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UNRAVELING THE MYSTERY OF NITRIC OXIDE: NOBEL PRIZE WINNERS ROBERT FURCHGOTT, LOUIS IGNARRO, AND FERID MURAD

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In the 21st century, none of the scientists denies the determining role of the cardiovascular system and its central organ, the heart. The ongoing attempts to design new medications, elaborate effective trainings, heart transplant programs testify that humanity does not abandon attempts to improve and prolong human life, especially given the fact that the world's biggest killer is ischemic heart disease. The most significant achievements in this field receive the highest rating in the scientific community – the Nobel Prize. In 1998, the Nobel Prize in Physiology or Medicine was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signaling molecule in cardiovascular system". Their discovery triggered an international boom in research on nitric oxide. The paper aims to outline briefly the main stages of the scientific activity of R.F. Furchgott, L.J. Ignarro and F. Murad.

K e y w o r d s: nitric oxide, nitroglycerin, Robert Furchgott, Louis Ignarro, Ferid Murad, the Nobel Prize in Physiology or Medicine.

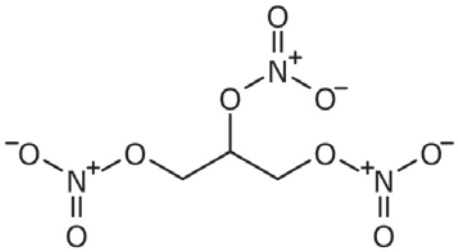
The ongoing attempts to design new medications, elaborate effective trainings, heart transplant programs testify that humanity does not abandon attempts to improve and prolong human life, especially given the fact that the "world's biggest killer is ischemic heart disease, responsible for 16% of the world's total deaths" [1]. The most significant achievements in this field receive the highest rating in the scientific community – the Nobel Prize [2]. In 1998, the Nobel Prize in Physiology or Medicine was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signaling molecule in cardiovascular system" [3].

Nitric oxide (NO) is a small "universal" molecule, which involved in many processes in living organisms. This chemical compound is also called nitrogen monoxide. It is colorless toxic gas that performs chemical signaling functions in humans and animals and has various applications in medicine [4]. Nitric oxide was discovered by an English clergyman, political theorist, and scientist Joseph Priestley. Priestley coined it nitrous air [5].

Though nitric oxide is considered an air pollutant, it also plays a very important role in a human body being a signaling molecule. It controls vascular tone; relaxes vascular smooth muscles and reduces blood pressure; dilates vessels and relieves the pain of angina; inhibits the aggregation of platelets within the vessels and prevents thrombotic events. Nitric oxide acts as a neurotransmitter; increases cerebral blood flow and oxygenation of the brain; acts as one of the important mediators in penile erection; dilates pulmonary vessels; regulates the relaxation of smooth muscles; controls peristalsis; increases blood flow to the kidney, as well as the glomerular filtration rate and the production of urine; modulates T cell-mediated immune response;

controls cutaneous microcirculation and shows antimicrobial properties against micro-organisms. In the human body it is produced from the amino acid L-arginine by the enzyme nitric oxide synthase (NOS) and from inorganic nitrates in green leafy vegetables, fruits, cereals, and cured meat [6].

Nitric oxide is a major active substance of nitroglycerin (also known as glyceryl trinitrate) – a medication used for heart conditions, such as angina pectoris and chronic heart failure. According to the ClinCalc DrugStats Database, nitroglycerin was the 184th most commonly prescribed medication in the United States in 2019 [7].



Nitroglycerin

Nitroglycerin was discovered in 1847 by Ascanio Sobrero, the student of the French chemist Theophile-Jules Pelouze. The explosive properties of nitroglycerin were appreciated immediately. However, it took a little longer to estimate its medical effects. Sobrero experimented with nitroglycerin and noted the headache, "a phenomenon quickly attributed to cerebral vasodilation. This simple clinical observation – that nitroglycerin dilates the vasculature – sparked a century-long dialogue between clinical pharmacologists and basic vascular physiologists, a dialogue that enabled many of the discoveries that are essential to our current understanding of the biologic functions of nitric oxide" [8]. Nitroglycerin as the drug is a dilute form of nitroglycerin – a powerful and unstable explosive [9].

