

# AUTONOMIC BIOLOGY: from beheaded animals to a spate of Nobel Prizes

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*Autonomic biology grew slowly from puzzling observations made using crude techniques in the late 1800s. Its development was refined in the great universities of Cambridge and Oxford, but it was the financial strength of giant corporations and foundations, along with the development of new therapies, that moved the field forward. Talented biochemists, pharmacologists, and vascular and molecular biologists have made seminal contributions to our understanding of autonomic biology. The field is rich with Nobel laureates. Interdisciplinary teams were the rule and not the exception. Laboratory mishaps and small conferences also played an important role. The development of autonomic biology is a clear example of how basic and clinical science, academia and industry, and ultimately talent, have combined to enrich the field of medicine.*

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Among the ten seminal concepts of cardiology that this issue of *Dialogues* is looking at from a historical perspective, and which can be likened to trees in a vast forest, autonomic biology probably is one of the youngest trees, with the fastest growth. Before the technical term of “autonomic” had been explicitly defined, there was a long period of subterranean growth of the root system, reflecting the slow and methodical process that led to the discovery and understanding of the autonomic nervous system. The actual moment the seedling broke through the earth and the term “autonomic” was coined can be pinpointed to 1898. The “trunk” is most definitely represented by E. P. Sharpey-Schafer, who as Professor of Medicine at the University of London and a member of the Department of Medicine at St Thomas’ Hospital Medical School, moved the field forward most forcibly in the 1940s and 1950s. As a practicing physician, he was able to carry out detailed studies in patients, which defined how the circulation was regulated under a variety of stressful conditions. We probably owe Sharpey-Schafer the greatest debt of gratitude for paving the way for many others who refined this field at the anatomic, physiological, and molecular levels. He provided the impetus that led to several Nobel

Prize-winning discoveries that changed the way we treat patients. This essay focuses on the process of discovery rather than the specific discoveries in an attempt to identify the seedling, roots, trunk, and branches provided by those who have made the most meaningful contributions to autonomic biology.

## THE SEEDLING

As always, terminology is important. The expression “autonomic nervous system” was probably introduced in 1898, when John Newport Langley (1852-1925) (*Figure 1, next page*), a Cambridge physiologist, used it to imply that its actions were independent, but still “... under control of a higher power.” Langley believed that the innervation of glands and involuntary smooth muscles was governed by a system that was independent of the voluntary nervous system.<sup>1</sup> Langley’s report, which was not widely accepted, used the terms “sympathy” and “sympathetic.” Prior to the 19th century, knowledge of the autonomic nervous system was based almost exclusively on animal and human dissections. Albert Rognard and Paul Laye (1861-1890) studied the stimulation of the vagus nerve and the secretion of gastric juice in beheaded animals. Camillo Golgi (1844-1926) deserves credit for pointing out that the whole nervous system is like a net or net-



**Figure 1.**  
John Newport Langley  
(1862-1925).  
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Physiology, University  
of Cambridge.

work (a reticulum), while Santiago Ramon y Cajal (1852-1934) first proposed that each nerve cell was a single or independent unit. Both shared the Nobel Prize for Physiology or Medicine, in spite of having never reconciled their divergent views. Charles Sherrington (1857-1952), using much improved histological techniques, proposed the word “synapse” in 1897 to describe the terminal neuron and its effector organ. Sherrington and Edgar Douglas Adrian shared the Nobel Prize in Physiology or Medicine in 1932 for their discoveries regarding the function of neurons.

Walter Gaskell (1847-1914), another Cambridge physiologist, deserves much of the credit for elucidating the anatomic complexities of the autonomic nervous system.<sup>2</sup> Gaskell also delineated the morphology and the function of the two separate arms of the autonomic nervous system—what we now refer to as sympathetic and parasympathetic, and coined the terms “visceral” and “involuntary.” There was disagreement about a possible third network, the “enteric” nervous system. Langley, a contemporary working in the same department who used drugs to investigate and differentiate the two arms of the autonomic nervous system, confirmed Gaskell’s work, and postulated the existence of a mech-

anism whereby these nerves communicated with the effector organ—but he doubted the existence of chemical messengers.

