

Evan D. Kharasch, M.D., Ph.D., Recipient of the 2011 Excellence in Research Award

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THE American Society of Anesthesiologists' Excellence in Research Award recognizes an individual for outstanding achievement in research that has had an important effect on the practice of anesthesiology. The recipient's work must "represent a body of original, mature and sustained contribution to the advancement of the science of anesthesiology." This year's awardee, Dr. Evan Kharasch, has led our specialty in advancing the understanding and practice of clinical pharmacology, the core science that forms the basis for anesthetic practice. His work has produced insights in pharmacokinetics, drug metabolism, toxicity, and pharmacogenetics, and has resulted in fundamental improvements in the way in which we use anesthetic and analgesic agents.

Evan had a precocious beginning to his career of inquiry, conducting original biochemistry experiments as a high school student and gaining recognition as a national "top forty" by the Westinghouse Science Talent search. He then completed his B.S., M.D., and Ph.D. degrees at Northwestern University over the remarkable span of just 9 yr! During that time, he worked on mechanisms of action and metabolism of antineoplastic agents, beginning his life-long interest in pharmacology and drug metabolism.

The next stop in Dr. Kharasch's training was Seattle, where he began his anesthesiology career as an intern and resident at the University of Washington. Unsurprisingly, He conducted several investigations while a resident, and was among the first in our specialty to study the effects of anesthesia, mechanical ventilation, and cardiopulmonary bypass on the newly discovered hormone, atrial natriuretic factor.¹ Always prescient, Dr. Kharasch anticipated the recent trend of integrating research with clinical residency; he took a year off during his residency for a National Institutes of Health-sponsored postdoctoral fellowship in clinical research.

I first met Evan during his postresidency job search and it was clear that he had an ambitious research agenda to apply the emerging understanding of cytochrome P450 isoforms to the metabolism of anesthetics and analgesics. He took a po-



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sition on the anesthesiology faculty at University of Washington and immediately initiated strong collaborative relationships with the talented faculty at the School of Pharmacy. Over the next several years, Dr. Kharasch proceeded to methodically define the enzymes responsible for metabolizing inhalational anesthetics,² alfentanil,³ and other agents in humans. Concomitant with his studies identifying the enzymatic basis for metabolism of anesthetics, Dr. Kharasch also identified the active and inactive metabolites that resulted from enzymatic biotransformation. To accomplish this, he became expert in small molecule mass spectrometry, enabling him to become a leader in developing drug and metabolite assays, as well as an early participant in the emerging fields of proteomics and metabolomics.

In the early 1990s, it was proposed that the new inhalational anesthetic, sevoflurane, was nephrotoxic because its metabolism generated free fluoride ions. In a series of elegant experiments, Dr. Kharasch elucidated the enzymes responsible for metabolizing sevoflurane and demonstrated that it did indeed produce free fluoride in plasma.^{4,5} However, he went on to show that it was in-

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trarenal fluoride production rather than plasma fluoride concentrations that produced renal tubular injury,⁶ explaining why methoxyflurane but not sevoflurane was nephrotoxic. Dr. Kharasch's laboratory subsequently showed that a nephrotoxic sevoflurane degradation product, referred to as Compound A, did not produce renal injury in humans.⁷ This careful pharmacologic work refuted the objections and enabled the clinical introduction of sevoflurane, now the most frequently used inhalational anesthetic agent. In related work, Dr. Kharasch identified the specific cytochrome P450 isoform responsible for producing the toxic halothane metabolites thought to cause halothane hepatitis.⁸

Evan has subsequently focused his laboratory's analytical skills on a host of additional drugs including cyclooxxygenase-2 inhibitors, benzodiazepines, antiretroviral agents, and opiates in particular. Notably, he has clarified the metabolic pathways for methadone in humans, identifying the basis of interindividual variability and paving the way for safer administration.⁹ His current work focuses on mechanisms of interindividual variability in opioid disposition and response, the role of transporters in drug disposition, and alternative routes of drug administration for chronic and breakthrough cancer pain. Recently, Dr. Kharasch's laboratory has entered the new field of biomarkers. They have identified and validated two urine protein biomarkers, aquaporin-1 and adipophilin, for renal cell carcinoma.¹⁰ These biomarkers are both sensitive and specific and hold the promise of providing a screening test for the early detection of this lethal disease.

Evan's scientific efforts have always pursued the solutions to important clinical questions, and his approaches have preceded rather than followed "scientific fashion." When most scientists were turning to cell culture and transgenic mouse models and departments of pharmacology were disappearing, Dr. Kharasch's laboratory steadfastly focused on the application of modern analytic and genetic techniques to clinical pharmacology in humans. Before the term was in vogue, his work was the embodiment of translational research, taking clinical observations to the laboratory, testing his findings in human subjects, and then applying them to practice. Finally, before "pharmacogenetics" became a buzzword, Dr. Kharasch was identifying the basis for interindividual variability in drug disposition and response, focusing on sequence variants in cytochrome P450 isoforms. The product of this persistence and perseverance is a huge body of clinical pharmacologic knowledge and great improvements in the drugs we use and how we administer them.

While he conducted his research, Dr. Kharasch simultaneously devoted himself to mentoring and rigorously training physicians and scientists aiming to pursue serious careers in investigation. He has trained dozens of students and fellows, many of whom have gone on to successful and productive academic careers. Six years ago Evan joined the Department of Anesthesiology at Washington University

in St. Louis as the Russell D. and Mary B. Sheldon Professor of Anesthesiology and Director of the Division of Clinical and Translational Research (which he cleverly named DoCToR). In that role, he has provided rigorous mentorship to clinicians from anesthesiology and other specialties as well as to postdoctoral fellows. Several of these mentees have already emerged as successful, federally-funded investigators. In recognition of his contributions to their training, Dr. Kharasch was nominated by his trainees and awarded the 2010 Mentoring Excellence in Research Award from the Foundation for Anesthesia Education and Research.

Through his myriad research experiences, Dr. Kharasch has developed deep and broad knowledge about our national research infrastructure and how to efficiently navigate it. He also honed the skills to develop and implement research administrative systems at the local level, first through his role as Associate Program Director of the General Clinical Research Center and then as Assistant Dean for Clinical Research at the University of Washington. He then built an outstanding infrastructure for anesthesiology clinical research in St. Louis. In 2010 Dr. Kharasch was appointed Vice Chancellor for Research at Washington University, overseeing one of the largest academic biomedical research enterprises in the United States. In his short tenure in this position he has already introduced new energy and ideas and has had a significant positive effect on the organization. It should be a source of pride for our specialty that an anesthesiologist-scientist is in this nationally influential position of research leadership.

Not only is Dr. Kharasch a precocious, prescient, and persistently productive scientist, he is an engaging individual with a multitude of interests. He is married to Karen Kharasch, a highly successful research administrator in her own right. They both have eclectic tastes and are aficionados of symphony, opera, and minor league baseball (the Gateway Grizzlies). Evan is also an avid skier and bicyclist, although skiing is slightly less accessible in St. Louis than it was in Seattle! I am proud to count Evan as a friend and colleague, and I am honored to write this description of his remarkable talents and accomplishments. I congratulate Dr. Kharasch on this well-deserved award, the highest research recognition that our specialty can give.

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