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Journal-related Activities at the 2004 American Society of Anesthesiologists Annual Meeting

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13th Annual Journal Symposium: Pharmacogenomics and Anesthesia: Determinants of Individual Response and Outcome

Tuesday, October 26, 2004, 8:00 AM to 11:50 AM, in Ballroom D-E, Las Vegas Hilton, Las Vegas, Nevada

The 13th Annual ANESTHESIOLOGY Journal Symposium examines the application of pharmacogenomics to anesthesia, and in particular how genetic variability affects the way in which patients respond to drugs in anesthesia practice. Over the last 5 yr there has been an explosion in the knowledge and technology of genomics in clinical pharmacology, allowing the study of specific drug action in disease states.

Pharmacogenomics has allowed us to identify the underlying mechanisms for much of the inherited variability in drug response. This can occur due to genetic variability in drug metabolism, drug receptor function, and drug transporter function. We know, for example, that opioid drugs are metabolized by specific P450 (and synthetic) enzyme systems in the liver, controlled by among other things, genetic factors. For many years, metabolism has been seen to be an important determinant of drug pharmacokinetics and that remains to be true. However, over the last 10 yr we have realized that membrane transporters are also vital to drug disposition. The efflux transporter, P-glycoprotein (a product of the MRD1 gene), is important in the role of opioid disposition, in addition to many other drugs in clinical use. Hence, single nucleotide polymorphisms demonstrated for drug metabolism, drug receptors, and transporter systems may contribute to genetic variability. The genetic variability in these systems may play a role in variability in clinical response, adverse effects, and drug interactions in anesthetic practice. At present, we titrate opioid dose to the patient's clinical response; understanding of opioid drug-related polymorphisms might allow us to more accurately tailor opioid dose for specific subsets of the population. Finally, it is now recognized that even apparently environmental effects have a genetic component, so that, for example, enzyme induction by drugs or environmental stimuli shows genetic variability.

The future will demand the translation of the genetic testing described at this symposium into routine patient care. Such translation will require the extension of these small clinical studies demonstrating genetic variability to larger, well designed, adequately powered studies demonstrating altered clinically relevant anesthetic outcome . . . drug toxicity/altered effect.

Understanding of the effects of genetics on drug response will require not only the identification of the polymorphisms that may account for that variability (genotype), but also large population-based studies to demonstrate the interindividual variability in drug response (phenotype). We who anesthetize many thousands of patients on a daily basis should be poised to conduct and to lead these types of studies.

The "holy grail" of pharmacogenomics is "personalized medicine": the correct drug at the correct dose based on a patient's genetic makeup. This Symposium will prepare anesthesiologists to participate in pharmacogenetic research and understand the issues surrounding the application of pharmacogenomics in the operating room.

The Symposium will be moderated by Evan D. Kharasch, M.D., Ph.D., and Margaret Wood, M.B., Ch.B., of the University of Washington, Seattle, Washington, and Columbia University, New York, New York, respectively. The speakers include:

- Kenneth Thummel, Ph.D., Professor of Pharmaceutics, Associate Dean for Research, University of Washington School of Pharmacy, Seattle, Washington
- Paul A. Insel, M.D., Professor of Pharmacology and Medicine, Director, Medical Scientist Training Program, Editor, *Molecular Pharmacology,* University of California, San Diego, California
- Jeffrey R. Balser, M.D., Ph.D., Associate Vice Chancellor for Research, Chair of Anesthesiology, The James Tayloe Gwathmey Professor of Anesthesiology and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee
- Jeff Mogil, Ph.D., Department of Psychology, McGill University, Montreal, Quebec, Canada

Speakers will provide an overview and focused information on how pharmacogenomics can influence drug

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disposition and pharmacokinetics, autonomic nervous system pharmacogenomics, pharmacogenomics of responses to cardiovascular drugs, and the pharmacogenetics of pain, analgesia, and anesthesia. These lectures will be accompanied by the presentation of 16 posters selected for their relevance to the Symposium topic.

