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John H. Eisenach, M.D., Recipient of the 2008 Presidential Scholar Award

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IN 1995, the National Institutes of Health (NIH) Director's Panel on Clinical Research met to review the status of clinical research in the United States and to make recommendations about how to ensure effective continuance. In the same year, John H. Eisenach, M.D., finished his first year of medical school at the University of Colorado (Denver, Colorado), expanding the scope of his premed research experience in microbiology to investigate physiologic disease states. John accepted the challenge of developing a rat model of acute lung injury after mesenteric ischemia–reperfusion. Before starting his second year, John had proven that inhaled nitric oxide during gut ischemia improved endothelium-dependent pulmonary artery vasodilation and reduced lung neutrophil accumulation.[1,2] From there, a fondness for integrative physiology and a natural interest in anesthesiology was born. Dr. Eisenach graduated from Colorado in 1998, at which time the formative recommendations by the NIH Director's Panel were instituted under the initial program announcement "K23: Mentored Career Development Award in Patient-Oriented Research." This award formed an important part of the NIH initiative to attract and retain talented individuals to the challenges of patient-oriented research.

For residency, Dr. Eisenach selected the Mayo Clinic in Rochester, Minnesota, because of the long-standing tradition of human and integrative physiology research, and also because of the small-town lifestyle reminiscent of his upbringing on a farm in Fort Morgan, Colorado. He immediately planned a research rotation under the mentorship of anesthesiologist Michael J. Joyner, M.D., an internationally recognized expert in the autonomic control of the circulation and the responses of humans to mental and physical stresses. Dr. Joyner is a direct "academic descendent" of John T. Shepherd, M.D., M.Ch., D.Sc., Mayo Emeritus Professor, former president of the American Heart Association, and cofounder of the Mayo Medical School. Dr. Shepherd "descended" from Henry Barcroft, M.D. (1904–1998), who initially characterized nervous control of muscle blood flow by showing that patients undergoing sympathectomy for hyperhidrosis had an initial marked increase in limb blood flow but that the flow returned to normal over several weeks' time, a phenomenon that is still unexplained today.[3] Barcroft's famous father (Sir Joseph) described the oxygen hemoglobin dissociation curve a century ago. Why is this relevant? Because under the watchful eyes of Dr. Joyner and Dr. Shepherd, Dr. Eisenach's first investigation during residency demonstrated that in patients who had previously undergone sympathectomy for hyperhidrosis, endothelium-dependent and -independent forearm vasodilation was similar to controls, although the sympathetically mediated forearm vasoconstrictor response to lower body negative pressure was essentially abolished in the patients.[4] This also highlights the generational continuity in human physiology research at the Mayo Clinic for more than 50 yr.

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During the same residency research rotation, Dr. Eisenach assisted in the first human study to report that after 5 days of a controlled normal sodium diet, single nucleotide polymorphisms in the β_2-adrenergic receptor (β_2-AR) gene influenced the forearm vasodilator response to intraarterial administration of a β-adrenergic receptor agonist, and the effect was dependent on the generation of endothelial nitric oxide.[5] Combined with the work in the sympathectomy patients, this formed the scientific foundation for a career development research application, and soon after the NIH implementation of

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the K23 program, Dr. Eisenach received a 5-yr K23 award titled "β-2 Receptor Polymorphisms and Vasodilation in Humans." Rounding out his residency, Dr. Eisenach won several awards from the Midwest Anesthesia Resident's Conference, including Third Place Overall "Best of Show" in 2001, and was a Foundation for Anesthesia Education and Research scholar to the American Society of Anesthesiologists annual meeting. At Mayo he received the Richard A. Theye Award for Clinical Anesthesia Residency Research and was appointed to the Mayo Rochester staff in 2002.