In 1879, nitroglycerin was introduced as a therapy for angina pectoris by the British physician William Murrell. It is interesting to note that the famous scientist, inventor, businessman, and founder of the Nobel Prizes Alfred Nobel, who had suffered from heart disease in the last years of his life, was already being treated with small doses of nitroglycerin – a substance contained in explosives he invented that, in fact, brought him fabulous wealth [10].

A century later, an American physician and pharmacologist Ferid Murad showed that the molecule released from nitroglycerin and related compounds was nitric oxide, which relaxed smooth muscle by elevating intracellular cyclic GMP. His discovery introduced "a new principle for transferring signals between cells; a gas as a signal-transferring molecule had never been observed before. The missing steps in the signaling process were duly filled in by Furchgott and Ignarro, for which the three eventually shared the 1998 Nobel Prize" [11].

Robert Francis Furchgott [12]

Robert Francis Furchgott, a prominent American biochemist of Jewish origin, was born on June 4, 1916, in Charleston, South Carolina, the U.S., to Arthur Furchgott, a department store owner, and his wife Pena Furchgott. Robert grew up in a lovely rural place, where he developed his love for nature. He attended nature study classes, field trips to nearby woods and beaches and became a shell collector and bird watcher. In 1929, Robert's family moved to Orangeburg, South Carolina, a small town where his mother had some family members. There he spent his high school years and decided to become a scientist. This idea was supported by his parents. After school, Robert wanted to attend the University of North Carolina at Chapel Hill. But it was the time of the Great Depression and his father could not afford tuition, that is why Robert spent his freshman year at the University of South Carolina, where his tuition was much less. In 1934, Furchgott's family moved to Goldsboro, North Carolina, and Robert as a resident of the state had a chance to register at the University of North Carolina as a sophomore majoring in chemistry [13]. In 1937, Robert Furchgott graduated from the University of North Carolina at Chapel Hill with a Degree in Chemistry. Sending out dozens of letters in order to get a graduate fellowship or teaching assistantship, Robert unexpectedly got an offer of a teaching assistantship at the Physiological Chemistry Department of Northwestern Univer-

sity Medical School in Chicago. And a new round of his life started there.

Robert Furchgott took physical chemistry, physiology, bacteriology, biochemistry courses at Northwestern University. During his study, Robert became very interested in the physical chemistry of the red blood cell membrane and decided to make his research on the red blood cells as a Ph.D. thesis project. In 1940, Robert defended his thesis and earned a Ph.D. Degree in Biochemistry. Then he was offered a postdoctoral position in the laboratory at Cornell University Medical School in New York City. Furchgott joined Ephraim Shorr's group, where he had spent nine years focusing on cardiovascular research [14].

During his first two years at Cornell, Robert was engaged in the project on phosphate exchange and turnover. Though the methods, as well as lab equipment, were outdated, Robert and his colleagues "did manage with chemical and some early enzymatic methods to show the extremely fast turnover of creatinine phosphate and the terminal phosphate of ATP in resting cardiac muscle" [13]. This work was presented in the paper "Phosphate exchange in resting cardiac muscle as indicated by radioactive studies" [15]. After the U.S. entered World War II, Shorr's laboratory turned their attention to wartime issues, especially hemorrhagic shock. Being involved in research on circulatory shock and tissue metabolism, Furchgott joined Eugene DuBois's Department of Physiology at Cornell as an instructor. "Furchgott found evidence for a natural substance that contributes to irreversible vasodilation, and attempted to isolate it using strategies that presaged his approach to studying EDRF some 40 years later" [14].

