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Special Issue on Pharmacogenomics and Anesthesia: Work Presented at the 2004 Journal Symposium

IN this issue of ANESTHESIOLOGY, we mark the beginning of another annual event. Last year, for the first time, the Journal published a "special issue" containing manuscripts of research presented at the ANESTHESIOLOGY-sponsored Symposium at the Annual Meeting of the American Society of Anesthesiologists. In an accompanying editorial, the Editor-in-Chief, Michael M. Todd, M.D., stated his hope that the issue would be the first in a series of annual special issues. In the present issue, we feature 10 manuscripts based (in part) on research presented at the 2004 Journal-sponsored Symposium, "Pharmacogenomics and Anesthesia: Determinants of Individual Response and Outcome." This being the first anniversary of the special issue, we can now inaugurate it as an annual event.

The Journal Symposium examined the application of recent advances in pharmacogenetics to anesthesia, with a focus on how genetic variability affects our patients' response to drugs. Pharmacogenetic variability may influence drug metabolism, drug transport, receptor structure and function, cell signaling, and the myriad of downstream responses we perceive in daily practice. The past few years (we're now a decade into the "postgenome" era) have witnessed explosive growth in technological capabilities, genome mapping, molecular and human genetics, computational biology, and "omics." In addition to pharmacogenomics, we have functional and structural genomics, transcriptomics, proteomics, metabolomics, and others. The exponential increase in this research is evidenced by simply viewing the articles indexed in MEDLINE that address pharmacogenetics and pharmacogenomics (fig. 1).

Yet what is new, is old. Sir William Osler, in 1892, said, "*If it were not for the great variability among individuals, medicine might as well be a science and not an art.*" The term pharmacogenetics dates back to 1959.[1] Anesthesiology as a specialty provided some of the first insights into the clinical impact of pharmacogenetics. Prolonged apnea after succinylcholine, thiopental-induced acute porphyria, and malignant hyperthermia were clinical problems of the 1960s whose investigation

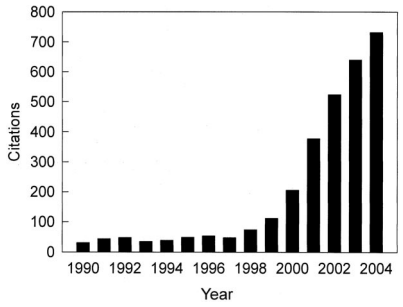

Fig. 1. Annual citations in PubMed listed in response to the search terms pharmacogenetics or pharmacogenomics.

helped craft the developing new science of pharmacogenetics. Today we perhaps take for granted the knowledge that they are genetically-based problems, due to variants in pseudocholinesterase, deficient heme synthesis, and the ryanodine receptor, respectively. Reading the first reports of these problems gives insight into how far we have progressed. The cover of this month's ANESTHESIOLOGY exemplifies this progress, depicting the ryanodine receptor gene and the myriad polymorphisms that have been identified to date.

Some of the greatest challenges of the "postgenome era" will be managing the unprecedented amount of information generated, educating physicians to understand and use the new biology, communicating new knowledge to clinicians and patients, and translating it into clinical advances. Towards that aim, ANESTHESIOLOGY chose "Pharmacogenomics and Anesthesia" as the theme for the 2004 Symposium. The Symposium featured lectures on "Pharmacogenomics of Drug Disposition," by Kenneth Thummel, Ph.D. (Professor of Pharmaceutics and Associate Dean for Research, University of Washington School of Pharmacy, Seattle, Washington); "Autonomic Nervous System Pharmacogenomics," by Paul A. Insel, M.D. (Professor of Pharmacology and Medicine and Director of the Medical Scientist [M.D.-Ph.D.] Training Program, University of California, San Diego, California); and "Pharmacogenetics of Responses to Cardiovascular Drugs," by Brian Donahue, M.D., Ph.D. (Assistant Professor of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee). All of these speakers graciously agreed to be recorded and provide their slides, and we are pleased to offer their presentations as a Web Enhancement to this month's issue.

In addition to these plenary lectures, there were 16 posters selected for presentation at the Symposium. These authors were invited to submit a formal manuscript relating to their work, which underwent peer review. In this issue we feature 10 such articles, along

Additional material related to this editorial can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate editorial and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or in the HTML version of the editorial. This Editorial View accompanies the Symposium articles in this issue.