### THE ROOTS

Henry Dale (1875-1968) (*Figure 2*), a student of Gaskell and Langley, moved from Cambridge at the suggestion of Henry Wellcome to the



**Figure 2.** Sir Henry Dale (1875-1968). © The Nobel Foundation.

Wellcome Physiologic Research Laboratories to study ergot alkaloids. His early contemporary at Cambridge, Thomas Elliott (1877-1961), had observed that stimulation of the hypogastric nerve could be mimicked by the action of a substance he called “adrenaline.”<sup>3</sup> When he presented his results to the Physiological Society in 1904, he suggest-

ed that adrenaline was liberated from autonomic nerves. His work, which at the time was considered “ambiguous,” was probably the first formal suggestion of chemical neurotransmission. Dale observed that ergot “paralyzed” the structures that adrenaline stimulated,<sup>4</sup> but unlike Elliott, never proposed a formal explanation. Dale, however, went on to study with George Barger (1878-1939), a chemist with whom he described the structure of adrenaline and related amines. Together, they coined the term “sympathomimetic.” Dale remained mystified about why large doses of adrenaline caused “vasoconstriction,” whereas small doses caused “vasodilation,” and privately referred to this as “the central mystery.” To Dale, however, belongs the notion of chemical neurotransmission, later to be proven, and again the subject of a Nobel Prize in 1970 for Sir Bernard Katz (1911-2003). It was also Dale who first proposed the terms “cholinergic” and “adrenergic,” a usage he believed would assist clear thinking. These discoveries relating to “chemical transmission of nerve impulses” won Dale the Nobel Prize in 1936.

The American physiologist Walter B. Cannon (1871-1945) provided further support for the observations of Dale and colleagues, but Cannon and Arturo Rosenblueth (1900-1970) obfuscated these issues by coining new terminology, including the terms sympathin E (excitatory) and sympathin I (inhibitory),<sup>5</sup> which was promoted by their popular book, *Autonomic Neuro-effector Systems*. Some thought the book unnecessarily complicated. Ray Ahlquist, using a range of adrenergic agonists, first postulated the terms  $\alpha$ -receptors and  $\beta$ -receptors in 1948, which allowed reinterpretation of previous confusing work.<sup>6</sup> In the 1950s and 1960s, it became clear that not all autonomic nerves were adrener-



**Figure 3.** Edward Peter Sharpey-Schafer (1908-1963).  
Courtesy J. Sharpey-Schafer.

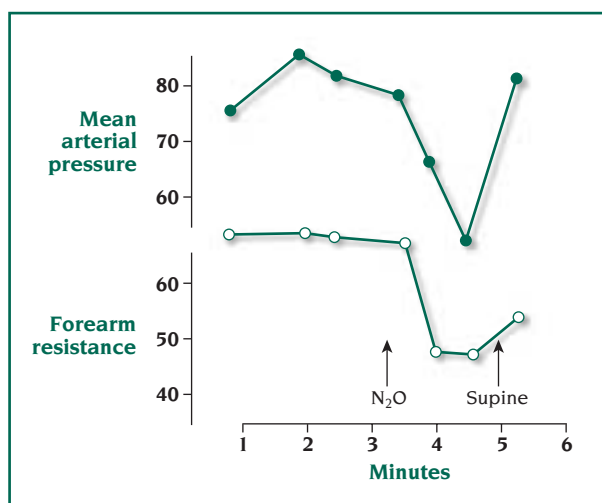
gic or cholinergic. Burnstock (born 1929), who suggested that other neurotransmitter chemicals could also be released,<sup>7</sup> for which he was criticized, was ultimately proven correct, as the number of known neurotransmitters continues to grow.

### THE TRUNK

Professor Edward Peter Sharpey-Schafer (1908-1963) (*Figure 3*) was one of the grandsons of the English physiologist Sir Edward Albert Sharpey-Schafer (1850-1935), who invented the first prone-pressure method (Schafer method) of artificial respiration, and made important contributions relating to adrenaline, insulin, and the pituitary and other endocrine glands. The younger Sharpey-Schafer was a highly respected cardiologist and clinical physiologist at University College Hospital in London, who was described as having “the highest IQ and the lowest pH in England.” He and colleagues produced a stream of 27 papers mainly in the 1950s and 1960s related to the autonomic nervous system and the peripheral circulation in heart failure, shock, and syncope. The work was done on patients in his laboratory at St Thomas’ Hospital. The papers,

many of which were written by him as sole author, are short (1-2 pages) and to the point. Sharpey-Schafer was able to measure venous and arterial tone, and like many great physiologists, he took advantage of emerging technology to advance his understanding of physiology.<sup>8</sup> In 1958, he published a paper describing patients who developed spontaneous nausea during N<sub>2</sub>O anesthesia

various drug therapies in patients with heart failure in the 1970s and 80s. Sharpey-Schafer observed that venous tone was increased in patients with heart failure, but fell toward normal when treatment was given.<sup>10</sup> He also showed that adrenaline and other amines constricted veins, whereas nitrates dilated the venous system, which led him to suggest that the sympathetic nerv-



