In Memoriam
John R. Vane (1927–2004)

Ryszard J. Gryglewski, John C. McGiff

“Let us now praise famous men.”¹ John R. Vane died on November 26, 2004, marking the end of an era of pharmacological sciences that rested on global biological concepts and addressed nature’s grand design, the human body in motion, not in stasis.

John Vane was born in Tardebigg, Worcestershire on March 29, 1927, the youngest of 3 children. His father was the son of Russian immigrants and his mother’s family farmed in Worcestershire. The Vane family lived in a suburb of Birmingham, where they weathered World War II, colored by the trappings of war: nights were frequently spent in an air-raid shelter at the bottom of the garden.

John Vane studied chemistry at Birmingham University, a subject that did not satisfy his native curiosity. On graduation in 1946, a letter arrived in the Department of Chemistry from Professor J. Harold Burn, Chairman of Pharmacology at Oxford, inquiring if any of the recent graduates would like to be trained in pharmacology. John Vane said “yes” while thinking “I’ll do anything but chemistry.” At Oxford, Professor Burn recognized John’s driving curiosity to probe the undiscovered and channeled it into the area of experimental pharmacology. A telling remark is John Vane’s comment on being designated a pharmacologist, “the label hid the truth, as labeling tied one to a discipline.” He preferred the label, “experimentalist.”²

J. Harold Burn was a remarkable energizer of young scientists, as revealed in John Vane’s commentary on him. This is also a splendid recapitulation of John Vane’s own impact on biological sciences. “If anyone can be said to have molded the subject of pharmacology around the world, it is J. Harold Burn. He did this through his particular style of research, through the lucidity of his writings, but most of all through the school which he founded. His laboratory gradually became the most active and important center for pharmacological research in the U.K. and the main school for training of young pharmacologists. It was his energy and inspiration that set my career into one of adventure in the fields of bioassay and pharmacology. It was Burn who reinforced for me the essence of experimentation and that is, never to ignore the unusual.”³ The past is prelude to the present as the disciple becomes the mentor. In his own laboratories, John Vane reproduced this hospitable environment for discovery and pursuing new directions in which young scientists matured and thrived. One of his most famous pupils paid tribute to his mentor in a memorable phrase: “John’s unique personality sculpted my scientific life.”

In a 1984 commencement address,² John Vane urged young scientists “to be simplifiers and not complicators! Do simple experiments and make simple hypotheses—there are plenty of others who will come along and show how much more complicated the answer really is; but at least for a few years a concept will exist that is elegant and easily understood.” John Vane then enumerated the preeminent attributes of a successful scientist: “flexibility, curiosity and intellectual endeavor. There is another element which some call luck and others call serendipity, or discovery through the ‘happy accident.’ I would urge you never to ignore the unusual.”

An extraordinary example of pursuit of the unusual was the discovery of angiotensin-converting enzyme inhibitors (ACEI), which many regard as the most important drug discovery of the past half-century. In 1965, a young Brazilian scientist, Sergio Ferreira, joined John Vane’s laboratory as a postdoctoral fellow at the Royal College of Surgeons (RCS). Sergio had been working on the vasoactive properties of peptides isolated from the venom of a Brazilian pit viper, Bothrops jararaca (called the “mother-in-law” snake because it strikes unprovoked!).⁴ These peptides exhibited potent hypotensive properties, in part by inhibiting destruction of kinins...
and were so named “bradykinin potentiating factor”. Down the hall at the RCS, Mick Bakhle was working on lung ACE; the peptides isolated from the snake venom were tested on lung ACE and were shown to inhibit conversion of angiotensin I to angiotensin II in addition to potentiating bradykinin (kininase II = ACE). Thus was constructed the intellectual cradle for the development of ACEI that was hastened by John Vane’s serving as a consultant to Squibb, where captopril was conceived and synthesized by Ondetti and Cushman in response to the discoveries made by Vane, Ferreira, and Bakhle at the RCS.

The many discoveries of John Vane rested on the ingenious applications of bioassay methods incorporated in the principle of parallel pharmacological assays in which bioassay tissues are arranged in a cascade and superfused with either an organ’s perfusate or circulating blood. The tissues are selected to “detect biological activity,” which are the unique fingerprints of “chemically unstable compounds whose activity would otherwise be lost in an extraction procedure.” In this manner, thromboxane (rabbit aorta contracting substance [RCS!]) and prostacyclin (PGI2) were first detected and characterized. These studies gave evidence of the triumph of intellect over technology.

To recognize John Vane’s most important contributions, which may overshadow or rival the elucidation of the mechanism of action of aspirin, we cite: (1) the circulatory dynamics of the renin-angiotensin system; (2) the metabolic and endocrine function of the lung whereby circulating hormones are degraded (kinins), generated (prostacyclin), and transformed (angiotensin I → II); and (3) the endothelium as a generator of biological mediators, particularly prostacyclin, that act as guardians of the integrity of the blood–endothelial interface.

The discovery of the mechanism of action of aspirin looms large because it serves as the basis of a paradigm ripe with therapeutic implications. The most pervasive is the use of low-dose aspirin to prevent thrombotic events by inhibiting platelet cyclooxygenase, thereby preventing generation of the pro-thrombotic eicosanoid, thromboxane A2, while sparing the platelet anti-aggregatory, dilator vascular hormone, prostacyclin (PGI2). (Is there anyone out there older than 60 not taking 1 baby aspirin per day?)

We grieve the passage of our colleague and friend but rejoice in his legacy in which we are all beneficiaries. Beyond the ideational legacy is the William Harvey Institute, which stands as a beacon and reminder of the life and achievements of John Vane. The succession is secure because the William Harvey Institute is directed by a distinguished scientist, Rod Flower, a former student and lifetime colleague of John Vane.

**Milestones**

1948: Married Elizabeth Daphne Page. They had two daughters, Mandy and Nikki

1953: DPhil, University of Oxford

1955: Assistant Professor in Pharmacology, Yale

1966: Professor of Experimental Pharmacology, London University

The Royal College of Surgeons of England

1973: Group Research and Development Director

The Wellcome Foundation

1974: Fellow of the Royal Society

1982: Nobel Prize in Physiology and Medicine

1983: Knight Bachelor in New Year Honors List for services to pharmaceutical research

1986: Founded William Harvey Research Institute

Chairman and Director

1995: Director General, William Harvey Research Institute

St. Bartholomew’s and The Royal London School of Medicine and Dentistry

1997: Honorary President, William Harvey Research Foundation

**References**


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