

BEYOND DISCOVERY™

THE PATH FROM RESEARCH TO HUMAN BENEFIT

FROM EXPLOSIVES TO THE GAS THAT HEALS NITRIC OXIDE IN BIOLOGY AND MEDICINE

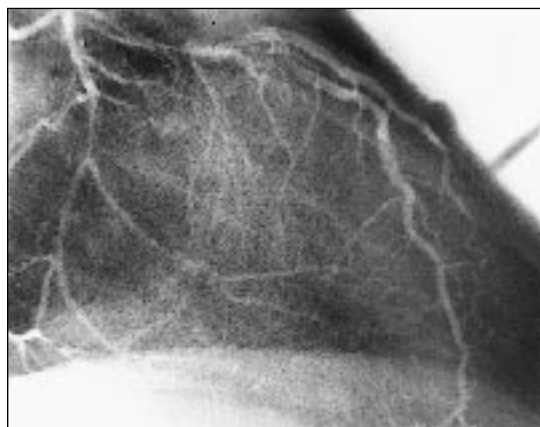
Less than two months before his death in December 1896, Alfred Nobel wrote a note to a colleague: "Isn't it the irony of fate that I have been prescribed nitro-glycerin, to be taken internally! They call it Trinitrin, so as not to scare the chemist and the public." Nobel suffered recurring attacks of the intense chest pain known as angina pectoris, and physicians of his day knew that nitroglycerin—the active ingredient in dynamite—provided effective relief. The irony, of course, was that the Swedish inventor and industrialist had made much of his considerable fortune from developing and manufacturing dynamite. Moreover, from his own laboratory experiments, Nobel had learned that exposure to the chemical caused severe headaches. He declined to take it for his angina.

Although nineteenth-century scientists understood why nitroglycerin was a potent explosive, they had no idea what made it an effective treatment for angina. Somehow it relaxed the smooth muscles that surround blood vessels, allowing the vessels to dilate so that more blood could flow to the starved heart muscle. The secret of nitroglycerin emerged at last in the 1970s, when researchers realized that it works by reacting in the body to form a messenger molecule called nitric oxide, or NO.

Outside the body, NO is an unstable, potentially toxic gas

that forms in lightning strikes and car exhaust. But as a messenger molecule inside the body it plays a crucial regulatory role. Every cell type and tissue sends and receives messages—telling muscle cells when to contract, for instance, or fat cells when to release their stores. Several message systems regulate our web of blood vessels so that they deliver oxygen-carrying blood to the tissues and organs that need it most while also keeping our blood pressure at an appropriate level. The various messengers selectively dilate or constrict blood vessels, diverting blood flow as the body requires—to the gastrointestinal tract after a meal, for example, or to the muscles of movement in an emergency.

Nitric oxide is at the center of the most important relaxation system, thus explaining why nitroglycerin helps angina patients. But NO's importance does not stop with angina. Inhaled NO can help premature babies when the blood vessels in their lungs are not absorbing oxygen adequately. Local application of NO-related drugs may prevent cells from growing and blocking repaired arteries. Drugs that release NO at the site of an



Angiogram showing a coronary artery in a human heart. (Curtis Green, MD, University of Vermont Medical Center)



infection also may help immune cells kill invading pathogens and tumor cells.

As often occurs in science, the path to using NO in such diverse medical treatments was guided by chance observations and was filled with odd turns. Just over a century after Alfred Nobel's death, the prizes that he founded with his fortune would be awarded to three researchers who had set out to investigate the mechanisms of the body's signaling systems—work that ultimately led to an understanding of how an explosive chemical can also relieve the pain caused by cardiovascular disease.

The Heart and Blood Pressure

Circulatory diseases can be treated more effectively today than in the nineteenth century because we understand a lot about how blood circulates and what controls the dynamics of that circulation. There was a time, however, when the very idea of circulation was not accepted. In the second century the Greek anatomist Galen declared correctly that arteries carry blood, not air, but he left behind some stunning misconceptions in other areas, suggesting, for example, that the liver was the center of the blood system. Many of those errors were swept away by *De Motu Cordis* (On the Motions of the Heart), a seminal work by William Harvey published in 1628. “Just as the king is the first and highest authority in the state,” Harvey declared, “so the heart governs the whole body!”