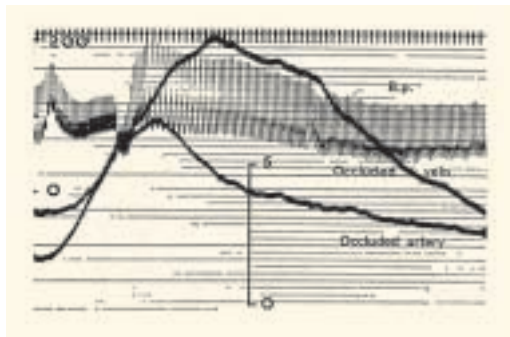
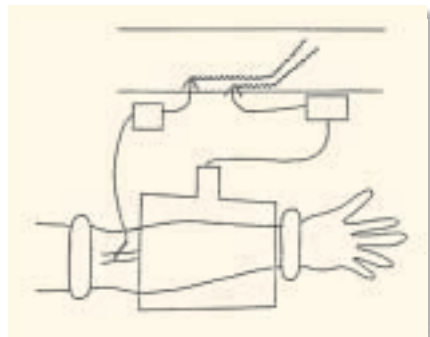
**Figure 4.** Vasodilation caused by N<sub>2</sub>O administration.

Reproduced from reference 9: Sharpey-Schafer EP, Hyater GJ, Barlow ED. Mechanism of acute hypotension from fear or nausea. *BMJ*. 1958; 46(5101): 878-880. Copyright © 1958, British Medical Journal Publishing Group Ltd.

for tooth extraction, or following the administration of apomorphine for chronic alcoholism (*Figure 4*).<sup>9</sup> He found nausea led to peripheral vasodilation, a fall in diastolic pressures of the heart, hypotension, and syncope. He postulated that virtual emptying of the ventricular chamber during systole activates an afferent mechanism that produces fainting,<sup>9</sup> which also occurs when sublingual nitroglycerin causes hypotension, bradycardia, and syncope. His observations remain an integral part of the fundamental mechanism of neurocardiogenic syncope as it is understood today.

Sharpey-Schafer devised a method for measuring changes in the tone of forearm veins, a technique later taught to me (G. S. F.) by Jay N. Cohn in Minnesota and used by us to study reflex control mechanisms and

ous system is activated in heart failure, though its effects could be counteracted by nitrates (*Figure 5, next page*).<sup>11</sup> Earlier, Sharpey-Schafer had demonstrated that forearm blood flow was reduced in patients with congestive heart failure, and that the erect posture caused vasoconstriction in normal subjects and vasodilation in patients with heart failure.<sup>12</sup> Today, we know that the vasodilation produced by nitrates is probably mediated by nitric oxide (NO). Sharpey-Schafer and Ginsberg pointed out that nitrates relieved angina by reducing the work of the heart, which they ascribed to dilation of the veins, and not by increasing coronary blood flow.<sup>10</sup> At the time they made this discovery, it went against the central dogma to suggest that nitroglycerin relieved angina by dilating coronary arteries.



$\frac{\Delta P}{\Delta T} / \frac{\Delta V}{\Delta T}$  : venous pressure increment per unit flow = venous tone (mm Hg/mL)

**Figure 5.** Measurement of venous tone during the Valsalva maneuver.

Reproduced from reference 11: Sharpey-Schafer EP. Venous tone: effects of reflex changes, humoral agents and exercise. Br Med Bull. 1963;19:145-148. Copyright © 1963, Oxford University Press.

