combinations are nearly endless and mean that the enzymes that handle different drugs may or may not be functioning depending on age.

A major area of research for Dr Hines centers on the liver, which, of all organs in the body, has the greatest concentration of drug metabolizing enzymes. He has sought to identify when genes turn on and begin producing drug metabolizing enzymes, as well as how this might affect response to therapy or adverse reactions.

His team quickly discovered tremendous variability, not just from gene to gene, but also person to person. Now, they are concentrating not only on mapping out when different genes in the liver system turn on in individuals, but also examining what could be regulating that variability.

Dr Hines' group also has a National Institutes of Health subcontract with one of the pioneers in the field who actually discovered the genetic variation on CYP2C9 that impacts warfarin, Allan Rettie, PhD, at the University of Washington. The Medical College team is focusing on an African American population of patients at Froedtert Hospital. As a demographic, African Americans require a higher average dose of warfarin than do Caucasians. (For that matter, Caucasians require higher doses than Asians, and children at an early age require higher doses than adults). The research hopefully will explain what causes these differences.

Doctor McCarver is heading a number of projects at the basic science level, some of which overlap into the field of toxicogenetics. For example, she is studying how a particular enzyme handles chlorzoxazone, a muscle relaxant. The research is looking at the compound in the context of both alcohol and solvents in the environment while considering specific genetic polymorphisms and how they interrelate to exposure, and how the two together relate to outcomes of infants of women who were exposed during pregnancy. Further pharmacogenetics research is aimed at how that enzyme is regulated. Doctor McCarver also has a project looking at methadone metabolism in infants and the genetic factors, in conjunction with age, that influence it.

Other faculty members in the section have research dedicated to genetics' effect on the proteins that transfer thiopurines in and out of cells as well as the pharmacogenetics of pain management.

Together, Dr Hines and Dr McCarver are leading a pharmacogenetics initiative expected to roll out in July. The clinical protocol will be a pilot in Children's Hospital of Wisconsin's First-time Seizure Clinic. Using a gene chip—a piece of technology that contains information on 150-200 different genes—every child admitted to the clinic will have his or her genes tested. The patient's genetic make-up should help doctors decide what particular drug will be best for the child for seizure control and what dose might be optimal.

The clinic admits approximately 400 children a year who have had a seizure for the first time. Since the drugs used for seizure control have a high adverse toxicity rate, choosing the best drug and dose is very important. The project unites the genetic expertise of Uli Broeckel, MD, associate professor of Medicine, and David P. Bick, MD, associate professor of Pediatrics, both researchers in the Medical College's Human and Molecular Genetics Center, with the neuropharmacology knowledge of Charles J. Marcuccilli, MD, PhD, assistant professor of Pediatric Neurology at the Medical College.

As more investigations take place, practicing physicians will be challenged to keep current and make use of the resulting information. Most important, according to Dr McCarver, will be a physician's knowledge of clinical pharmacology; for example, what enzyme handles a drug, whether the drug is inactivated or activated by metabolism, and what receptor in the body is involved. We expect the materialization of more Web sites and searchable databases that list such information, but clinicians will need to understand the concepts to make use of the tools.

Of course, pharmacogenetics is just a piece of a larger landscape that aids in diagnoses and treatment. Age, diet, and interaction with other medications are all confounding factors that must be considered if pharmacogenetics is to be used successfully in clinics. The more our studies uncover, however, the more we realize that pharmacogenetics is an opportunity to improve outcomes in virtually all disease areas, and that is worth our full attention.

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