An even greater contribution of *De Motu Cordis*, however, was Harvey's insight that blood circulates.



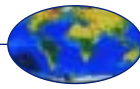
William Harvey (standing) displaying the structure of a goat heart to King Charles I. (The Royal College of Physicians, London)



Artist's depiction of Hales's horse experiment showing that the pressure of the horse's circulation forced blood up the glass tube. (Corbis-Bettman).

To determine the direction of blood movement to and from the heart, Harvey dissected and tied off blood vessels. He concluded that a huge volume of blood moves away from the heart and into the tissues. This quantity of blood could not possibly be created anew at the heart or disappear as food in the tissues. Rather, the blood must flow to the tissues and then return to the heart in a continuous cycle.

A century later, Stephen Hales, a curate in the English country town of Teddington, realized that Harvey's steady cycle of circulating blood actually varied over time. In a series of experiments with horses, a sheep, a doe, and an assortment of dogs, Hales defined the concept of blood pressure. His central experiment, published in 1733, involved tying down a mare, inserting a narrow brass pipe into an artery, and fitting a 9-foot-long vertical glass tube to the pipe. The pressure of the horse's circulation forced the blood up the glass tube to a height of 8 feet, 3 inches. With the beating (rapid, we presume) of the horse's heart, the blood rose and fell by 2 to 4 inches. Hales recognized that the peak pressure reflected the exertions of the contracting heart, and that the low pressure was a measure of how much the blood vessels throughout the body resisted blood flow.



Hales also found that removing blood from the animals caused their blood pressure to drop. However, this was not the only way to affect blood pressure. A few years earlier, in 1727, a French physiologist named Pourfois du Petit had reported that cutting a nerve at the neck caused a blood vessel in the eye to dilate; other experiments demonstrating constriction of blood vessels followed. By the early 1800s anatomists had figured out that the smooth muscles surrounding blood vessels contracted or relaxed in response to signals from various nerves, thereby squeezing the blood vessels or allowing them to dilate.

Measuring blood pressure became practical as Hales's brass and glass contraption was gradually refined during the nineteenth century. In 1854, the physiologist Karl von Vierordt of Tübingen, Germany, realized that the same assessment could be made by measuring how much external pressure was needed to stop blood flow. Vierordt came up with a cumbersome system of weights and levers that eventually led to the idea of the blood pressure cuff. After several improvements, the modern version of this device debuted in 1905, enabling physicians to correlate blood vessel dilation with lowered blood pressure. Clearly, the body maintained exquisite control over blood pressure, and it did so at least partly through the nerves, but the details of this process remained hidden.

An Explosive Medication

While progress in understanding the workings of the circulatory system continued in a more or less logical fashion, the same cannot be said for understanding the treatment of angina. In the late 1700s several English physicians correlated the angina suffered by living patients with the obstruction of heart blood vessels found in postmortems of the same patients. Despite these early insights, many leading physicians through much of the following century blamed the chest pain on indigestion and treated angina with soda or chalk to relieve stomach acidity. Even the acceptance that the heart was the center of the problem did not help matters much: a paper in the July 27, 1867, *Lancet* by T. Lauder Brunton of the Royal Infirmary, Edinburgh, listed brandy, ether, ammonia, and chloroform as possible treatments for angina. Patients treated with chloroform stopped reporting pain temporarily, Brunton noted, but resumed when they had recovered from the “partial stupefaction” induced by the chloroform.

Brunton's real discovery in this paper was that a substance called amyl nitrite reduced both angina pain and blood pressure. A number of clues had prompted him to test amyl nitrite. Eight years earlier a chemist who had inhaled it while doing a routine series of chemical experiments had reported that it made him flushed and caused his arteries and heart to pound. Brunton also knew that amyl nitrate dilated blood vessels in a frog's foot and had heard from others that it reduced blood pressure in humans. Although Brunton was on the right track, he mistakenly believed that amyl nitrite worked by relaxing blood vessels throughout the body. In fact, the important site of amyl nitrite action is on heart blood vessels at the site of a blockage.

