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[Home](#) > Uncovering The Effects Of Nitric Oxide On The Cardiovascular System

## Uncovering The Effects Of Nitric Oxide On The Cardiovascular System

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### 1998 Nobel Prize Medicine

Robert F. Furchgott, Louis J. Ignarro and Ferid Murad were awarded the Nobel Prize in Medicine or Physiology of 1998 for their norm-breaking discoveries regarding the effects of nitric oxide on the cardiovascular system.

In their brilliant series of independent researches and experiments, they were able to show that nitric oxide acts as a signal molecule to elicit vasodilatation or dilation of the blood vessels.

The banner features the Explorable logo and the text "Quiz Time!". Below this are three quiz cards:

- Card 1: Image of red roller skates on a wooden deck. Quiz: Psychology 101 Part 2
- Card 2: Image of a fan of colorful pencils. Quiz: Psychology 101 Part 2
- Card 3: Image of a Ferris wheel at sunset. Quiz: Flags in Europe

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## Background of Nitric Oxide

Air in our atmosphere is composed of 79% nitrogen. When nitrogen is burned, it produces nitric oxide [1]. It is also considered one of the most common air pollutants due to its sheer volume. An example of this is the high nitric oxide content of our car's exhaust fumes. Nitric oxide is also considered as an unstable and reactive gas especially in the presence of oxygen. It changes and reacts to other substances that come close to it. It is so unstable that it can be converted to nitrate and nitrite in a matter of seconds. It was also known to be

present and produced by lower organisms such as bacteria but it was not expected to be of great importance to higher organisms.

## **The Minds Behind the Discovery**

Robert Furchgott was born on the 4th of June 1916 in Charleston, South California. As a child, he was an avid shell collector and a bird watcher. Within the first couple of years in high school, he knew that he wanted to become a scientist. He then entered University at Chapel Hill as chemistry major. By his senior years, his preference was physical organic chemistry. He then finished his Ph.D. in Biochemistry at Northwestern University in the year 1940. In 1956, he became acquainted with researches in cardiovascular system when he conducted experiments on photorelaxation of blood vessels, factors in the contractility of cardiac muscle, peripheral adrenergic mechanisms and endothelium-dependent relaxation.

Louis Ignarro was born on the 31st of May 1941 in Brooklyn, New York. He entered Central Grade School and Long Beach High School with a strong interest in chemistry. He then applied to Columbia University in New York to study chemistry and pharmacy. He earned his B.A. in Pharmacy in 1962. He then finished his Ph.D. in Pharmacology in the University of Minnesota in the year 1966. He also became a professor of the Department of Pharmacology of Tulane University, School of Medicine in New Orleans. In 1985, he also became of professor of the Department of Pharmacology of UCLA School of Medicine in Los Angeles, California.

Ferid Murad was born on the 14th of September 1936 in Whiting Indiana. At the age of 12, he knew that he will become a doctor. He earned his undergraduate chemistry degree at DePauw University and his M.D. and Ph.D. in Pharmacology from Case Western Reserve University in 1965. He became a professor in the University of Virginia in 1970. He also served as the vice-president of the Abbott Laboratories in 1988. He also became a professor and Director Emeritus of The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Disease. He also holds the John S. Dunn Distinguished Chair in Physiology and Medicine.

## **The Discovery**

In 1977, Murad tried to analyze how vasodilating drugs act upon the cardiovascular system to achieve this result. In his experiments, he observed that some drugs, such as nitroglycerin, caused a release of nitric oxide in the body, which relaxes the smooth muscle cells. He was then fascinated by this result since gases were not known to regulate such important cellular functions. But he conducted no succeeding experiments to establish the role of nitric oxide in smooth muscle relaxation.

Three years after the discovery of Murad, Furchgott also tried to work on the effects of drugs on blood vessels. Initially, he had contradicting results since he noted that same drugs sometimes cause vasoconstriction, on another test vasodilatation. He then hypothesized that the effects of the drugs vary depending on the status of the endothelium. He thought that the effects of the drugs may vary if the endothelium in the blood vessels were intact or damaged. This hypothesis was verified in 1980 when he successfully showed that acetylcholine causes vasodilatation only if the endothelium is intact. He then concluded that the blood vessels dilate due to the intact endothelium's production of an unknown signal molecule which he called

endothelium-derived relaxing factor or EDRF.

Due to the paper written by Murad in 1977, Ignarro thought that nitric oxide can be the cause of vascular smooth muscle relaxing action of nitroglycerin and that cyclic GMP might be its second messenger. In 1979, he conducted an experiment wherein he injected nitric oxide gas bubbles into an organ bath containing a precontracted bovine coronary artery strip. He noted a significant and rapid relaxation of the coronary artery strip. This vasorelaxant effect was noted to be inhibited by methylene blue which was known to inhibit guanylate cyclase which causes an increase in cyclic GMP levels.

Due to these results, he was able to prove the effects of nitric oxide on the cardiovascular system as a vasorelaxant and cyclic GMP was the second messenger. In 1983, he conducted a study to identify the EDRF that Furchgott discovered and he realized that EDRF and NO shared similar pharmacological and biochemical properties. EDRF and NO both activated guanylate cyclase and elevated cyclic GMP. The cyclic GMP levels and the vasorelaxant effects of both EDRF and NO were inhibited by methylene blue. He then concluded that the EDRF of Furchgott is NO.

The discovery of the effects of nitric oxide on the cardiovascular system and its role as a signaling molecule astounded the entire scientific community. Signaling molecules are called neurotransmitters and NO, as a gas, does not fit into this traditional definition of neurotransmitters. Neurotransmitters are produced, stored and used when needed but NO is not produced in advanced or stored. Neurotransmitters, in the traditional way, only affects nearby neurons but NO, as a gas, diffuses in all directions and is not limited to a local effect.

## Clinical Relevance

Ignarro enumerated several applications of nitric oxide on the cardiovascular system and to other organ systems of the body. Based on these properties of NO, new drugs can be developed such as vasodilators and antiplatelet agents and antiproliferative agents for the treatment of hypertension, atherosclerosis, stroke, angina pectoris, heart failure, and vascular complications of diabetes, gastrointestinal ulcers, impotency and other vascular disorders. An excellent example of the application of basic information learned about NO has been the development of sildenafil or Viagra, which has revolutionized the treatment of impotency. Other novel therapeutic benefits of NO will include the prevention and treatment of gastrointestinal ulcers, inflammatory bowel disease, and related gastrointestinal disorders as well as urinary incontinence.

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### Links

[1] <http://www.cvphysiology.com/Blood%20Flow/BF011.htm>