## THE BRANCHES

The fact that Sharpey-Schafer could develop and maintain a hospital-based laboratory to study human subjects and patients with circulatory dysfunction was the key to translating observations that previously could only be made in the physiological animal laboratories. His work led to the development of numerous “human physiology” laboratories, headed by such luminaries as Shillingford, Braunwald, Gorlin, Cohn, Chatterjee, and other investigators, some of whom participated in the Myocardial Infarction Research Units (MIRUs) funded in the United States by the National Institutes of Health (NIH) in the 1970s. It became clear that critically ill patients could be safely studied at the bedside. The branches grew out, however, in many directions. The central theme was circulatory physiology and its interaction with the autonomic nervous system. Neurohormones, nitric oxide, and the pharmacology of the adrenergic receptor came somewhat later.

### Ray Ahlquist

As mentioned, Ahlquist (1914-1983) should be credited with organizing and finally resolving some of the ambiguities regarding the autonomic

ic nervous system, particularly the terminology.<sup>13</sup> Working at the Medical College of Georgia in Augusta, he defined the two major classes of “adrenoceptors,” with a range of different potencies for catecholamines. He predicted that  $\alpha$ -receptors would be more sensitive to norepinephrine, whereas  $\beta$ -receptors would be preferentially more sensitive to isoproterenol, and least responsive to norepinephrine. Of course, today we know there are numerous subtypes of “adrenoceptors”, but Ahlquist’s explanation of sympathetic nervous system receptors has withstood the test of time and is still used today. Ahlquist also went on to define cholinergic receptors, including muscarinic, ganglionic, and somatic subtypes, and brought clarity to the field of autonomic biology.

### Sir James W. Black

Sir James Black (*Figure 6*) was responsible for a major “branch” in the development of our understanding of autonomic biology. He was the fourth of five boys born in 1924 into a staunch Baptist home in Uddingston, Scotland, and chose to study medicine under the influence of an older brother, William, at St Andrews University. It was there that he began his disciplined studies under the tutelage of D’Arcy Wentworth

Thompson, the great Victorian polymath. Black married shortly after graduation and joined the Physiology Department under Professor R. C. Garry.

In 1947, Black moved to Singapore to the King Edward VII College of Medicine. He returned in 1950 to the University of Glasgow, where, in 1956, stimulated by Ahlquist’s work,



**Figure 6.** Sir James W. Black (born 1925). © The Nobel Foundation.

he set out to find a specific adrenaline receptor antagonist. He worked in the Pharmaceuticals Department of ICI (Imperial Chemical Industries), the giant British chemical company, from 1958 to 1964; there he changed from being a physiologist to a pharmacologist. Black and Brian Prit-



chard, a clinical pharmacologist at the University College, London, went on to develop propranolol, a  $\beta$ -receptor antagonist, and promoted its use when Pritchard discovered its antihypertensive effect. The clinical implications were enormous, far beyond the initial hopes for propranolol.  $\beta$ -Blockers remain a centerpiece in the treatment of hypertension, heart failure, and other conditions.

By 1963, Black was interested in starting a new program at ICI. Propranolol had become a reality, and he wanted to use this as a model to develop a histamine receptor blocker to reduce gastric acid. He moved to Smith, Kline and French Laboratories (SKF) to run their Biologic Research Lab in 1964, where, with William Duncan heading the Biochemistry Department, they maintained a productive partnership at SKF for 15 years. Black assembled a highly successful team, and modeling the histamine program after the  $\beta$ -receptor program, launched the  $H_2$ -receptor blocker program in 1972, that was to lead to the discovery of cimetidine.

From 1973 to 1977, Black served as the University College of London (UCL) Chair of Pharmacology. By academic standards, his teaching and research ideas were considered too wispy and expensive, and in 1977 he left to join John Vane's group at the Wellcome Foundation. From 1977 to 1984, he worked at the Foundation, but was disappointed with his managerial role, and began to pursue analytical pharmacology in a small, independent, academic research unit within the Foundation. King's College of London and their medical school smoothed difficulties in Black's small academic unit through their support. In intellectual terms, surrounded by talented young researchers and PhD stu-



**Figure 7.** Sir John R. Vane (1927-2004). © The Nobel Foundation.

dents, Sir James Black found his niche. In 1988, he was awarded the Nobel Prize in Physiology or Medicine, shared with Gertrude Elion and George Hitchings, for their discoveries of important principles for drug treatment.

Black used many tools during the process of his discoveries, starting with physiology, moving to pharmacology, and working closely with biochemists. He demonstrated the power of a multidisciplinary approach and the usefulness of moving between industry and academy. His work could not have been done without the resources available from both enterprises.