Although amyl nitrite reduces angina symptoms rapidly, the relief is short lived. In the hope of finding a more sustained treatment, scientists began looking at related chemicals, including nitroglycerin. Invented in 1846 by Italian chemist Ascanio Sobrero, nitroglycerin was so volatile a liquid that Sobrero—whose face was badly scarred in a nitroglycerin explosion—thought it too dangerous to be practical. In the 1860s, however, Alfred Nobel found a way to make it safe enough to use in construction work. By mixing nitroglycerin with silica, he turned the liquid into a paste that could be shaped into blasting rods. In 1867 he patented the material, calling it dynamite. Twelve years later, in 1879, William Murrell of Westminster Hospital in London, England, endorsed nitroglycerin—diluted to make it nonexplosive—as a longer-lasting remedy for angina.

Listening to the Cell's Messages

Discovering how nitroglycerin works in the body involved understanding the chemical signaling system between and within cells. Since the late 1930s, scientists had known that small molecules such as the hormone adrenaline (also called epinephrine) and the nerve chemical, or neurotransmitter, acetylcholine transmit nerve impulses. These molecules act on the outside of the cell by combining with proteins, called receptors, on the cell surface. Indeed, several Nobel prizes were awarded for the discovery of the functions of these first messengers, as they are known. For some time, however, no one knew how the activation of a surface receptor by these messengers was translated into activity in the cell. That required the discovery of a so-called second messenger.



In 1957 Earl Sutherland and Theodore Rall at Western Reserve University (now Case Western Reserve University) in Cleveland, Ohio, were investigating adrenaline. The hormone, a key player in the fight-or-flight response, travels through the blood as a signal that danger may be imminent. The researchers wanted to learn how adrenaline tells liver cells to process glycogen, a stored form of energy, to make the more readily consumable sugar glucose. To study the mechanics of the cellular response to adrenaline, Sutherland and Rall put liver cells in a tube and broke the cells open before adding adrenaline. They found, however, that doing this stopped the reaction. The broken-open cells, whose outer membrane was now effectively separated from the cells' contents, no longer made glucose in response to adrenaline. However, when the researchers added adrenaline to the outer membrane of the cell, which had been separated from the cells' inner contents, the adrenaline became attached to a receptor and triggered the production of a second chemical messenger. Sutherland and Rall identified this second messenger as cyclic-adenosine monophosphate (cAMP). Adding cAMP to the inner contents of the cell completed the molecular communication circuit and turned on glucose production. For this and his subsequent work, Sutherland was awarded the 1971 Nobel Prize in Physiology or Medicine.

Having taken the adrenaline response as his starting point, Sutherland had discovered the molecule,

cAMP, that directed the response. A few years later he turned to a puzzle that began at the other end of the equation. Sutherland knew the structure of cyclic-guanosine monophosphate, cGMP, a chemical relative of cAMP that had been identified in urine in 1963—but he couldn't find a process in the body that used cGMP as its messenger. He and others had found that a number of different hormones instruct different types of cells to make cAMP and that the effect of increased cAMP production depends on the target cell. Liver cells respond to cAMP by producing glucose, for example, while salivary glands send fluid out of the cell. But while the responses varied, the second messenger was always cAMP, not cGMP.

Ferid Murad began to tease out some clues to cGMP function in the early 1970s. Murad had worked with Sutherland on cAMP in the 1960s before setting up his own laboratory at the University of Virginia in Charlottesville to study cGMP. Murad knew from Sutherland's work that a protein in the cell membrane was needed to manufacture cAMP. So he started by separating out the analogous protein—an enzyme called guanylyl cyclase (GC)—involved in the production of cGMP. While studying the production of cGMP in liver and brain cells, Murad found that the version of GC on the cell membrane differed from the version floating around inside the cell. To examine the two versions of GC in isolation, he added some

Time Line

This time line shows the chain of research that led to an understanding of nitric oxide in biologic systems and the development of some of its medical uses.

1628

William Harvey establishes that blood circulates.

1846

Ascanio Sobrero synthesizes the explosive nitroglycerin.

1879

William Murrell establishes nitroglycerin as an angina treatment.

1979

Louis Ignarro bubbles NO into a solution near an artery and gets a relaxation response.

1981

Ignarro finds that NO inhibits platelet aggregation and increases cGMP.

1733

Stephen Hales measures blood pressure.

1854

Karl von Vierordt makes the first indirect blood pressure measurement.

