OBITUARY

Sir John Vane FRS

William Harvey Research Institute

Sir John Vane's career as one of the greatest pharmacologists of the twentieth century was made all the more remarkable because of his accidental entrance into the field. As someone who had an all-consuming passion for chemistry experiments during his childhood — originating in the family kitchen using a Bunsen burner attached to the gas stove — John became frustrated by the lack of enthusiasm for his desire to experiment as a graduate at the University of Birmingham, UK. When offered the chance to do pharmacology at Oxford with J. H. Burn afterwards, John immediately accepted, followed almost as immediately by a visit the library to find out what pharmacology was all about. As John later admitted, this offer reshaped his career. It was an offer that also helped to reshape pharmacology.

After a 2-year-spell in the Department of Pharmacology at Yale with Arnold Welch, John returned to the UK. During his years with Gustav Born at the Royal College of Surgeons, John perfected his signature 'blood-bathed organ cascade' — a combination and extraordinary development of John Gaddum's parallel bioassay and superfusion techniques of 1953. Blood from animals, or sometimes humans, was passed continuously over a series of strips of smooth muscle chosen for their exquisite sensitivity to, and ability to differentiate between, the substances under investigation. This technique enabled John to measure instantaneously, dynamically and with great specificity the levels of one or more blood hormones, such as angiotensin and bradykinin.

Working with Sergio Ferreira, Mick Bakhle and others, John observed that the pulmonary circulation was a major site for the destruction of bradykinin as well as for the conversion of angiotensin I to angiotensin II. Speculating that both phenomena were attributable to the same enzyme, they deduced that the 'bradykinin potentiating factor' from *Bothrops jararaca* venom, which inhibited bradykinin proteolysis, might also block angiotensin I conversion and could prove a useful therapy for hypertension. John took the idea to Squibb, where Welch had become Research Director, and this led to the development of the revolutionary angiotensin-converting enzyme (ACE) inhibitors.

1971 brought another breakthrough. Aspirin had been developed in the 1890s, yet there had been no intellectually coherent explanation for its therapeutic action and side effects. One Monday, John walked into the lab proclaiming that over the weekend he had come up with a wonderful idea about how aspirin was linked to the cardiovascular system. John's interest in prostaglandins had been kindled some years earlier and he conceived the notion that aspirin worked by inhibiting the generation of these mediators. Almost overnight, he turned around the research focus of our lab to tackle his hunch; experimental proof was soon obtained and this concept, which he advanced mainly with Ferreira, Salvador Moncada and myself, profoundly influenced the field including the development of COX2 inhibitors, and helped to earn John the Nobel Prize in Physiology or Medicine in 1982.

In 1973 John moved to the Wellcome Foundation as R&D Director, and took Ferreira, Moncada, myself, Gerry Higgs and others with him to build a personal research group. Although friends discouraged him from moving into industry, John replied that those who believe that good science can only be achieved in academia were wrong. In 1976, working mainly with Moncada, Richard Gryglewski and Stuart Bunting, John's group discovered the potent vasodilator and anti-aggregatory prostaglandin 'X', later renamed prostacyclin (PGI_2). Analogues were later approved for the treatment of pulmonary hypertension and antithrombotic indications. Under John's management, Wellcome produced several other important drugs, including acyclovir (Zovirax), atracurium besylate (Tracrium) and lamotrigine (Lamictal).

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After an invitation from St Bartholomew's Hospital Medical School in 1986, and start-up funding from Glaxo Group Research, John brought together a new group — comprising Erik Änggård, Nigel Benjamin, Iain MacIntyre, David Tomlinson, Brendan Whittle, Derek Willoughby and his old colleagues Born and myself — to form The William Harvey Research Institute. Major funding from Ono Pharmaceuticals in Japan enabled his institute to expand rapidly and it soon became a pharmacological powerhouse, specializing in research into inflammation and cardiovascular disease. John even found time to start up (with Änggård) a new company, Vanguard Medica Ltd. (now Vernalis). He retired as full-time director of the institute in 1995 but remained Honorary Chairman of the charitable William Harvey Research Foundation until his death, from pneumonia, on Friday 19 November, aged 77.

John's legacy is not just in what he achieved, but in the manner in which he achieved it. He was an heir to the physiological tradition of pharmacology and, having watched the molecular biology revolution unfold from the sidelines, retained confidence in bioassays as an engine for the generation of new ideas and discoveries throughout his life. John created and moulded a generation of pharmacologists, gathered from many different countries, all captivated and inspired by his curiosity, his desire and his understanding of the research process. His phrases such as "Never ignore the unusual" and "Always do the simple experiment first" summed up his research ethics, and these phrases have been inherited by his willing students to inspire a new generation of pharmacologists.

On receiving his Nobel Prize, John said that he disagreed with those who said that the major discoveries had been made. There were still plenty of things to discover, he said; the trick is to find the right path from one to the other. Like John's vision and achievements, his message resonates as much now, if not more, in the field of drug discovery as it did then.

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