John Vane, who died peacefully of pneumonia on 19 November 2004, was heir to the physiological tradition of pharmacology and one of its greatest exponents. However, he became a biological scientist essentially by accident. His first choice of career, stemming from a childhood hobby, was chemistry and he graduated from the University of Birmingham with a Bachelors degree in that subject in 1946. But John, who was an experimentalist by nature, did not find the actual practice of chemistry as rewarding as he had imagined.

Discussing his future with his head of department, he was told that J H Burn in Oxford was seeking graduates to be trained in pharmacology. John later wrote ‘without hesitation I grasped the opportunity and immediately went to the library to find out what pharmacology was all about.’ The study of experimental pharmacology turned out to be exactly what he was looking for and he never forgot Burn’s inspirational early influence on his work and thinking.

After qualifying, John spent a short time at Sheffield University before returning to Oxford for postgraduate studies with G Dawes. In those days it was common for post doctoral scientists to do a stint in the USA and after receiving his DPhil John was invited by A Welch to join the Department of Pharmacology at Yale as an Assistant Professor. These early years were formative ones for John and one may trace the roots of much of his subsequent work back to these early influences and to the friendships he forged at this time.

In 1955 John returned to the UK and embarked upon what might be regarded as the first of his three major creative periods. He joined WDM Paton’s Department of Pharmacology at the Institute of Basic Medical Sciences which was (after some time at Queens Square) located at the Royal College of Surgeons of England in London. John rose quickly through the academic ranks gaining a personal chair himself in 1966. GVR Born, a friend of John from his Oxford days, had succeeded Paton in 1961 and under the joint influence of Born and Vane, the department at the Royal College provided an astonishingly productive intellectual environment which published much cutting edge science, nurtured many careers and rose to great prominence.

It was during these years that John perfected his signature ‘blood bathed organ cascade’; a combination, and a development along extraordinary lines, of JH Gaddum’s parallel bioassay and superfusion techniques of 1953. Blood from animals, or sometimes humans, was passed continuously over a series of isolated tissues chosen for their exquisite sensitivity to, and ability to differentiate between, hormones or other substances under investigation. This technique enabled John to measure instantaneously and with great specificity, the levels of one or more blood hormones. The dynamic nature of this technique suited his temperament for insights and ideas came quickly to him and he was impatient to test them.

When animal blood was used it could be sampled from many different sites in the body and recirculated into the venous return enabling John to pinpoint the organs responsible for the release and removal of hormones such as angiotensin and bradykinin. Working on this problem with SH Ferreira, YS Bakhle and others he 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. The group speculated that both phenomena were attributable to the same enzyme and deduced that the ‘bradykinin potentiating factor’ from Bothrops jararaca venom, which inhibited bradykinin proteolysis, might also block angiotensin I conversion and furthermore, that this strategy could prove a useful therapy for hypertension. John took the idea to Squibb where Welch, John’s mentor from Yale, was by then Research Director. The outcome of this initiative was the development of the revolutionary ACE inhibitors.

A few years later, in 1971, John began what is generally regarded as his finest piece of work. Aspirin was a drug that had been around since the end of the 19th century, but for all its utility it had defied every attempt to unravel the underlying mechanism that linked together its distinctive therapeutic and side effects – a pharmacological profile that was also shared by many other ‘non-steroidal anti-inflammatories’. John’s interest in prostaglandins had been kindled some years earlier and...
over a weekend he conceived the notion that perhaps aspirin worked by inhibiting the generation of these multi-faceted mediators. He turned again to his bio-assay system for the answer and within a few days he had convinced himself and his colleagues that this indeed was the missing mechanism of action. This concept, which he further expanded mainly with Ferreira, S Moncada and RJ Flower, profoundly influenced the field including (in the 1990s) the development of Cox-2 inhibitors.

1973 saw a change in John’s circumstances. Born had taken a chair in Cambridge and John was offered the position of Group Research and Development Director of the (then) Wellcome Foundation, in Beckenham, Kent. In those days ‘The Foundation’ was a unique institution; a pharmaceutical company whose profits were gifted to the charitable Wellcome Trust. Perhaps John was encouraged to accept this post by the thought that Sir Henry Dale, one of his intellectual heroes, was recruited by Henry Wellcome and was crucial to the early development of the company.

The 13 years that John spent at Wellcome presented him with a new and different set of challenges. He had no more time for lab work as such but continued to exert his influence on research in different ways. John had very definite views about drug discovery believing that if you recruited the most motivated scientists and allowed them to work on problems of their own choice in a well supported environment, then new ideas about disease mechanisms and ultimately new drugs would inevitably ensue. To implement this vision he took Ferreira, Moncada, Flower, GA Higgs and others with him to form a nucleus of his personal research group. In 1976, working mainly through Moncada, R Gryglewski and S Bunting, John’s group discovered the potent vasodilator and anti-aggregatory prostaglandin ‘X’. The mystery substance was characterised in collaboration with Upjohn and renamed prostacyclin (PGI2). Analogues were later approved for the treatment of pulmonary hypertension and antithrombotic indications. Under John’s management, Wellcome produced several other important drugs including Zovirax, Tracrium and Lamictal.

By now, John’s contributions to his discipline were increasingly recognised. In 1974 he was made a Fellow of the Royal Society, in 1977 he won the Albert Lasker Basic Medical Research Award and in 1982 he shared with B Samuelsson and S Bergström, the Nobel Prize for Physiology or Medicine for his work on aspirin. In 1984 he was knighted in the New Years Honours list for services to pharmaceutical science. Over 50 other honorary degrees and fellowships followed over the years.