### Sir John R. Vane

Sir John Vane (1927-2004) (*Figure 7*) was born in Tardebigg, Worcestershire, one of three children. He attended the University in Birmingham, but believed that his chemistry classes lacked for suitable training in experimentation, and moved to Oxford to study pharmacology. There he joined Professor Harold Burn in 1946 who provided Vane with lasting inspiration. Vane went on to share the Nobel Prize in Physiology or Medicine in 1982 for the discovery of prostaglandins and related substances. He is widely recognized

for his work on the antiplatelet effects of aspirin.

Most of Vane's time was spent at Oxford, though he did a 2-year stint in Yale. He then returned to the UK, and joined W. D. M. Paton's Department of Pharmacology, at the Institute of Basic Medical Sciences, eventually located at the Royal College of Surgeons in London. It was here that Vane and his group developed the cascade superfusion bioassay technique that made it possible to measure the instantaneous release of vasoactive hormones into the circulation or in the fluid perfusing isolated organs. Like so many great scientists, a methodological breakthrough allowed Vane and his colleagues to create new ideas and move his field forward.

In 1973, like Henry Dale, Vane was recruited to work at the Wellcome Foundation as Group Research and Development Director, and like Dale, he accepted the appointment and had no regrets, despite warnings from friends and colleagues. It was here that prostacyclin was discovered and its pharmacology developed. Working with Salvador Moncada, he went on to make major discoveries related to endothelial relaxing factor,<sup>14</sup> later discovered to be nitric oxide (NO). Vane forged the link between aspirin and prostaglandins, but had phenomenal success in the broad area of vascular biology, especially the vasoactive properties of smooth muscle unrelated to the autonomic nervous system. Like Black, he moved between academy and industry with ease, worked in small groups, and had no formal training in biology.

### Robert F. Furchgott

Robert Furchgott (*Figure 8, next page*) was born in 1916 in Charleston, SC. He studied at the University of

North Carolina, took his PhD at Northwestern University, and had various positions at NIH, Geigy, Cornell, Washington University and a long tenure at SUNY Downstate, where he performed his most important work. Furchgott shared the Nobel Prize in Physiology or Medicine with Louis Ignarro and Ferid Murad in 1998 for discoveries concerning NO as a signaling molecule in the cardiovascular system.



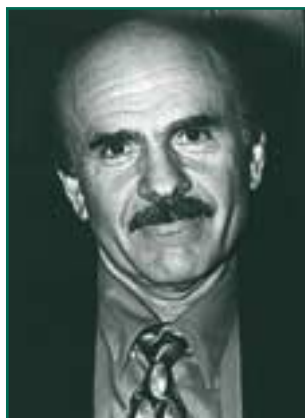
**Figure 8.** Robert F. Furchgott (born 1916).  
© The Nobel Foundation.

Within the first few years of high school, Furchgott knew he would like to be a scientist. His studies were primarily in biochemistry and physiology. His early work concerned the structure and function of proteins and red blood cell membranes. He did graduate work at Cold Spring Harbor where he learned a more quantitative approach to biology, and worked at Cornell University after being awarded his PhD at Northwestern. He stayed at Cornell from 1940 to 1949. The practical needs of the war years turned his interests toward circulatory shock and the cardiovascular system. He then began his groundbreaking work with isolated smooth muscle preparations. He moved to Washington University in 1949 where he worked with Oliver Lowry from 1949 until 1956. For Furchgott, this was a time of

great interdisciplinary activity between biochemistry, physiology, and pharmacology. In 1956, he moved to Brooklyn (SUNY) where he has remained ever since. In May 1978, an accidental finding as a result of a technician's error changed the course of research in his laboratory and led to the seminal discovery relating to endothelium-derived relaxing factor (EDRF).<sup>15</sup> Prior to his Nobel award-winning work, he had become a smooth muscle pharmacologist, and studied sympathetic postganglionic denervation, and how specific drugs potentiate the response of effector organs. He studied a large number of receptor theories and mechanisms, and published a classification of adrenoceptors, differentiating them by pharmacological procedures.