Dr. Thummel will introduce some of the genetic polymorphisms that are known to affect human drug biotransformation or transport processes and alter pharmacological effects. This will include a background of the molecular mechanisms by which altered catalytic function can occur and their relationship to the pharmacokinetic and pharmacodynamic penetrance of the variant allele. His presentation will conclude with a discussion of genetic mutations in the cytochrome P450 3A5 (*CYP3A5*) gene that contribute to interindividual differences in the hepatic, intestinal, and renal metabolism of drugs. Practical examples will include drugs used in anesthesia and critical care, and how pharmacogenetic variability might influence therapeutic outcomes.

Dr. Insel will lecture on autonomic nervous system pharmacogenomics. Human beings vary from one another in their autonomic nervous system reactivity. Evolving evidence indicates that such variability results from variation in the genes that encode autonomic nervous system components. Intersubject differences in the genes for pre- and postsynaptic receptors provide one example of genetic variability that has been shown to influence both disease progression and drug responsiveness. Such genetic variants can influence either activation or deactivation (desensitization) of autonomic receptor signaling. Application of genetic assays for these receptors is currently a research tool but may become part of the standard-of-care as more information is forthcoming.

Dr. Balser will describe the pharmacogenomics of responses to cardiovascular drugs. Variability in response is a major limitation to the safe and effective use of drug therapy in cardiovascular disease. In particular, the same drugs used to treat heart rhythm disturbances may in some cases elicit more malignant, life-threatening arrhythmias. Recently, advances in our understanding of variable drug response have arisen from the identification of mutations in genes that evoke rare syndromes, such as the congenital long QT syndrome, that occur in the absence of drug therapy. Nonetheless, although rare mutations in these genes elicit profound disease, it is now clear that far more common mutations (known as single nucleotide polymorphisms) evoke only subtle changes in the protein-products of the same genes. These single nucleotide polymorphisms render mild disease, or even a loss of functional reserve, that creates the potential for drug-induced adverse events, such as Torsades de Pointes. Moreover, identification of mutations in genes that underlie rare syndromes allows the use of model systems, such as C. elegans, to identify additional modulator genes that may carry single nucleotide polymorphisms evoking variable drug response through the same mechanistic pathway. These approaches are leading to the assembly of a more complete database of the common genetic variants that elicit variable drug response in cardiovascular disease, and will eventually allow prospective therapeutic decisions based upon individual DNA fingerprints.

Dr. Mogil will speak about the genetic basis of variability in sensitivity to painful stimuli. His laboratory has performed extensive investigations of the response of inbred mouse strains to a variety of nociceptive assays and analgesic manipulations. Current work in his laboratory suggests that apparent differences in the sensitivity of mouse strains to isoflurane's ability to suppress responding to a noxious tail clip may relate to genetically determined sensitivity to the tail clip *per se*.

In addition to the lectures noted above, 16 posters will be presented and available for discussion at the Symposium. Areas of interest include opioid receptor polymorphism, anesthetic action and red hair (melanocortin receptor gene), muscle relaxant pharmacogenetics, malignant hyperthermia genetics, polymorphism of drug metabolism, cardiovascular function and receptor polymorphism, and anesthetic mechanism of action. Hence, the introductory lectures link and provide a basis for discussion of the selected Abstracts. The text for each Abstract can be found on the ASA-Abstract Web site or in the CD-ROM that is included with this issue of the Journal.

A118G μ-Opioid Receptor Gene Polymorphism Does Not Protect against Opioid-Induced Respiratory Depression Despite Reduced Analgesic Response by Albert Dahan, Ray Romberg, Erik Olofsen, Hans Bijl, Elise Sarton. Leiden University Medical Center, Leiden, Netherlands. *[1598]*

Decreased Local Anesthetic Efficacy in Subjects with Naturally Red Hair by Edwin B. Liem, Teresa V. Joiner, Kentaro Tsueda, Daniel I. Sessler. University of Louisville, Louisville, Kentucky. *[1599]*