In 1986, aged 59, John left the Wellcome Foundation but the idea that he might simply retire and enjoy the fruits of a life’s work was simply not an option for him. An invitation from St Bartholomew’s Hospital Medical School, brokered by another old friend D Willoughby, coupled with an offer of some start-up funding from Glaxo Group Research, gave John the opportunity to start up a new lab; he accepted this challenge with alacrity thereby initiating the third major phase of his career. As always when starting a fresh venture, John’s technique was to surround himself with colleagues that he trusted and respected and to work together with them to build up a critical mass of talented researchers. Groups headed by E Ånggård, N Benjamin, I MacIntyre, D Tomlinson, B Whittle and Willoughby, as well as old colleagues Born and Flower, joined with John to promote his vision of a free-standing Institute devoted to excellence in inflammation and cardiovascular

Schematic diagram of the blood-bathed organ cascade. This diagram first appeared in John Vane’s 1968 Gaddum Memorial Lecture to the Pharmacological Society and was later reproduced by Vane in his Nobel lecture. The cascade can also be seen in the picture of John Vane, above.

research. From this confluence of research groups arose The William Harvey Research Institute. Major funding from Ono Pharmaceuticals in Japan enabled the institute rapidly to expand and it soon became a veritable powerhouse with a staff of over 120 people.

John himself, whilst rarely doing lab work, continued to influence the direction of the science focusing again mainly upon hormones influencing the heart and blood vessels as well as on the pharmacology of the Cox-2 inhibitors. He even found time to start up (with Ånggård) a new company, Vernalis. He retired as full-time Director of the Institute in 1995 but still maintained his office and continued to influence the course of research and to direct young people. Following the merger of the Institute with the medical school in 2000 John took over the role of Honorary Chairman of the charitable William Harvey Research Foundation.

In getting to know John, there inevitably came a point when one was introduced to his family. John had married Daphne during their Oxford days where their two daughters, Nikki and Miranda, had also been born. Although by nature rather a shy man, John was immensely sociable and, together with Daphne and his daughters, frequently entertained friends and colleagues at their home, in restaurants and at scientific meetings around the world. Such parties were legendary and always carried off with enormous panache. Close colleagues were adopted by the Vanes as a sort of extended family which burgeoned as they made many life-long friends. Whenever scientists get together they like to discuss data, experiments and ideas which often make dull listening for others. But if this bothered Daphne, with her background in the liberal arts, she never showed it and always treated John’s colleagues with great grace and charm. John was devoted to his ‘girls’, as he called them, and they provided the strongly supportive base from which he was able to launch his frequent and punishing schedules of work and travel.

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### John Vane’s speech at the Nobel Banquet December 10, 1982

‘Your Majesties, Your Royal Highnesses, Ladies and Gentlemen...

It is sometimes said that the major discoveries have already been made and that there is nothing important left to find. This attitude is altogether too pessimistic. There are plenty of ideas and plenty of things left to discover. The trick is to find the right path from one to the other. The medicines of today are based upon thousands of years of knowledge accumulated from folklore, serendipity and scientific discovery. The new medicines of tomorrow will be based on the discoveries that are being made now, arising from basic research in laboratories around the world. Fundamental discoveries can and should be made in industry or academies, but to carry that knowledge forward and to develop a new drug to the market has to depend on the resources of industry. In many countries now, research in universities is under severe financial restraint.

This is a short-sighted policy. Ways have to be found to maintain university research untrammelled by requirements of forecasting application or usefulness. Those who wish to study the sex-life of butterflies, or the activities associated with snake venom or seminal fluid should be encouraged to do so. It is such improbable beginnings that lead, by convoluted pathways, to new concepts and then, perhaps some 20 years later, to new types of drugs.’

(Reprinted with permission from the Nobel Foundation)

Science, with its uncompromising regard for facts and evidence rather than beliefs is one arena where people can truly work together unhindered by considerations of race, colour, creed or gender. Like most scientists John was a committed internationalist in this respect. His labs were full of researchers from around the world and UK scientists usually constituted a minority. Of particular significance was John’s relationship with the Polish scientific community which began in the late ‘60s during the cold war era. John made many trips to Poland during those difficult times, often taking hard-to-obtain scientific equipment and reagents with him and offering Polish scientists the opportunity to visit the West and to work in his laboratory. He made many close friends there and visited the country each year, invariably accompanied by Daphne, to attend scientific meetings. In 2003, John was accorded a rare honour in recognition of his contributions to the Anglo-Polish scientific collaboration when he was awarded the Polish Order of Merit at a ceremony in Warsaw.

As in many fields of medical research, John’s own studies often depended upon laboratory animals. This drew unwelcome attention from the animal rights extremists who, being humanitarians, pursued a particularly vindictive campaign against him. Hate mail was sent; fire bombs thrown at his house; graffiti was daubed on outbuildings. These terror tactics did not deter him from his work and he was always an eloquent advocate for the responsible use of animals in scientific research and a source of moral support to others who had suffered in a similar way. He would have been very gratified by the efforts now being made by the BPS, the Physiological Society and the pharmaceutical industry to promote training in in vivo techniques.

John Vane was a towering figure in the physiological tradition of pharmacology. He watched the molecular biology revolution unfold from the sidelines and his confidence in bioassay as an engine for the generation of new ideas and discoveries remained undiminished throughout his life. Though he is gone, his students, his research style, his extensive publications and his institute are a continuing testimony to his enormous influence as a scientist and as a man.

R J Flower
William Harvey Research Institute. St Bartholomew’s and the Royal London School of Medicine and Dentistry. London. UK

This article is a shortened version of an obituary which first appeared in pA2, the Members’ magazine of the British Pharmacological Society and is reproduced here with permission.

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Members may like to know that over £2,500 has been raised for Cancer BACUP in memory of Rob Clarke who died last August (Physiology News 2004, 57, 49)