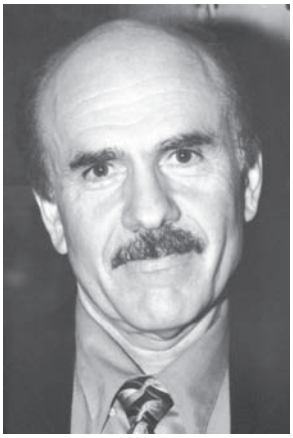
In 1949, Robert Furchgott got his first faculty position – the assistant professorship – at Washington University School of Medicine, where he examined the effects of drugs on blood vessels. He had spent seven years there before accepting the position of Chairman of the Department of Pharmacology at the State University of New York (SUNY) College of Medicine in Brooklyn. During his Washington University years, Furchgott continued his work on energy-metabolism and function of rabbit intestinal smooth muscle becoming more and more interested in using the aortic strip for studies on drug-receptor interactions. Robert also began the research on the pharmacology of in vitro cardiac muscle preparation, namely the isolated electrically-driven right atrium of the guinea pigs. It was Washington University where Robert Furchgott developed his lifelong interest in drug-receptor interactions, particularly in the adrenergic system that regulates blood vessel flow and smooth muscle tone.

In 1956, the new "era" started in Furchgott's life. After joining the Department of Pharmacology at SUNY College of Medicine, he continued his research on blood-vessel pharmacology. In addition, he spent time organizing the department and learning the new role of a chairman. The first trip abroad took place in 1960: Robert was invited to present his paper at a CIBA Foundation Conference on Adrenergic Mechanisms in London. His sabbatical year 1962-1963 he spent in the Department of Physiology of the University of Geneva doing research, teaching, and writing papers. The second sabbatical leave in 1971 Furchgott spent in the medical school of the University of California at San Diego, where he became a visiting professor. He wanted to learn the Steve Mayer's method for analysis of cyclic AMP, however, he devoted a lot of time to duties as a President of the American Society for Pharmacology and Experimental Therapeutics [13]. Returning to Brooklyn, Robert continued research on the role of receptors located on prejunctional terminals of adrenergic nerves. His research was reflected in a review "The Classification of Adrenoceptors (Adrenergic Receptors). An Evaluation from the Standpoint of Receptor Theory" [16].

The Department of Pharmacology at the State University of New York College of Medicine became very special to Robert Furchgott – it was there where the famous scientist made his prize-winning discoveries. In 1978, he discovered a substance produced by endothelial cells that causes relaxation of vascular smooth muscle and coined it endothelium-derived relaxing factor (EDRF) [13, 17]. This substance later proved to be nitric oxide [18, 19]. This discovery led to the award of the 1998 Nobel Prize in Physiology or Medicine (jointly with Louis J. Ignarro and Ferid Murad).

In 1982, Robert Furchgott resigned from the chairmanship of the Department of Pharmacology, but he continued his creative life as a professor. In 1989, he retired from the professorship. This retirement allowed him to spend some months each year as an Adjunct Professor in the Department of Molecular and Cellular Pharmacology of the University of Miami School of Medicine [13]. In 2008, Furchgott moved to Seattle's Ravenna neighborhood. He died on May 19, 2009.

Dr. Furchgott received the Nobel Prize in Physiology or Medicine 1998 [19]



Louis J. Ignarro [20]

Robert Furchgott was married twice. He married Lenore Mandelbaum in 1941 and lived with her until she passed away. They had three daughters: Jane, Terry, and Susan. His later years he spent with Margaret Gallagher Roth, who died in 2006 [17]. As he said: "*I have been very fortunate in having wives who encouraged my work, even though it often reduced the time I could give to family matters*" [13].

Even though Robert Furchgott received a Gairdner Foundation International Award for his groundbreaking discoveries (1991), the Albert Lasker Award for Basic Medical Research (1996), the Nobel Prize in Physiology or Medicine (1998), the Golden Plate Award of the American Academy of Achievement (1999), he was a mild-mannered, generous, and modest person. He wrote: "*In thinking back about what aspects of my research have given me the greatest pleasure, I would not place the honors and awards first. I think that my greatest pleasure has come from each first demonstration in my laboratory that experiments designed to test a new hypothesis developed to explain some earlier, often puzzling or paradoxical findings, have given results consistent with the hypothesis*" [13].