1977

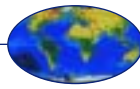
Ferid Murad finds that NO increases the activity of guanylyl cyclase and relaxes smooth muscles.

1980

Robert Furchgott discovers that the endothelium releases a factor (EDRF) that relaxes blood vessels.

1981

Steven Tannenbaum determines that mammals make nitrate.



chemicals that he knew would shut off other proteins that might affect cGMP production. To his surprise, some of the chemicals that he added to the test tube actually turned on GC, so that the GC made more cGMP. When he added the chemicals to various tissues, including trachea and intestine, the chemicals not only turned on GC (as in the test tube) but also relaxed the smooth muscles of these tissues. Murad also found that known dilators, including nitroglycerin, turned on GC in the test tube.

One thing united the chemicals that turned on GC, Murad discovered: they could all react to form nitric oxide (NO). In 1977 he demonstrated that NO turned on GC and relaxed smooth muscle. Two years later Louis Ignarro at Tulane University, New Orleans, found that bubbling NO near an isolated artery triggered a relaxation response. Could NO be a messenger in the body? The body made adrenaline to trigger the production of cAMP, which in turn triggered glucose production, so perhaps the body was making NO to trigger the production of cGMP and blood vessel dilation.

The idea seemed far-fetched. Nitric oxide, an air pollutant and lung irritant produced in car exhaust and lightning strikes, can cause chemical burns. Clearly, the body reacted to NO, but surely it was not a substance the body normally used. Outlandish as it was, the idea would turn out to be correct, but it would be many years before the final proof would be accepted.

The Discovery of EDRF

In the meantime, more clues were accumulating from another direction. One of the problems that Robert Furchgott of the State University of New York (SUNY) in Brooklyn set out to solve in the 1950s was how blood vessel dilation works on the molecular level. Furchgott's starting point was the neurotransmitter acetylcholine, which was known to make blood vessels dilate when injected into animals. Presumably the acetylcholine was instructing the muscle cells that surround blood vessels to relax, thus increasing the diameter of the blood vessels. To get at the steps between acetylcholine and dilation, Furchgott tried to replicate the acetylcholine response in the laboratory, using isolated strips of blood vessels and the muscles surrounding them. A lengthening of the strips would indicate that the muscles were relaxing and, by inference, that the blood vessel was dilating. But with acetylcholine he saw the strips shorten (muscle contraction instead of relaxation) every time. This was a puzzle that Furchgott temporarily set to one side.

Many years later Furchgott planned an experiment to determine the relative potencies of several chemicals as relaxing agents of blood vessels. Carbachol, a chemical relative of acetylcholine (which Furchgott's puzzling earlier experiments had shown

1983
Murad, and later others, find that blood vessel relaxation is associated with increased cGMP.

1986
At a conference, Ignarro and Furchgott independently speculate that EDRF is NO.

1987
Salvador Moncada and Ignarro independently publish chemical evidence that EDRF is NO.

1988
Moncada discovers that NO is made from L-arginine.

1998
Furchgott, Murad, and Ignarro are awarded the Nobel Prize for Physiology or Medicine

1985
Michael Marletta detects inorganic nitrite and nitrate made by mouse macrophages.

1987
John Hibbs and Michael Marletta find that arginine increases nitrite and nitrate formation in macrophages.

1988
John Garthwaite detects NO made by nerve cells.

1991
David Bredt and Solomon Snyder clone bNOS.



was a contracting agent), was to be used to contract the blood vessel preparations so that Furchgott could then observe the relaxing effects of the three agents he was investigating.

Furchgott laid out a detailed protocol for his technician, David Davidson, which began with tests to see that the tissue was reacting correctly. First came a test contraction with the neurotransmitter norepinephrine, then a wash with fresh saline solution to remove the norepinephrine, and then a test contraction with carbachol. After another wash to remove the carbachol, the actual experiment would commence. The experiment was planned for May 5, 1978. As it happened, Davidson forgot the first wash. To the blood vessel preparation, still contracted by the norepinephrine, he added the carbachol. But rather than contracting further, the vessel relaxed.