Do Sex, μ-Opioid Receptor (MOR) Gene Polymorphism, Placebo Response and Baseline Pain Explain Part of the Analgesic Response Variability of the μ-Opioid Alfentanil by Raymonda R. Romberg, Erik Olofsen, Hans Bijl, Albert Dahan. Lieden University Medical Center, Leiden, Zuid-Holland, Netherlands. *[1600]*

The Melanocortin Receptor Gene Mediates Female Specific μ-Opioid Analgesia in Humans and Mice by Albert Dahan, Hans Bijl, Elise Sarton, Roger Fillingim, Jeff Mogil. Leiden University Medical Center, Leiden, Netherlands. *[1601]*

Response to Mivacurium in Patients Carrying the K-Variant in the Butyrylcholinesterase Gene by Mona R. Gätke, Jørgen Viby-Mogensen, Doris Østergaard, Jens R. Bundgaard. Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. *[1602]*

Comprehensive Screening of the RYR1 Gene for Malignant Hyperthermia Susceptibility by Nyamkhishig Sambuughin, Heather Holley, Barbara Brandom, Tom Nelson, Sheila Muldoon. Barrow Neurologic Institute, Phoenix, Arizona. *[1603]*

Pharmacogenomics of Nitrous Oxide by Kirk Hogan, Deborah Rusy, Thomas Broderick, Dawn Green, Jennifer Halsey. University of Wisconsin, Madison, Wisconsin. *[1604]*

The Hypnotic Requirement for Propofol in Women with Red Hair: Preliminary Results by Anthony G. Doufas, Yunus M. Shah, Ryu Komatsu, Papiya Sengupta, Daniel I. Sessler. University of Louisville, Louisville, Kentucky. *[1605]*

Efficacy of Antiemetic Prophylaxis with Granisetron and Dolasetron Depends on Cytochrome P-450 2D6 Genotypes by Piotr K. Janicki. Penn State Hershey Medical Center, Hershey, Pennsylvania. *[1606]*

False-Positive Non-Synonymous Single Nucleotide Polymorphism (SNP) of Human Opioid-Like Receptor (OP4) Gene by Piotr K. Janicki, Gregg Schuler, Victor Ruiz-Velasco. Penn State Hershey Medical Center, Hershey, Pennsylvania. *[1607]*

Effect of Targeted NMDA Receptor Epsilon1 Subunit Gene Disruption on Nitrous Oxide Anesthesia in Mice by Yuki Sato, Aki Sato, Takaniri Murayama, Masayoshi Mishina, Norimasa Seo. Jichi Medical School, Kawachi, Tochigi, Japan. *[1608]*

Effect of α-2b Adrenoceptor Polymorphism on Vasoconstriction in Humans by Claudia K. Stapelfeldt, Pekka Talke, Amir Snapir, Mika Scheinin. University Hospital Kiel, Kiel, Germany. *[1609]*

Pharmacogenetic and Kinetic Determinants of Alfentanil Metabolism by Expressed Cytochrome P4503A by Theresa M. Klees, Pam Sheffels, Ola Dale, Evan D. Kharasch. Norwegian University of Science and Technology, Trondheim, Norway. *[1610]*

Pharmacogenomics Affects Postoperative Nausea and Vomiting: The Effects of CYP2D6 Allele Frequency on Ondansetron Prophylaxis Failure by Keith A. Candiotti, Fani Nhuch, Aimee Kamat, David A. Lubarsky, David J. Birnbach. University of Miami, Miami, Florida. *[1611]*

Genotyping the Cholinesterase in Patients with Clinically Prolonged Action of Succinylcholin by Thierry Girard, Hans Ginz, Martin Siegemund, Evgueni Voronkov, Albert Urwyler. University Hospital, Kantonsspital, Basel, Switzerland. *[1612]*

Ethnic Differences in Response to Rocuronium? A Comparison of the Effects in Israeli Arabs and Israeli Caucasian Jews by Anath Laver-Segal, Mark Rothstein, Leonid Reitman. Hillel Yaffe Medical Center, Hadera, Israel. *[1613]*

ASCCA/Journal Abstract Session: Mentors and Mentees in Critical Care Research—Individual Contributions to a Theme

