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Editorial: Ferid murad, at 80: A legacy of science, medicine, and mentorship

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Ferid Murad, MD, PhD at 80: A Legacy of Science, Medicine, and Mentorship

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for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system

The Nobel Prize in Physiology or Medicine 1998, The Nobel Foundation

It is hard to believe that it is has been nearly twenty years since the Nobel Prize was awarded for the discovery of nitric oxide to Robert Furchgott, Louis Ignarro, and Ferid Murad. This, and the many other awards that these investigators received over the years, recognized the paradigm-changing importance of their discovery that a gas like nitric oxide could function as a hormone and mediate signaling that was essential to the physiology and pathophysiology in the cardiovascular, and virtually all other biological, systems. Individually, they contributed pieces to the puzzle that ultimately brought these novel molecular insights into specific relief. Dr. Furchgott was the first to recognize the generation by the endothelium of a signaling molecule that relaxed vascular smooth muscle, termed endothelium-derived relaxing factor. Dr. Ignarro's work, in parallel with Dr. Furchgott, revealed that EDRF was actually nitric oxide, the active agent which produced smooth muscle relaxation. In a separate series of studies, Dr. Murad revealed that nitrovasodilators exerted their predominant pharmacologic effect on blood vessel relaxation because they served as a source for nitric oxide generation. Moreover, he demonstrated that the primary biological receptor for nitric oxide was cytosolic, or soluble, guanylate cyclase which regulated vascular smooth muscle contractility through the enzymatic conversion of GTP to the second messenger cyclic GMP.

The revelation in the 1980's that nitric oxide was a hormone that signaled, at least in part, through guanylate cyclase and cGMP, was paradigm-shifting and established a field which has grown exponentially over the ensuing years. One "marker" of the impact that these seminal discoveries had is the number of publications they stimulated. Indeed, before these discoveries, there were only a few hundred papers in the world's literature on the biology of nitric oxide. However, in the 30 years after these discoveries were revealed, there have been nearly 150,000 papers that focus on nitric oxide biology and medicine. In that context, these discoveries became the foundation for dissecting the molecular mechanisms regulating the natural production of nitric oxide, through the family of nitric oxide synthases. Indeed, the regulation of this synthesis and downstream nitric oxide signaling was identified as a key step in the physiology of the cardiovascular, nervous, reproductive, musculoskeletal, and immunological systems, to name a few. Further, they nucleated studies that defined the major mechanisms of nitric oxide signaling beyond guanylate cyclase and cyclic GMP, including the post-translational modification of proteins by nitric oxide and its reactive derivatives, like peroxynitrite. In turn, these insights offered novel perspectives on the pathophysiology contributing to a host of disorders including, but not limited to, vascular insufficiency syndromes, inflammatory diseases, pulmonary disease, psychiatric disorders, and cancer. Moreover, these discoveries identified essential components of the nitric oxide signaling cascade as targets for novel therapeutic approaches to disease management, with active pharmacotherapies available for cardiovascular disease, impotence, and pulmonary diseases, to name a few.

Discovery consists of seeing what everybody has seen and thinking what nobody has thought