Furchgott had added acetylcholine or carbachol to vessels treated with various chemicals many times before and seen only contraction. The only difference in experimental procedure was that this time he was using *rings* of blood vessels instead of strips. In further experiments Furchgott took rings, all of which had relaxed in preliminary tests with acetylcholine, cut them into strips, and retested the strips with acetylcholine. Infuriatingly, some of these strips continued to relax, but some of them now contracted. He noticed that the ones that contracted had curled up when they were cut earlier and had required some manipulation. Perhaps the manipulation had done some damage.

Sure enough, rubbing any of the strips on their inner surface took away their ability to relax when acetylcholine was added. Furchgott recognized that the methodical way that he had prepared the strips—always pulling the cut surface over his finger to keep it out of the way—had wiped off something crucial.

Furchgott demonstrated experimentally in 1980 that the missing something was endothelial cells, which form the lining of blood vessels. When he made a sandwich of two blood vessels—one with endothelial cells and one without—both strips would relax in response to acetylcholine. The acetylcholine seemed to instruct the endothelial cells to make a second messenger—which Furchgott dubbed endothelium-derived relaxing factor, or EDRF. The EDRF then directed the relaxation of the surrounding muscle cells in both strips.

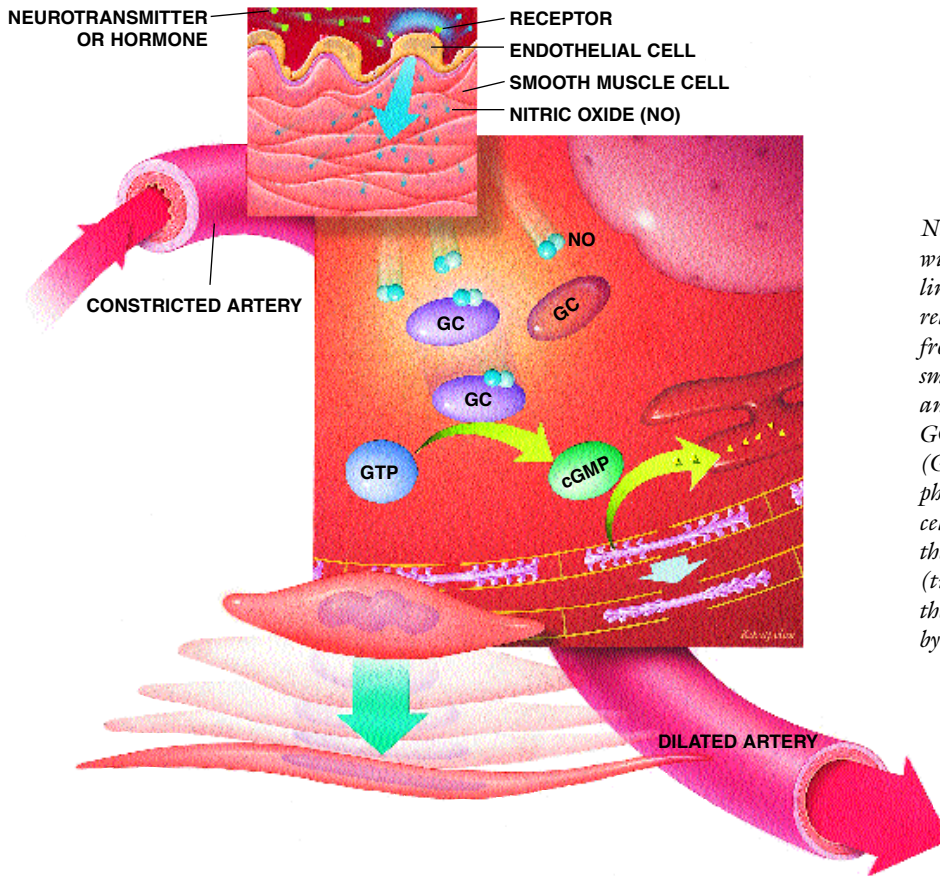
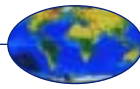
Although Furchgott knew that EDRF existed, he could not isolate and identify it. For the moment it was simply defined as the substance produced by acetylcholine treatment of endothelial cells. Meanwhile, for scientists NO remained a separate chemical and medical oddity. Why would the body have a system for responding to this gas?

