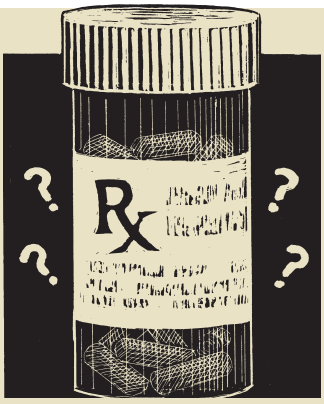
On the cusp of change

By Stephen P. Spielberg, M.D., Ph.D.



SUZANNE DEJOHN

The ultimate goal of pharmacogenomics is delivering the right dose of the right medicine to the right patient.

Physicians have long noted that patients have varying responses to a given medication. Some respond well and their condition improves; others do not. Some develop rare but severe and currently unpredictable side effects; most do not.

The study of this variability—which is often based in genetics—is called pharmacogenetics or pharmacogenomics. As this issue of Dartmouth Medicine rolls off the presses, we will be hosting our first pharmacogenomics symposium at Dartmouth. This event, organized by Dr. Lionel Lewis in our Section of Clinical Pharmacology, will celebrate the field's enormous advances in recent years, as well as its huge potential.

I've been involved in the discipline since the early 1970s. One of my mentors, Dr. Werner Kalow, noted in the 1950s at the University of Toronto some rare outcomes of anesthesia—including failure to recover muscle tone after administration of the muscle relaxant succinylcholine. Using the scientific tools available at the time, he figured out that this was due to lack of an enzyme called pseudocholinesterase, and that its absence was inherited. Other investigators began studying identical and fraternal twins and demonstrated that much of the variation in response to medicines is inherited. Of course, factors such as age, gender, food, the disease being treated, and interactions with other medicines can also modify a drug's response.

Lens: Now fast-forward to today. The genomic revolution has given us sophisticated tools to analyze genes' contributions to why we get sick and to how we respond to therapy. Dr. Kalow continues to work in the field, having moved from clinical observation to biochemistry, population genetics, and modern genomics to address the questions that have fascinated him for over half a century. He has taught generations of students, fellows, and colleagues how to look at human pharmacotherapy through the lens of pharmacogenetic variability.

Dr. Kalow exemplifies the human curiosity that drives basic research, pushes the limits of current knowledge, embraces new technology, eschews the blinders of a specific field, and remains open to where science leads. He had the brilliance to recognize what was important about his early observation, he followed the science, and other scientists followed him. When I began doing pharmacogenetic research, symposiums on the subject often had as many speakers as audience members. Today, overflow audiences in large auditoriums are the norm. Dr. Kalow has lived to see his vision take flight.

But despite the relative sophistication in the way drugs are developed today, there remain enormous roadblocks to converting scientific advances into medicines, to making those medicines affordable, and to making them available to all who need them. Solving these problems is not the domain of one discipline but of many—chemistry, pharmacology, toxicology, clinical medicine, outcomes evaluation, health economics, sociology, ethics, and government regulation. And, now, pharmacogenomics.

The goal of pharmacogenomics is to individualize therapy—to more precisely diagnose the cause of a given person's disease (not just "hypertension," for example, but "hypertension due to such and such") and to better predict that person's risk of side effects from a given drug. The ultimate goal is delivering the right dose of the right medicine to the right patient.

Model: But this is not the way we now develop or use medicines in the U.S. Pharmaceutical firms rely on "blockbusters"—drugs used by large numbers of patients to generate large profits that will, hopefully, be reinvested in developing new drugs. But the loss of a single blockbuster through expiration of its patent (the antidepressant Zoloft being a recent example) or withdrawal from the market (as with Vioxx) can have a huge negative impact on a company's research efforts. And this economic model does not support the creation of drugs aimed at small markets even though they may offer more effectiveness and less side-effect risk. Risk is now a major driver of drug costs. So we run huge clinical trials to look for rare side effects, rather than seeking ways to predict, screen for, and prevent adverse effects.

What does this mean for Dartmouth? These are complex times, but that has always been the case in medicine. More importantly, these are times when, if we are skillful and willing, we have the opportunity to provide care for our patients in ways that physicians of the past could only dream about. It will require collaboration and cooperation. It will require us to question, to critique, to continuously evaluate what we do. It will require us to look beyond our own fields, to heed experts in other disciplines. And it will require us to rethink how we educate medical students about a therapeutic world that may look very different from the model of today.

Better care: I believe Dartmouth is uniquely situated to accomplish many of these goals. We have, for example, been national leaders in shared decision-making and in basing medical choices on data, not opinion or tradition. Yet even so, the data we now have to work with is based on averages—this drug helps 60% of people with condition X, with a 1 in 10,000 risk of a severe side effect. What a difference it would make if, through pharmacogenetics, we could provide an individualized prediction of benefit and risk! Our sponsorship of the pharmacogenomics symposium is just one example of how we are positioning ourselves to be on the cusp of this change—to better care for our patients and to better prepare our students for the complexities and the opportunities that science will continue to present. ■

"For the Record" offers commentary from the dean of Dartmouth Medical School. Spielberg, a pediatrician and a pharmacologist, has just begun his fourth year as DMS's dean.