### Louis J. Ignarro

Louis Ignarro (*Figure 9*) was born in 1921 in Brooklyn. He received his bachelor's degree in Pharmacy from Columbia in 1962, and was granted



**Figure 9.** Louis J. Ignarro (born 1921). © The Nobel Foundation.

his PhD in 1966 from the University of Minnesota. From 1979 to 1985 he was on the faculty of Tulane, and moved to UCLA in 1985 where he is Professor in the Department of Molecular and Medical Pharmacology. Ignarro shared the Nobel Prize

in Physiology or Medicine in 1998 with Furchgott and Murad. Following his training at Minnesota, which he considered the best pharmacology department in the country, Ignarro left for NIH where he studied the chemistry of  $\beta$ -adrenergic receptors. Here he worked with such luminaries as Brodie and Axelrod. He went from NIH to Geigy, where he took an interest in cyclic GMP, moving to Tulane in 1973 as an Assistant Professor of Pharmacology. The study of cGMP led to work on blood vessels, nitroglycerin, and eventually nitric oxide, that allowed Ignarro to elucidate the mechanism of nitroglycerin as a vasodilator, and how NO activates guanylate cyclase.<sup>16</sup>

In 1985, Ignarro moved to UCLA. In the summer of 1986, he and Furchgott presented the results of experiments demonstrating that EDRF was NO at a small conference on vascular biology held at the Mayo Clinic organized by Paul Vanhoutte. Ignarro recognized that the naturally occurring physiological neurotransmitter involved in the penile erectile response in mammals was NO released from nerves. He also distinguished himself as an outstanding classroom teacher, being awarded 10 Golden Apple awards at UCLA.

### Paul Vanhoutte

Paul Vanhoutte, (*Figure 10*), was born (1940) and educated in Belgium. He held a variety of tenured positions at the University of Antwerp (1973-1981), the Mayo Clinic (1981-1989), and Baylor College of Medicine (1989-1995), and interacted with American and European specialists in biomedical science. Vanhoutte studied smooth muscle pharmacology extensively during his career. During his tenure as Director of Discovery Research at



**Figure 10.** Paul M. Vanhoutte (born 1940). © Servier

Servier (1995-2004), he supervised the discovery and preclinical development of drugs designed for the treatment of cardiovascular diseases, diabetes, obesity, central nervous system disorders, cancer, and osteoarthritis. His research interests are in cardiovascular pharmacology and therapeutics, in particular, endothelium-dependent relaxation, hyperpolarization, and contraction. His major scientific contribution has been to appreciate and analyze the importance of endothelial cells in the control of the underlying vascular smooth muscle in health and disease, and to highlight the complexity of that regulatory balance.

### Robert Lefkowitz

Robert Lefkowitz, (Figure 11), born in 1943, is a graduate of the prestigious Bronx School of Math and Science in New York and is currently Duke Professor of Biochemistry at Duke University. His contributions to our understanding of the biochemistry and molecular biology of the  $\beta$ -adrenoceptor are monumental. In a series of important papers, Lefkowitz and colleagues described the structure, function, and mechanism of activation and desensitization of the adenylate cyclase-coupled  $\beta$ -adrenergic receptors.<sup>17</sup> Since  $\beta$ -adrenergic receptors are the primary myocardial targets of the sympathetic nervous system, this work

carries special significance for cardiologists. Lefkowitz demonstrated posttranslational molecular modifications of the human  $\beta_2$ -adrenergic receptor, pointing out the uniqueness of the molecule, which has no introns to be spliced out during its biochemical construction. Such ob-



**Figure 11.** Robert Lefkowitz (born 1943). © Duke University.

servations have implications for evolutionary theory, and their importance extends well beyond the information used for drug development.

### CONCLUSION

The road to success in the study of autonomic biology is crowded with Nobel laureates who made seminal contributions to this difficult, but exciting field. It is also a textbook example of how the roots engendered the trunk and the branches of the tree; eg, how thoughtful observations using whole animal preparations led first to the discovery of effector molecules, and ultimately to an understanding of the cellular signaling systems that mediate critical biologic responses. As with many scientific disciplines, it took time to establish the nomenclature, which to some extent held up early progress. Clarity was brought to the field by the development of new techniques and methodologies. Today, all this important work has

come to fruition in the form of a much more precise understanding of the interface between molecules such as NO and smooth muscle biology. Much of this work has also led to an appreciation of the endothelium as the body's largest organ. It is likely that new drugs and therapies will be targeted to specifically enhance the production of NO and diminish nitrosative stress.

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