Saturday, October 23, 2004, 9:00 AM to 11:00 AM, in Ballroom D-E, Las Vegas Hilton, Las Vegas, Nevada

Next month's Annual Meeting will feature a "track" devoted to Critical Care Medicine. As part of this minisymposium, the American Society of Critical Care Anesthesiologists and ANESTHESIOLOGY will jointly sponsor an Abstract session focusing on two themes. First, the session will highlight the diverse nature of investigation in critical care. It will include clinical and "bench" research, studies ranging from basic biochemistry to outcomes/systems-based investigations and work involving abnormalities in a number of different organ systems. The second theme will touch on one of the keys to success in research—appropriate mentorship. To examine this, we have adopted a unique format. First, the junior investigator will present the work detailed in a specifically selected Abstract. This will be followed by a short discussion by the senior investigator. This second presentation will demonstrate how the specific work "fits in" to the overall theme of investigation pursued in his/her laboratory. In addition, the mentor will highlight the importance of the specific work and of the overall theme in aiding our understanding of the pathogenesis of critical illness and to improving care in the intensive care unit.

A total of seven Abstracts will be presented. The text for each Abstract can be found on the ASA-Abstract Web site or in the CD-ROM that is included with this issue of the Journal.

Role of Hypoxic Pulmonary Vasoconstriction in Ovine Lung Injury by Martin Westphal, Perenlei Enkhbaatar, Naoki Morita, Lillian D. Traber, Daniel L. Traber. University of Texas Medical Branch, Galveston, Texas. *[134]*

This study is a classic approach to an age-old problem in critical care. Critical care units evolved, in part, from the respiratory care units of the last great polio epidemic. Understanding the mechanisms that contribute to lung injury represents a long-standing and important gap in our ability to treat patients. The pulmonary circulation is of paramount importance in the pulmonary response to injury. It is now known that nitric oxide is an important mediator of pulmonary vascular tone. In this study, Dr. Westphal examines the NO in the pathophysiology of burn and smoke-induced lung injury. Afterwards, Dan Traber, a preeminent physiologist, will briefly discuss the importance of studying lung injury using classic physiologic approaches.

Local Anesthetics Reduce Mortality and Protect against Renal and Hepatic Dysfunction in Murine Septic Peritonitis by George Gallos, Dean R. Jones,

Samih H. Nasr, Charles W. Emala, H.T. Lee. Columbia University, New York, New York. *[340]*

Renal failure remains an important determinant of mortality and morbidity in critically ill patients, especially those with sepsis. However, the pathogenesis is poorly understood and therapeutic options are few. In this abstract, George Gallos from the Department of Anesthesiology at Columbia Presbyterian Hospital in New York examines the use of lidocaine in an animal model of sepsis, cecal ligation, and puncture. In the follow-up, Dr. H.T. Lee, a promising investigator, will discuss his investigations into renal insufficiency and the determinants of renal failure.

Evidence of Myocardial Hibernation in the Septic Heart by Richard J. Levy, Christina Y. Yoo, Paul D. Acton, Joel S. Karp, Clifford S. Deutschman. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. *[730]*

Myocardial dysfunction is one of the hallmarks of sepsis. In intriguing work, Richard Levy from Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine has shown that this in part results from cytopathic hypoxia, an inability to use molecular oxygen. Further, these abnormalities have their roots in dysfunction of cytochrome c oxidase, a key enzyme in the electron transport chain. The work presented here will examine the similarities between myocardial dysfunction in sepsis and the state of "hibernation" observed in ischemic heart tissue. His presentation will be followed by a short discourse on molecular dysfunction in sepsis by the session moderator, Clifford S. Deutschman.