An American pharmacologist **Louis J. Ignarro** was born on May 31, 1941, in Brooklyn, New York, the U.S., in a family of Italian immigrants. Growing up in Long Beach, a suburb of New York City, on the shore of Long Island, a little boy was fond of building sand castles, and his friends predicted he would become an architect or engineer. But fate is a mysterious thing, and at the age of eight, Louis got a present – his first chemistry set, which appeared to be much more fun than building sand castles. Louis's love for chemistry remained strong during his study at Central Grade School and Long Beach High School. This persistent interest eventually led him to apply to Columbia University to study chemistry and pharmacy. In 1962, Louis Ignarro received a Bachelor's Degree in Pharmacy. Upon graduation from Columbia University, Louis applied to graduate school in pharmacology and was admitted to the pharmacology program at the University of Minnesota in Minneapolis. At that time, this department was considered to be one of the best. Here Louis developed a better understanding why and how neurons of the sympathetic nervous system innervate the heart and produce and release norepinephrine [21]. Ignarro's major was pharmacology and minor – cardiovascular physiology. He also took courses in biochemistry, anatomy, and especially enzymology, which was taught by Paul D. Boyer, the future Nobel Prize winner (the Nobel Prize in Chemistry 1997) [22]. In 1966, Louis Ignarro received a Ph.D. in Pharmacology from the University of Minnesota.

Ignarro's research was continued at the National Institutes of Health (NIH) in the Laboratory of Chemical Pharmacology in the National Heart, Lung and Blood Institute. The institute's atmosphere was favorable for learning new things and discussing new ideas. In 1968, Louis left NIH to accept the responsibility of heading the biochemical and anti-inflammatory program at Geigy Pharmaceuticals. Together with a group of researchers, Ignarro developed new drugs (diclofenac) and was able to continue research into new areas of pharmacology including cyclic GMP [23]. After Geigy Pharmaceuticals merged with Ciba Pharmaceuticals, Louis Ignarro decided to start academic research and teaching that led him

to the position of Assistant Professor of Pharmacology at Tulane University School of Medicine in New Orleans. Making a significant contribution to the study of cyclic GMP and cyclic nucleotides in general, Ignarro shifted his attention to blood vessels, given the fact he was quite interested in the Ferid Murad group's work. As Ignarro said: "It occurred to me that nitric oxide might account for the vascular smooth muscle relaxing action of nitroglycerin and that cyclic GMP might be the second messenger responsible for mediation the vasorelaxant effect of nitric oxide" [21]. In 1979, Louis Ignarro showed that nitric oxide could relax vascular smooth muscles [24]. Continuing his research at Tulane, Louis Ignarro finally realized that the properties of nitric oxide were the same as those seen in the endothelium derived relaxing factor (EDRF) identified three years earlier by Robert Furchgott. Ignarro and Furchgott came to similar conclusions about nitric oxide as the EDRF and they both reported their findings at the conferences in 1986. Like a story on DNA discovery, this "scientific coincidence" obviously demonstrates that ideas, when the time comes, are in the air [25, 26]. In 1998, Louis Ignarro shared the Nobel Prize in Physiology or Medicine with Robert Furchgott and Ferid Murad.

Louis Ignarro receiving his Nobel Prize from the hands of His Majesty the King [27]

After his divorce, Louis Ignarro left Tulane University and began his academic career at UCLA School of Medicine. It was in 1985. His daughter Heather joined him and attended California State University at Northridge. In 1994, Ignarro met Sharon Elizabeth Williams, a medical student at UCLA. In 1997, Louis and Sharon were married.

Louis Ignarro had worked as a consultant for Herbalife for many years. He was a member of the Herbalife Nutrition Advisory Board [28] and collaborated in developing nutritional supplements. For activities such as promoting Herbalife products, Ignarro was subjected to criticism [29]. Nevertheless, Ignarro's activities have been marked by a number of awards and recognitions, including Merck Research Award (1974), Arthritis Foundation Research Award (1975–1977), Tulane Medical School – Outstanding Teacher Award (1983), UCLA School of Medicine – Outstanding Teacher Award (1986), Roussel Uclaf Prize for Cell Communication and Signaling shared with Dr. Salvador Moncada and Dr. Robert Furchgott (1994), National Academy of Sciences (1999), Canadian Medal of Merit (2008), and many others.

