OBITUARY

Robert Furchgott (1916–2009)

Nobel laureate who pioneered research into nitric oxide.

In 1992, *Science* heralded nitric oxide (NO) as 'molecule of the year', less than six years after it had been identified as a physiological dilator of blood vessels, accounting for the activity of a molecule known as endothelium-derived relaxing factor (EDRF). On 19 May 2009, Robert Furchgott, whose research was most influential in leading to the discovery that NO is EDRF, died peacefully in Seattle, Washington, aged 92.

Bob, as he was known to friends (Robert to family), was born in Charleston, South Carolina, in 1916, and spent his high-school years in the small town of Orangeburg. He began college at the University of South Carolina, then transferred to the University of North Carolina in Chapel Hill a year later, when his father became a North Carolina resident. Furchgott worked his way through college as a technician in a laboratory studying the physical chemistry of cellulose.

His fascination with physical chemistry led to a graduate-school placement at Northwestern University Medical School in Chicago, Illinois, in a laboratory addressing the physical properties of red blood cells, the subject of his PhD thesis. In 1940, he joined Ephraim Shorr's group at Cornell University Medical School in New York City, where he spent nine years focusing on cardiovascular research. With the onset of the Second World War, the laboratory turned its attention to wartime issues, especially the physiology of irreversible haemorrhagic shock. 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.

Furchgott's first faculty position, in 1949, was in the pharmacology department at Washington University in St Louis, Missouri, where he began examining the effects of drugs on blood vessels. His first publication there, in 1953, includes a description of the effects of acetylcholine and sodium nitrite on the contraction of strips of rabbit aorta. In this work he made an observation that could have predicted the source of EDRF — acetylcholine, well known as a vasodilator in the intact organism, produced contractions only in blood vessels that he had prepared with consummate care, presumably inadvertently removing the EDRF-producing endothelial layer.

In St Louis, Furchgott also discovered photorelaxation when one of his preparations, which sat beneath a sunlit window, dilated much more than preparations in a darker section of the

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laboratory — in retrospect, it seems likely that photorelaxation reflects the release of NO by blood vessels in response to light.

After seven years in St Louis, Furchgott moved to what is now called the State University of New York (SUNY) Downstate Medical Center in Brooklyn as chair of pharmacology, where he continued his research on blood-vessel pharmacology as well as developing theories of blood-vessel-receptor activity. Experiments leading to the EDRF concept began about 22 years later, in 1978, when his technician failed to follow the standard protocol for preparing the rabbit aorta strips and, instead of contraction in response to acetylcholine, Furchgott saw relaxation. He was eager to troubleshoot this 'accident', and after several weeks realized that gentle rubbing of the endothelial layer of blood vessels transformed relaxation into contraction. One explanation was that acetylcholine acts on receptors on endothelial cells (removed by the rubbing) to trigger the release of a substance with relaxing activity — EDRF. He obtained direct evidence for this by making a 'sandwich' of a strip of aorta freed of endothelial cells to which he applied the endothelium of another aortic strip; this procedure transformed contraction into relaxation.

Over the next few years, various clues emerged that ultimately led to the identification of NO as EDRF. Calcium ionophores were effective in eliciting EDRF activity, which we now know reflects the requirement of NO synthase for calcium/calmodulin. Ferid Murad had shown that NO is the active metabolite of nitroglycerine, a drug that mediates its vasorelaxant effects by stimulating guanylyl cyclase, converting GTP to cyclic GMP. EDRF was also shown to stimulate cyclic GMP formation. Haemoglobin, known to interfere with the effects of NO on cyclic GMP, inhibited EDRF. And methylene blue, which inhibits stimulation of guanylyl cyclase by nitroglycerine-like drugs, also blocked EDRF activity. Billy Martin, working in the Furchgott lab, had noted that acidification of a tissue extract enhanced its vasorelaxant activity, and acidification is known to convert nitrite to NO. At about this time, Salvador Moncada and Paul Vanhoutte reported that superoxide rapidly inactivates EDRF and that superoxide dismutase prevents this.

On the basis of these clues, Furchgott carried out definitive experiments testing whether NO might be EDRF. Relaxation by both NO and EDRF was inhibited by haemoglobin, methylene blue and superoxide generators, and was potentiated by superoxide dismutase. Moreover, both NO and EDRF augmented levels of cyclic GMP. At a July 1986 symposium, Furchgott proposed that NO is EDRF. At the same meeting, Louis Ignarro presented findings using similar experimental approaches and with the same conclusion.

The identification of NO as EDRF was made when Furchgott was 70 years old, a feat of late-life productivity reminiscent of Hans Kosterlitz, who published his identification of the enkephalin pentapeptides as 'the brain's own morphine' in December 1975, when he was 72.

In 1996, Furchgott shared the Albert Lasker Basic Medical Research Award with Ferid Murad. In 1998, Murad, Ignarro and Furchgott shared the Nobel Prize in Physiology or Medicine "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system".

In contrast to many self-promoting, hyper-ambitious scientists, Furchgott was ever mild mannered, self-effacing and generous to a fault. With his first wife Lenore Mandelbaum, he had three daughters, Terry, Jane and Sue, who survive him along with four grandchildren and a great-grandchild. Lenore died in 1983, after which he married Maggie Roth, who died several years ago.

In 2008 he moved to a retirement community in Seattle. His voracious curiosity never flagged. According to Sue, "he visited every single museum, even obscure ones at least once, many more than once". She summarized her father's principal attributes: "He was a real southern gentleman." I concur.

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