SV40 Vector Transfection into the Pulmonary Epithelium after Cecal Ligation and Puncture in Rats by Luminita Eid, Mahmoud Abd El-Latif, Clifford S. Deutschman, Ariella Oppenheim, Yoram G. Weiss. Hadassah Hebrew University Medical Center, Jerusaelm, Israel. *[1046]*

Investigators have recently begun to appreciate the molecular basis underlying acute lung injury and adult respiratory distress syndrome. Others have shown that gene therapy is a viable approach to altering protein expression in the lung. Most studies have used adenoviral vectors. In this abstract, Dr. Eid demonstrates the use of another virus, the SV40 Herpes, as a vector for pulmonary transduction in an animal model of adult respiratory distress syndrome. In the ensuing discussion, Yoram Weiss will discuss the use of gene therapy in treating acute lung disease and his success using an adenoviral vector to ameliorate sepsis-induced lung injury.

Eliminating Catheter-Related Blood Stream Infections in the Intensive Care Unit by Sean M. Berenholtz, Peter J. Pronovost, Pamela A. Lipsett, Todd Dorman, Trish M. Perl. Johns Hopkins University, Baltimore, Maryland. *[619]*

This abstract highlights two important aspects of clinical care in the intensive care unit—prevention of infection and the use of the Quality Improvement system to address important problems in patient safety. Line sepsis is a formidable intensive care unit issue that should be preventable. Sean Berenholtz of Johns Hopkins Hospital has used a systemic approach to identify possible areas where interventions might help reduce the incidence of catheter-related infection. By using a systems-based approach, he and his coworkers have altered the incidence of infection. In the follow-up, Todd Dorman, director of critical care medicine, will examine the use of the systems-based approach in improving patient safety.

Increasing the Efficacy of Active and Passive Immunization against the Type III Secretion System of *Pseudomonas aeruginosa* in Immunocompromised Mice by Kiyoshi Moriyama, Jeanine P. Wiener-Kronish, Teiji Sawa. University of California, San Francisco, San Francisco, California. *[1091]*

Critical illness increases susceptibility to infection, especially with microorganisms that are not normally pathogenic. Most investigators have focused on host responses, but a better understanding of the features that make a microbe pathogenic is also important. This work demonstrates why. Identification of factors that increase pathogen virulence will indicate potential targets for intervention. Here, Dr. Moriyama uses passive and active immunization against a *Pseudomonas aeruginosa* toxin to protect immunocompromised animals from lethal infection. In the subsequent presentation, Jeanine Wiener-Kronish will discuss the importance of investigating pathogen virulence factors in providing treatment for and protection from intensive care unit–acquired infection.

Decreased Expression of Uncoupling Proteins (UCPs) in Skeletal Muscle Following Burn Injury by Masao Kaneki, Kaiko Kunii, Kyungho Chang, J.A. Jeevendra Martyn. Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. *[1479]*

Myopathy and neuropathy are components of the Multiple Organ Dysfunction Syndrome and contributors to morbidity and mortality in the intensive care unit. The etiology of muscle wasting is poorly understood. Part of the process seems to involve skeletal muscle apoptosis, initiated in part by mitochondrial dysfunction. In this presentation, Dr. Kaneki will examine the role of uncoupling proteins, antiapoptotic factors found in a number of tissues, in the development of muscle wasting following burn injury. Afterward, Dr. Martyn will discuss the factors involved in myopathy and the important but underappreciated role played by this disorder in the critically ill.

Overall, this is an exciting program that highlights some of the most important aspects of research into critical illness. This session is part of a weekend-long track devoted to critical care. The entire track, compris-

ing plenary lectures, refresher courses, point-counterpoint debates, abstract presentations, and panel discussions, promises to be educational and entertaining. Please plan to attend—it will be well worth your time.

Interested readers should also not overlook the myriad other science-related presentations at this year's Annual Meeting, including, on Monday, October 25, 2004, the Rovenstine Lecture, the 2nd Annual Celebration of Research Session (to follow the Rovenstine Lecture—with lunch provided!), and the 4th Annual FAER Honorary Research Lecture (which follows the Celebration), as well as the many excellent posters that will be presented throughout the meeting. Finally, on Tuesday, October 26, 2004, plan to attend the Plenary Session entitled "Translational Research: Nitric Oxide as a Unique Signaling Molecule in Biology," delivered by Louis J. Ignarro, Ph.D., recipient of the 1998 Nobel Prize in Medicine for his work in the discovery of the biologic actions of nitric oxide.