Ferid Murad [30]

Ferid Murad – a co-winner of the 1998 Nobel Prize in Physiology or Medicine – is a famous American physician and pharmacologist. He was born on September 14, 1936, in Whiting, Indiana, the U.S., in the family of Albanian immigrant Jabir Murat Ejupi and Henrietta Josephine Bowman from Alton, Illinois. His parents ran a restaurant and had to work long hours. Their children also worked there. The parents' poverty and lack of education influenced Ferid and his younger brothers John Abderhaman and Turhon Allen to obtain a good education in order to advance their careers (one of his brothers became a dentist and another – a professor of anthropology). As Ferid said, at the age of 12 he knew he was going to become a doctor: "I learned from my mother and grandmother Bowman about compassion and generosity for people and this in turn influenced my career choice in medicine" [30]. In the eighth grade, Ferid wrote an essay on his top three career choices, which were a physician, a teacher, and a pharmacist. And these dreams became true. "Today I do just that, as

I am a board-certified physician and internist doing both basic and clinical research with considerable teaching in medicine, pharmacology and clinical pharmacology and with a Ph.D. in pharmacology" [30], Ferid Murad emphasized.

As far as Ferid's parents could not afford to help him with college fees, a young man has to choose between available options. He competed for a Rector Scholarship at DePauw University in Greencastle, Indiana. He had studied there from 1954 to 1958 enjoying chemistry and biology. In 1957, Ferid met Carol Ann Leopold, an English and Spanish major at DePauw and in 1958 they got married. They have four daughters and a son. Murad speaks very warmly about his family: "*My wife and children were very understanding. They grew up as wonderful children and adults in spite of my absence, obviously due to a devoted wife and mother. My current fetish is my 5 grandchildren who I try to spend as much time with as possible*" [30].

In 1958, Ferid Murad entered the newly launched M.D./Ph.D. program at Case Western Reserve University. Murad was focused on the research on the catecholamine effects on cyclic AMP formation. Becoming interested in agents that could block the effects of cyclic AMP on phosphorylase kinase and phosphorylase activation, he had to investigate cyclic AMP analogs and other nucleotides deeper [30]. In 1965, Ferid Murad earned a doctorate in pharmacology, as well as his medical degree [31].

Ferid Murad served an internship and residency at Massachusetts General Hospital (1965 –1967) before going to the National Institutes of Health as a clinical associate in the Heart Institute. He worked there until 1970 when he was invited as an Associate Professor in Medicine and Pharmacology at the University of Virginia. He had remained at the University of Virginia from 1970 to 1981 becoming one of the youngest professors (1975), the Director of the Clinical Research Center (1971), and the Director of Clinical Pharmacology (1973). Here he elaborated a research program with both clinical and basic studies. He trained many students and fellows making one of his dreams – to teach – true. As Ferid Murad put it, "*Of the 82 fellows and students I have trained and collaborated with to date twenty are professors, chairmen, research directors and division chiefs around the world. I view them as offspring and keep in contact with most of them in my travels. There is no question that one of my greatest accomplishments is to have participated in the training of such successful scientists in my own laboratory and also influenced the careers of many talented medical students, graduate students and housestaff*" [30].

Previously working on cyclic adenosine monophosphate, he moved on to cyclic guanosine monophosphate in 1970. In 1977, he demonstrated that nitroglycerin and some related heart drugs were pro-drugs converted into nitric oxide in the body. He showed that this colorless, odorless gas acts to increase the diameter of blood vessels, which leads to lowering blood pressure and increasing blood flow. "Since his discovery in 1977 there have been about 150,000 research publications with nitric oxide in various areas of biology" [32]. Later Robert Furchgott showed that cells in the endothelium of blood vessels produce a signaling molecule – endothelium-derived relaxing factor (EDRF), which signals smooth muscle cells in blood vessel walls to relax. Louis Ignarro, independently of Furchgott, identified endothelium-derived relaxing factor as nitric oxide [33]. Thus, independently made research had led to a great scientific discovery that received the attention of the Nobel Committee and eventually the Nobel Prize in Physiology or Medicine 1998, one of the recipients of which was Ferid Murad.

Ferid Murad receiving his Nobel Prize from the hands of His Majesty the King [34]

In 1981, Ferid Murad became a Chief of Medicine of the Palo Alto Veterans Hospital, a Stanford university affiliated hospital. He was a Professor of Medicine and the Associate Chairman of Medicine.