From the initial description of the sequence of the β_2-AR gene to the early characterization of common polymorphic variants, great interest in the influence of β_2-AR gene variation on cardiopulmonary function has emerged, primarily because of the ubiquitous distribution of β_2-AR in the body and the substantive role of the β_2-AR in the heart and lungs. Genetic variation in the β_2-AR is also a fundamental pharmacogenomic question for anesthesiologists, with widespread implications for the use of β-blockers in heart disease and perioperative management. Early in the K award, Dr. Eisenach became interested in the cardiovascular reactivity to common laboratory stressors to assess intermediate physiologic phenotypes with prognostic significance toward more distant complex phenotypes such as hypertension and heart disease. First, he determined that the Arg16/Gly β_2-AR polymorphism is associated with an altered heart rate and cardiac output response to isometric handgrip to fatigue.[6,7] Then, he found that the genotype associated with greater nitric oxide–dependent, β_2-AR–mediated vasodilation that was seen after a normal sodium diet in the earlier study[5] was no longer apparent after 5 days of dietary sodium restriction; furthermore, in the same genotype group, the low-sodium diet caused a decrease in resting cardiac output and stroke volume, and an increase in total peripheral resistance.[8] Finally, acute sodium loading by rapid intravenous saline administration caused β_2-AR polymorphism–dependent differences in natriuresis.[9] Taken together, these findings suggested that increases in sodium balance may augment effects of β_2-AR gene variation on cardiovascular and renal phenotypes, whereas decreases in sodium balance may abrogate these differences in cardiovascular function. Therefore, these studies provide evidence that the Arg16/Gly polymorphism may be a genetic marker of salt sensitivity.

In March of 2008, the K-related work came to fruition. Dr. Eisenach received an NIH National Heart, Lung, and Blood Institute R01 award titled "Beta2-Adrenergic Receptor Gene Variation and Cardiovascular Control in Humans." The overall goal of this 5-yr project is to advance the understanding of human β_2-AR gene haplotype variation and cardiovascular phenotype. His laboratory will conduct hypothesis-driven protocols to determine the genetic influence of blood pressure regulation in response to stressful maneuvers, medication infusions, and dietary sodium intake. By also determining the density and high and low binding affinity conformation of β_2-ARs on patient lymphocytes, this strategy will provide mechanistic detail of how genes interact with intermediate physiologic traits pertinent to the development of cardiovascular disease. Finally, the proposed studies are effects of "physiologic bridge building" between population-based association studies and *in vitro* cellular observations on genetic variation and cardiovascular regulation.

Concurrent with the advances in β_2-AR phenotyping, Dr. Eisenach has continued to investigate unique physiologic characteristics associated with hyperhidrosis.[10] He found an important physiologic measurement technique that has impacted operative care. In collaboration with Nisha Charkoudian, Ph.D., an expert in skin blood flow control, Dr. Eisenach developed a method to measure real-time palmar skin blood flow during thoracoscopic sympathotomy for patients with hyperhidrosis.[11] The "picture-in-picture" overlay of a skin blood flow window on a thoracoscopy monitor provides immediate feedback for sympathetic chain disruption. This changed surgical practice, as dedicated equipment to measure skin blood flow has become routine in these procedures at Mayo. Dr. Eisenach is now leading a prospective investigation of cardiovascular regulation in patients before and after sympathotomy surgery.

Teaching is of critical importance to John as he has mentored 19 learners at all levels, including medical students, international fellows, and anesthesia residents. He has translated his love of science into working with high school students in his laboratory. More recently, as the president elect of the local chapter of Sigma Xi Scientific Research Society, he has chaired the local Science Fairs Committee for the past 2 yr. He has a passion for helping these young scientists and has recruited the Mayo Clinic clinicians, scientists, and physician executives to help judge science fairs, thus exposing these young minds to individuals who work daily with the implications of science and scientific research. John spends his free time with his wife, Gina, and their three children.

The early career path that Dr. Eisenach has chosen is the model on which the future of academic anesthesiology can be built. He exemplifies and defines the term clinician–scientist. John has been able to bridge the laboratory with the operating room. In time, his work will influence the way in which anesthesiologists and intensivists treat heart disease from a physiologic and pharmacogenomics approach. His work continues a long tradition of basic science research at the Mayo Clinic in anesthesiology, and it is a great pleasure to see his groundbreaking work recognized in this fashion.

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