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with a review article. The topics include genetic influences on drug disposition, responses to various drugs across several classes, and receptor polymorphisms, and the articles represent authors from eight countries—truly an international effort. The goal of Journal Symposia is to feature dynamic areas and new research relevant to anesthesiology, and to stimulate investigators and encourage the publication of such work in ANESTHESIOLOGY. We invite you to read the fruits of such efforts in this month's issue.

The next Journal Symposium will be "Plasticity in Postoperative Pain," organized by Timothy J. Brennan, Ph.D., M.D. (Associate Professor, Department of Anesthesia, The University of Iowa, Iowa City, Iowa), and Srinivasa N. Raja, M.D. (Professor, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland). We look forward to this Symposium, and to next year's annual Symposium issue.

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Anesthesia and the Human Genome Project

The Quest for Accurate Prediction of Drug Responses

ANESTHESIA, like the rest of medicine, has always been a mixture of art and science. I have always told my trainees that anesthesia, like cooking, is best done "to taste," because no two patients responses are exactly alike. However, despite that caution, there have been occasions in my practice when the taste was very unexpected and led to an extraordinarily undesired outcome for my patient. In every case, these outcomes were examined to determine whether they could have been avoided. In almost all of these cases, the undesirable outcomes were found to be impossible to predict. In an ideal world, this would not be the case, and in this ideal world, patient care would be improved and medical costs would be decreased. In this issue, Palmer *et al.*[1] present an outstanding review of old, new, and future ways of making the dream of being able to better predict each patient's responses to the drugs we use every day become a reality.

The response of any given patient to anesthetic drugs is a classic example of the interaction of genes and environment. It depends on a complex formula including their individual genetic makeup, their endocrine and emotional states, and environmental factors that they have been exposed to in both their immediate and perhaps distant past. Anesthesiologists, even recently trained anesthesiologists, may have been briefly exposed to the "wonders" of modern molecular biology and the human genome project. However, for the most part anesthesiologists as a group tend to be unaware of how they are interacting with this branch of science in their everyday practice. The review of Palmer *et al.* will help to increase this awareness. It first provides an excellent guide to understanding the gobbledygook and alphabet soup that make up the language of geneticists, molecular biologists, and bioinformaticians who are the bulk of the experts in this field. Then, it discusses genetic conditions and interactions between genes an environment that are both relevant and important to every practicing anesthesiologist. These include the classic examples of pseudocholinesterase deficiency, halothane hepatitis, and malignant hyperthermia susceptibility as well as lesser-known traits associated with the duration of benzodiazepine action, opiate and nonsteroidal antiinflammatory drug action, and the perception of pain. The bibliography is extensive and a useful starting point for the reader to extend his or her knowledge base in this important area.

In their conclusions, Palmer *et al.* discuss some of the medical realities associated with taking advantage of these 21st century techniques, such as cost:benefit ratios and whether patients should be tested before or after a therapeutic problem. However, they sidestep the dilemma of the ethical problems of genetic testing and how we will manage the information after the "genie" is out of the bottle.

More importantly, this review points out a new oppor-

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David C. Warltier, M.D., Ph.D.,served as Handling Editor for this article.

tunity for our specialty to take the lead in doing medical research that is directly relevant to our clinical practice. One example of the practical importance of such studies might include being able to predict who would develop bleeding and who would develop graft thrombosis after coronary artery bypass grafting. With such predictive capability, we might alter our intraoperative management of the first group and give the second one larger doses of postoperative anticoagulants. A second example not discussed in the review but equally important is transcriptional profiling with the goal of silencing or induction of certain genes before anesthesia and surgery, *e.g.*, we may be able to alter gene expression in the elderly to prevent postanesthesia cognitive deficits and confusion. Or before surgery that would result in an ischemic injury, we may be able to induce genes responsible for defense mechanisms (*e.g.*, genes responsible for antiinflammation and resolution, the genes responsible for superoxide dismutase, catalase, or both). Lastly, understanding the genetic basis for pharmacogenetic disorders may be the backbone for creating gene therapy treatments to correct the disorder. We as anesthesiologists are in an ideal position with our intensive patient contact to initiate and facilitate the prospective sufficiently powered gene association studies that are critical for making these discoveries. In addition, because of our detailed preoperative evaluation, we are also in the ideal position to make certain that these studies include detailed patient demographics and carefully defined and measurable outcomes. If we do this, anesthesiologists will be in the position to both evaluate the clinical significance of various gene associations to our everyday practice and to put our specialty in the lead as contributors to this critically important area of medical discovery.

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