Albert Szent-Gyorgi

As he turns 80 this year, Dr. Murad can look back on a rich career filled with extraordinarily impactful molecular discovery and translation of those insights into novel therapeutic paradigms for individual patients and populations. His gift was to see something that everyone else had seen, the activity of nitrovasodilators, and then to doggedly pursue the underlying biology to define previously unknown molecular mechanisms which proved to be paradigm shifting and field-opening. It is in the context of those discoveries, and the occasion of this landmark birthday, that we curated this issue to highlight recent work in the field which he was instrumental in creating. In that context, the review by Sorokin (1) highlights new insights into the reciprocal interplay between nitric oxide and prostaglandin synthesis that appears to underlie normal physiology, and which becomes dysfunctional in the pathophysiology of a variety of systems, for example arthritides, tissue regeneration, and diabetic retinopathies. Zhao (2) highlights bioengineering studies in which nitric oxide-generating compounds are fabricated into structures and devices that can be applied to stably administer this hormone to improve vascular function, speed wound healing, or generate nitric oxide levels locally that are cytotoxic to tumors. Benhar (3), Cippitelli (4), and Kumar (5) focus on the role of nitric oxide in processes underlying tumorigenesis in a variety of systems. Indeed, they underscore the concept that the role of nitric oxide in inducing, or opposing, tumorigenesis depends on context (which cells make it, which receive it) and concentration. The concept of nitric oxide in brain function is examined in the review by Phillipu (6), who explores the role of this agent in regulating synaptic transmission. This theme is advanced by Koseling (7), who highlights the differential roles of the isoforms of soluble guanylate cyclase in mediating pre- and post-synaptic transmission in brain. In addition to normal physiology, the role of nitric oxide in pathophysiology in the central nervous system is underscored by Jimenez-Jimenez (8), who explores the role of dysfunctional nitric oxide signalling in the etiology of neurodegenerative diseases like Parkinson's disease. Similarly, the role of abnormal nitric oxide signaling in mechanisms contributing to psychoses is examined by both Hallak (9) and Pitsikas (10). Moreover, the role of abnormal nitric oxide signaling in mechanisms underlying neruo-inflammation in the context of HIV infection is reviewed by Persichini (11). Beyond the central nervous system, the role of nitric oxide signaling in the peripheral nervous system mediating nitrergic transmission in the GI tract which facilitates GI motility is explored by Friebe (12). In that context, this review underscores the potential role of abnormal nitric oxide signaling in mediating disorders of GI motility. Nitric oxide also plays a central role in the (patho)physiology of the airways, highlighted by Maniscalco (13), and bone, reviewed by Pilz (14). Indeed, the latter review highlights the potential role of regulators of nitric oxide signaling in preventing and reversing the effects of disorders of bone resorption, for example osteoporosis. Finally, Girotti (15) reviews the effects of nitric oxide in opposing the activities of photosensitizing agents, through redox mechanisms, which are the key to photodynamic therapy for a number of tumor types. This review underscores the potential utility of inhibitors of nitric oxide production in potentiating the anti-tumor effects of photodynamic therapy.

Spoon feeding in the long run teaches us nothing but the shape of the spoon

E.M. Forrester

Beyond the science, Dr. Murad has been the consummate mentor. He has trained scores of fellows, physician scientists, and doctoral students and many have gone on to leadership

positions in academia and the biopharmaceutical sector internationally. One of us (SAW) spent 8 years as a trainee with him and it is a rare opportunity for a former fellow to pay tribute to a mentor who continues to be an inspiration and key advisor professionally and personally. I first arrived in Dr. Murad's laboratory in 1979 as a relatively inexperienced newly minted PhD who trained in a small laboratory. Immersion into the Murad laboratory was culture shock because it was extremely large, internationally diverse, and brought together the talents and skills of many specialties and disciplines. My entry into this world was right at the time when the studies of nitrovasodilators, nitric oxide, and soluble guanylyl cyclase were the central focus of the laboratory. Instinctively, Ferid new exactly what was required to evolve a fellow into an independent scientist. As trainees, he insisted that we take ownership of, and responsibility for, our projects. He was masterful in formulating hypotheses, and he was astonishingly good at troubleshooting experiments. However, he made it a priority to have us troubleshoot our own experiments, and formulate our own biological hypotheses for testing. His philosophy was that if he spoon fed us, we would never learn to stand up on our own two legs. This "tough love" was effective, the years I spent with him somehow rubbed off, and now I take the same approach with my own trainees. Beyond these professional skills, Ferid taught me that the only questions worth chasing are the big ones that can shift the mechanistic paradigm, and that have the ability to impact therapeutic strategies and disease management paradigms for devastating illnesses. Ultimately, I internalized his lessons and have pursued an independent career in translational pharmacology in the area of cancer. I still depend on those lessons, and I still get together with my old mentor to discuss strategies to navigate the complexities of the professional, and personal, world. What began as a mentor-mentee relationship ultimately evolved into a lifelong friendship that I will always cherish.

So Dr. Murad, happy 80th birthday from your friends and colleagues, students and fellows, and all the beneficiaries of your seminal discoveries. You have created a legacy in science and medicine which are prodigious and extraordinary. Importantly, beyond what you have discovered, there are scores of us who are standing on your shoulders trying to get a glimpse of the next scientific horizons. We thank you for those broad shoulders and your support.