EDRF and NO Are United

The discovery of EDRF caused an explosion in research, with many different groups around the world making important contributions to the search for its identity. But the realization that EDRF and NO were one and the same substance took six years of intense research. From 1980 to 1986 reports of similarities between the two gradually mounted. In hindsight this may seem to have been an inevitable accumulation of data, but at the time the picture was quite confusing. NO is an extremely reactive free radical—a result of the molecule's unpaired electron in its outer electron "shell." This high reactivity meant that scientists trying to zero in on EDRF often unwittingly perturbed NO levels when they were trying to shut off other molecular pathways, leading the researchers to the erroneous conclusion that these other pathways were responsible for producing EDRF. Moreover, NO itself seemed a poor candidate for cellular messenger. Its reaction with oxygen, for example, leads to the formation of the corrosive gas nitrogen dioxide (NO₂), which is readily converted to nitric acid. (Note that NO and NO₂ are distinct from nitrous oxide or N₂O, the "laughing gas" used as an anesthetic by dentists.) No previously known biological signaling molecule was a free radical, let alone a radical that was a poisonous gas.

But then there were the mounting coincidences. For starters, EDRF and NO both caused blood vessel dilation, and both did so by turning on GC. This and other evidence led Ferid Murad to propose in 1986 that EDRF could be considered an "endogenous nitrate." The decisive experiments that identified EDRF as NO were performed independently by Ignarro at Tulane and the University of California, Los Angeles, by Furchgott at SUNY, and by Salvador Moncada at the Wellcome Research Laboratories in Beckenham, England. All three researchers found that NO and EDRF both decayed in a matter of seconds, were stabilized by the same conditions, and were turned off by the same battery of chemical treatments. In addition, Ignarro found that NO and EDRF underwent identical reactions with a complex chemical—an unlikely occurrence unless NO and EDRF were identical. Thus, EDRF was chemically identified to be NO.

Ignarro and Furchgott presented their results to a skeptical audience at a conference at the Mayo Clinic, in Rochester, Minnesota, in July 1986. Ignarro felt that not "a single person" in the audience believed



Neurotransmitter or hormone binds with receptors on endothelial cells lining the artery, which in response releases nitric oxide. NO molecules from the endothelium travel into smooth muscle cells where they activate an enzyme, guanylyl cyclase (GC). GC converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). After a cascade of cellular reactions (yellow triangles), the smooth muscle cells relax (turquoise and white arrows) and the blood vessel dilates. (Illustration by John W. Karapelou, © 1998.)

them, but when the data were published in both 1987 and 1988, opinion swung their way. Moncada clinched the argument in an important 1987 paper. In this widely cited article he unambiguously showed that NO was made by endothelial cells. First, he measured the amount of NO produced by a known relaxant (bradykinin) acting on cultured endothelial cells. Then he added exactly that amount of NO to a blood vessel and showed that the added NO could cause a full relaxant response. Thus, the actions of NO could explain the actions of EDRF. A commentary accompanying Moncada's paper described these findings as "the climax of one of the most exciting sagas in vascular physiology and pharmacology."

NO Branches Out

The suggestion that EDRF and NO were the same substance was supported by discoveries made concurrently by other research groups in the early 1980s. In 1981, for example, Ignarro found that NO stops blood cells called platelets from grouping together in a clot. NO could thus prevent blood vessel blockages in two ways—by widening the vessel and by turning

off the clotting process. The discovery of a second response to NO made it less likely that the first (relaxation of vessels) was just a fluke.

The case that NO is a biological messenger, and not just a chemical that the body reacts to, was boosted by a discovery that same year by Steven Tannenbaum of the Massachusetts Institute of Technology (MIT) in Cambridge. He and his colleagues found that mice purged of gut bacteria (which can make NO-related chemicals) still make and excrete nitrate (NO_3^-)—a logical wasteproduct if the body is making NO. In earlier work Tannenbaum had shown that human urinary nitrate levels increase dramatically during infection, and in 1985 Michael Marletta, then at MIT, found that immune cells called macrophages produce nitrate when confronted with a toxic molecule from bacteria. Further analysis by Marletta and by John Hibbs at the University of Utah showed that the macrophages were making NO, which helps kill the invading bacteria before rapidly decaying to form nitrite (NO_2^-) and nitrate. Finally, in 1988 John Garthwaite of the University of Liverpool, England, found that a brain messenger molecule called glutamate triggers nerve cells to release a chemical with striking similarities to EDRF. The chemical—which turned out to be NO—causes nearby cells to release their own nerve messengers, with a cascade of various effects.