In 1988, Ferid Murad left Stanford to become a Vice President at Abbot Laboratories, where he found himself under pressure dealing with the upper management, marketing staff, and researchers. After leaving Abbot in 1993, he became a founder, President and CEO of a new company – Molecular Geriatrics Corporation. After desperately seek-

ing funding in order to realize his plans, Ferid Murad decided to rejoin the academic community becoming the First Chair of a new Department of Integrative Biology, Pharmacology and Physiology at the University of Texas-Houston. He also created a new Division of Clinical Pharmacology [30]. In 2011-2016, Ferid Murad acted as a University Professor at George Washington University. Presently, Ferid Murad holds a position at Palo Alto Medical Center [32]. According to Murad, he had come full circle [30] and returned to his favorite academic environment.

Professor Ferid Murad has been the recipient of numerous awards including the Albert and Mary Lasker Award for Basic Medical Research in 1996 [35]. In 2019, Ferid Murad won the Shechtman International Leadership Award for "leadership through courage, conviction, persistence and willingness to break with the taboos and stereotypes in pioneering new ways of thinking that shape the future for a global sustainable development in the environment, economy and social points of view" [36].

The 1998 Nobel Prize in Physiology or Medicine sparked a heated debate about the role of a Honduran-British pharmacologist Salvador Moncada in the discoveries that earned this prize. His paper "Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor" [37], co-authored by R.M. Palmer and A.G. Ferrige, was published earlier than the similar work of L.J. Ignarro and his colleagues [38]. Salvador Moncada was surprised and disappointed at the decision of the Nobel Committee. His disappointment was shared by John Robert Vane – an English pharmacologist and co-winner of the 1982 Nobel Prize in Physiology or Medicine. An Argentinian biochemist and co-winner of the 1984 Nobel Prize in Physiology or Medicine Cesar Milstein argued that it was Moncada who first seriously approached Furchgott's hypotheses and proved them in his "key experiments". Certainly, not all researchers are as critical [39]. Considering Moncada's contribution to the research, the prize should have been awarded to four scientists, but the maximum number of award participants in one field of science traditionally does not exceed three people. In this regard, Robert Furchgott said, "*I'm just so sorry that they never decided in Nobel prize committees to give it to more than three people*" [40].

The discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system made by Robert Furchgott, Louis Ignarro and Ferid Murad triggered an international boom in research on this gas: "For instance, the principle behind the successful anti-impotence drug sildenafil citrate (Viagra) was based upon this research. Researchers suggested that nitric oxide could be a key to improved treatments for heart disease, shock, and cancer" [41]. In 1992, nitric oxide was named "The Molecule of the Year" [42].

РОЗГАДКА ТАЄМНИЦІ ОКСИДУ АЗОТУ: ЛАУРЕАТИ НОБЕЛІВСЬКОЇ ПРЕМІЇ РОБЕРТ ФЕРЧГОТТ, ЛУЇС ІГНАРРО І ФЕРІД МЮРАД

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У XXI столітті жоден із вчених не заперечує визначальної ролі серцево-судинної системи та її центрального органу – серця. Розробка сучасних ліків, ефективні тренінгові програми, програми трансплантації серця свідчать про те, що людство не відмовляється від спроб покращити та подовжити життя людини, особливо враховуючи той факт, що найбільшою вбивцею у світі є ішемічна хвороба серця. Найзначніші досягнення в цій галузі отримують найвищу оцінку в науковому середовищі – Нобелівську премію. У 1998 році Нобелівську премію з фізіології та/або медицини присудили Роберту Ферчготту, Луїсу Ігнарро та Феріду Мюраду «за відкриття ролі оксиду азоту як сигнальної молекули в регуляції серцево-судинної системи». Це відкриття спричинило міжнародний бум у дослідженні оксиду азоту. У цій статті представлено короткий огляд основних етапів наукової діяльності Р. Ферчготта, Л. Ігнарро та Ф. Мюрада.

Ключові слова: оксид азоту, нітрогліцерин, Роберт Ферчготт, Луїс Ігнарро, Ферід Мюрад, Нобелівська премія з фізіології та/або медицини.

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