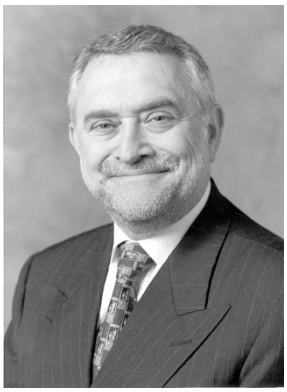
Seminal findings, highly cited papers, prizes and awards are an integral part of what defines a top-flight scientific career. *Nature Medicine* talked to one investigator whose work has been truly groundbreaking, but who, to the widespread surprise of the research community, was bypassed by both the Lasker and the Nobel committees for his discovery of nitric oxide's cardiovascular effects.

Salvador Moncada

Perhaps it was his deportation from El Salvador many years ago for political activism that taught Salvador Moncada the value of discretion. Certainly, as a man who has married into a European royal family, it is a behavior that he must practice on a daily basis. Now, three years after he was overlooked by the Nobel committee for his role in the discovery of nitric oxide (NO) in the vascular endothelium, Moncada retains a dignified public silence about the snub. "Institutions can give prizes to whomever they wish," he says. "I am happy with the work I've done."

Moncada's current directorship of the Wolfson Institute for Biomedical Research at University College London is a long way, both in conceptual and geographical terms, from his scientific origins. Born in the Central American country of Honduras, Moncada moved across the border to El Salvador at an early age and went on to qualify as an MD. His interest in cardiovascular science was triggered by working with Peruvian pharmacologist Augusto Campos, who was visiting the University of El Salvador for a year.



Scientific adventurer

The 1970s was a time of political unrest in El Salvador due to social inequalities, a poor economy and the repressive measures of dictatorship. Civil war broke out between the government and left-wing parties. Moncada joined the throngs of protestors with the result that he was deported to Honduras, and forced to leave behind his first wife and child.

Like all young investigators who are serious about building a career in research, he needed to gain experience working in an environment where the best intellects and equipment were on-hand. For many of his peers, that meant the US. But Moncada "...wanted to come to Europe for cultural reasons and for scientific reasons was particularly interested in research in the UK and I managed to get a fellowship to go to England in February, 1971."

Moncada secured a place in Sir John Vane's laboratory at the Royal College of Surgeons. "I was put in a project that was part of the discovery that aspirin-like drugs inhibit prostaglandin biosynthesis," he says-work for which Vane was later awarded the Nobel Prize.

However, a deep-seated belief that he owed something to the country of his birth compelled him to return to Honduras in 1974 "to see if it was possible to do research there." He was quickly disillusioned by the conditions. "There are more developed countries in Latin America such as Brazil, Argentina, Mexico, Chile, where research is possible. But Honduras is one of the most underdeveloped countries, so there's no infrastructure, no money and no connections with the outside world to do scientific research."

He returned to the UK and re-joined Vane who had moved to the Wellcome research laboratories in Beckenham. It is the atmosphere and philosophy of those laboratories that Moncada is now trying to recreate at the Wolfson Institute. "Wellcome was a very special place, unlike any other industrial lab; it was a very open and scientific environment with a lot of flexibility and a place where lots of scientific discoveries were made and transformed into medicine."

Moncada played a central role in the discovery of thromboxane synthetase and its inhibitors, and the anti-aggregatory agent, prostacyclin, for which he is named on the patent. The team also developed prostacyclin as a medicine for cardiopulmonary bypass operations and pulmonary hypertension.

It was in 1985, following a visit by Robert Furchgott to Beckenham, that Moncada began investigations to determine the identity of endothelium-derived releasing factor (EDRF). "I wasn't satisfied with the experimental model of mechanical removal of endothelium from strips of tissue, so we decided to culture large quantities of vascular endothelial cells. We measured EDRF coming from these cells and quickly made the first breakthrough that later enabled EDRF to be identified as NO-that EDRF was destroyed by superoxide radicals."

On Furchgott's speculation that EDRF might be related to NO, Moncada tested the activity of NO in his bioassay and found it to equate to EDRF. He then measured NO levels directly following cell stimulation using a chemiluminescence machine adapted from the automobile industry, which became the first demonstration that EDRF and NO are the same substance. Indeed, Moncada's Nature paper was the most cited work of 1987, and he acknowledges Furchgott's role in the abstract: "...it has recently been suggested by Furchgott that EDRF may be NO." With the conclusion, "Thus NO released from endothelial cells is indistinguishable from EDRF in terms of biological activity, stability and susceptibility to an inhibitor and to a potentiator. We suggest that EDRF and NO are identical." (Nature 327, 524; 1987). His team also discovered that NO was made from the amino acid L-arginine by an enzyme they named NO synthase.

Again, I ask him how he feels, having made the first biological identification of NO, discovered its synthetic pathway and developed a widely used bioassay for its measurement, to have been excluded from being one of the three scientists awarded a Nobel Prize for the work. But he is determined to let the story of his involvement speak for itself. "I've explained my work. The scientific community protested, not me. Because there are no objective data to analyze [for prize-giving] I have no comment to make. I know all three winners and I'm good friends with them." He then politely returns to discussing current chronic degenerative disease projects running at the Wolfson Institute.

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