



Wednesday, 14 October 2009
12:30-1:30 pm
Jordan Conference Center Auditorium
University of Virginia School of Medicine

History of the Health Sciences

The Walter Reed Award Lecture: WHICH ROAD TO THE NOBEL PRIZE?

**Ferid Murad, M.D., Ph.D., Nobel Prize in Physiology or Medicine (1998)
Regental Professor and John S. Dunn Distinguished Chair in Physiology and Medicine; Texas
Nobel Scholar at the University of Texas at Houston;
Director Emeritus, Brown Foundation Institute of Molecular Medicine for the Prevention of
Human Diseases and Director of the IMM Center for Cell Signaling;
University of Texas Health Science Center at Houston, Houston TX**

Marcia Day Childress, Ph.D., moderator

October of each year is Nobel Prize season—every few days come announcements of the coveted prizes' recipients for signal discoveries and achievements in a range of fields from science to literature. In 1998, physician-scientist Ferid Murad was awarded the Nobel Prize in Physiology or Medicine for his discovery and definition of the biological effects of nitric oxide in the human body. For many years a member of the University of Virginia School of Medicine faculty (1970-1981) and now an eminent professor at the University of Texas Health Science Center at Houston, Dr. Murad has devoted a distinguished career in academic medicine and industry to study of both the mechanisms of nitric oxide and its potential therapeutic applications.

Over the last thirty years, inquiry into the role of nitric oxide in cellular signaling has become one of biology's most rapidly growing areas, with more than 80,000 publications on record. A gas and free radical with an unshared electron that can regulate an ever-growing list of biological processes, nitric oxide is formed from L-arginine by enzymes called nitric oxide synthases, which are present in most cells and tissues. In many instances, nitric oxide mediates its biological effects by activating the soluble isoform of guanylyl cyclase and increasing cyclic GMP synthesis from GTP; cyclic GMP in turn can activate cyclic GMP-dependent protein kinase (PKG) and cause smooth muscles and blood vessels to relax, decrease platelet aggregation, and alter neuron function, with effects that range from decreasing blood pressure and blood clotting to increasing blood flow to tissues and altering memory and behavior. The effects of nitric oxide that occur independent of cyclic GMP formation are also numerous, including interacting with transition metals such as iron, thiol groups, other free radicals, oxygen, superoxide anion, and unsaturated fatty acids; other reactions can alter protein structure, function, and/or catalytic capacity, effects which likely regulate such disordering processes as bacterial infection, tissue inflammation, and tumor growth. While nitric oxide thus alters and regulates diverse important physiological events within cells, it also has an array of signaling functions, serving as an intracellular messenger, an antacid, a paracrine substance, a neurotransmitter, or a hormone capable of affecting distant sites. As with any messenger molecule, however, too little or too much nitric oxide can trigger pathological events.

Methods to regulate nitric oxide formation, metabolism, or function have been in clinical employ for more than a century, as with use, starting in the 1870s, of organic nitrates and nitroglycerin to ease discomfort of angina pectoris. In our time, there are multiple promising applications, including inhalation of low concentrations of nitric oxide by premature infants with pulmonary hypertension to boost survival rates. Ongoing clinical trials are examining how nitric oxide synthase inhibitors and nitric oxide scavengers might ameliorate hypotension during dialysis, septic shock, inflammatory disorders, and cancer therapy. Drug discovery and development are important

foci of nitric oxide research, with potential to add to the clinician's therapeutic armamentarium and enable medicine to manage or overcome many serious diseases by perturbing nitric oxide formation and metabolism in the body.

As part of this Medical Center Hour, Dr. Murad will be presented with the Walter Reed Award by the University of Virginia Medical Alumni Association.

Suggested resources:

1. Ignarro L and Murad F, eds. Nitric Oxide: Biochemistry, Molecular Biology and Therapeutic Implications. *Advances in Pharmacology* 34:1-516, Academic Press, 1995.
2. Murad F. Signal transduction using nitric oxide and cyclic guanoside monophosphate. Lasker Award. *JAMA* 276:1189-1192, 1996.
3. Murad F. Discovery of some of the biological effects of nitric oxide and its role in cellular signaling. Nobel Lecture, *Bioscience Reports* 19:133-154, 1999 and *Les Prix Nobel—1998*, pp 273-307, 1999.
4. Murad F. Shattuck Lecture: The discovery of nitric oxide and cyclic GMP in cell signaling and their role in drug development. *N Engl J Med* 355, 2003-2011, 2006.

Ferid Murad MD PhD is a graduate of DePauw University and Case Western Reserve University (MD, PhD). Following medical residency at Massachusetts General Hospital and an NIH Heart Institute fellowship, he was on the faculty at the University of Virginia as director of the Clinical Research Center and the Division of Clinical Pharmacology with appointments in Medicine and Pharmacology (1970-1981). He was chief of Medicine at Palo Alto Veterans Hospital (1981-1988) and associate chair (1982-1986) and chair of Medicine (1986-1988) at Stanford University. He was vice president for research and development at Abbott Laboratories and a professor at Northwestern University from 1988 to 1993. Dr. Murad has been active in both academic medicine and industry throughout his career, having founded or cofounded five biotechnology companies and advised cities and government leaders about technology development. His scientific work has addressed cell signaling and signal transduction systems. In 1998, Dr. Murad received the Nobel Prize in Medicine for his work with nitric oxide, the colorless, odorless gas that signals blood vessels to relax and widen so as to lower blood pressure. His ongoing research seeks better understanding of how information is transmitted between cells. At present, Dr. Murad is director emeritus of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, director of the IMM Center for Cell Signaling, Regental Professor and John S. Dunn Sr. Distinguished Chair in Physiology and Medicine, Texas Nobel Scholar at the University of Texas at Houston, and director of the UT Health Science Center at Houston Program in Intracellular Signaling. Among his awards and honors are the Albert and Mary Lasker Basic Medical Research Award, American Heart Association Ciba Award, Baxter Award for Distinguished Research in the Biomedical Sciences of the Association of American Medical Colleges, American Society of Clinical Pharmacology Distinguished Research Prize, and the President's Scholar Award from the University of Texas-Houston Health Science Center. A member of the National Academy of Sciences and the Institute of Medicine of the National Academy of Sciences, fellow of the American Academy of Arts and Sciences, and member of the Texas Academy of Medicine, Engineering and Science Technology, he belongs to several foreign academies and is an honorary or adjunct professor at many universities. He serves on the boards of a number of public and private companies, foundations, and universities. Of the 140 trainees who have worked with him in his laboratories, many are now academic or pharmaceutical industry leaders around the world.

Next Medical Center Hour: Wednesday, 21 October 2009

Koppaka V. Rao Lecture in Humanities in Medicine: WHEN DOCTORS BECOME PATIENTS
Robert Klitzman MD, Mailman School of Public Health, Columbia University, New York NY

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Learning objectives:

1. Appreciate the role of nitric oxide in the body's physiologic functions and regulatory systems and its prospects for clinical therapeutic uses.
2. Consider a successful physician-scientist's counsel regarding the processes of scientific discovery and exploration of therapeutic applications.