Gradually, the objections to NO's alleged role faded. The gas was made in cells in such tiny amounts and decayed so quickly that it was not toxic; at such low concentrations NO did not react to form the poisonous nitrogen dioxide. Indeed, some of NO's characteristics made it extremely useful as a messenger. Because NO moves easily from endothelial cells to the target muscle cells and also decays so quickly, the body's relaxation system can react quickly to a constantly changing environment.

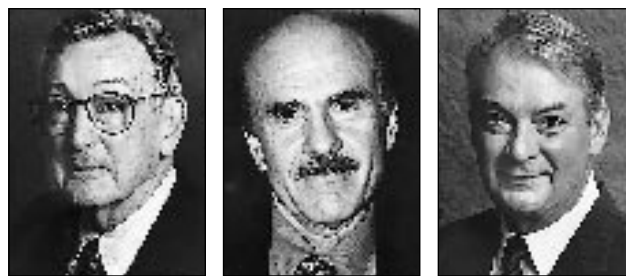
To fully understand how the system changes, however, scientists still had to find the protein that makes NO. A clue was available from earlier work performed by Hibbs and by Marletta, then at the University of Michigan, who both showed that macrophages make nitrite and nitrate from the amino acid L-arginine. Moncada completed the circle in 1988 by demonstrating that blood vessels make NO from L-arginine. The race was then on to isolate the protein enzyme that converted L-arginine to NO. In 1990 David Bredt and Solomon Snyder of Johns Hopkins University in Baltimore, Maryland, were the first to extract a pure active sample of the brain version of the protein, termed brain nitric oxide synthetase (bNOS or NOS-1). The next year they cloned the gene that encodes bNOS. Others followed up with related proteins that could also make NO, including a version from the endothelial cells that line blood vessels (eNOS or NOS-3) and another that was turned on, or induced, in macrophages during infections (iNOS or NOS-2). The significance of NO now was apparent to all.



Future Therapies

The uses for NO and NO-related therapies have expanded as researchers have learned more about how NO works in the circulatory, immune, and nervous systems. The diverse functions of NO also mean that the most effective drugs will be those that are active only where they are needed. Thus, inhaled NO for premature babies with persistent pulmonary hypertension has been a success because the NO is delivered only to the appropriate place—the blood vessels in the immature lungs that need help in harvesting oxygen. Another successful and profitable NO-related therapy is the impotence drug Viagra. By turning off an enzyme that destroys cGMP, Viagra keeps the cGMP signal on longer in penile muscles and dilates the blood vessels. The development of Viagra to treat impotence resulted from the early work of Ignarro, who showed that NO is the neurotransmitter causing penile erection.

Another way to get selective action is to make drugs that turn off only one version of NOS. For



1998 Nobel Prize winners for Physiology or Medicine Robert Furchgott, Louis Ignarro, and Ferid Murad. (The Nobel Foundation)

example, drugs that turn off iNOS (NOS-2), the version produced in macrophages, could be used for inflammatory and autoimmune diseases. Drugs that turn off bNOS (NOS-1), produced in brain cells, could reduce the cell death and brain damage that occur when the brain releases an excess of NO after it is injured or starved of oxygen in a stroke. Both types of drugs must avoid turning off eNOS (NOS-3), so that blood pressure and blood flow to the tissues are not affected.

In the 1990s it was widely expected that a Nobel Prize would be awarded for the discovery of EDRF and nitric oxide as important messengers in the body. Among the names widely touted as potential prize winners were Furchgott, Ignarro, Moncada, and Murad. Consistent with the constraint that no more than three persons share the prize, on December 10, 1998, the Nobel Foundation awarded Furchgott, Ignarro, and Murad the Nobel Prize for Physiology or Medicine for their part in unraveling the NO story.

This article, which was published in 2000 and has not been updated or revised, was written by science writer William Wells, Ph.D., with the assistance of Drs. David Bredt, Robert Furchgott, Louis Ignarro, Michael Marletta, Ferid Murad, Solomon Snyder, Steven Tannenbaum, and Sir John Vane for Beyond Discovery™: The Path from Research to Human Benefit, a project of the National Academy of Sciences.

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