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BY SALVADOR MONCADA FRS

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Sir John Robert Vane, who died on 19 November 2004, will be remembered as one of the most influential British pharmacologists. During his distinguished career he published more than 700 scientific papers and wrote or edited 20 books. His many awards include the Nobel Prize in Physiology or Medicine (1982) and a knighthood in 1984.

THE EARLY YEARS

John was born in Tardebigg, Worcestershire, on 29 March 1927. His father, Maurice Vane, was the son of immigrants from Russia, and his mother, Frances, came from a Worcestershire farming family. John was the youngest of three children.

He attended the King Edward VI High School in Edgbaston, Birmingham, where he was greatly influenced by a chemistry teacher, John Lambert, who was co-author of school textbooks ( Holderness and Lambert), and by a physics teacher (Mr Hall). He was given a chemistry set at the age of 12 years, which led to his first experiments, initially carried out in the kitchen and eventually in a wooden shed in the garden erected by his father, who ran a company that made portable buildings.

John began a degree course in chemistry at the University of Birmingham in 1944. There he realized that his interest did not lie in this subject, for he felt that the outcome of chemical reactions was too predictable. When asked by Maurice Stacey (FRS 1950), the professor of chemistry, what he wanted to do when he graduated he replied, ‘anything but chemistry’. By chance, Stacey had just received a letter from Harold Burn FRS at Oxford, who was looking for a young chemist who would like to train as a pharmacologist. John immediately volunteered, without knowing quite what pharmacology was. He went to Oxford in 1946, having obtained a degree in chemistry, and there discovered that the biological sciences were what
interested him; indeed, it was a move that reshaped his career. He found the atmosphere in Burn’s department exceptionally stimulating. Burn was a great teacher, who inspired him and greatly influenced his scientific development; he encouraged John’s love of experimentation and taught him never to ignore the unusual. It was in Burn’s laboratory that he learnt the techniques of bioassay that were to underpin his later work. As John used to say, ‘Bioassay measures biological assay’, and it is essentially a very simple technique by which a piece of animal tissue is immersed in a physiological solution in an organ bath and its responses to biologically active agents are studied.

At that time other notable pharmacologists working there included Raymond Ing (FRS 1951), Hugh Blaschko (FRS 1962) and Edith Bülbpring (FRS 1958), and there were many visiting scientists with whom he formed lasting friendships. In April 1948 he married Daphne Page and in 1949 he graduated with a degree in pharmacology.

THE LABORATORY YEARS

After he obtained his degree John spent a few months in Sheffield University in the pharmacology department with D. R. Wood. He then returned to Oxford to study for a DPhil at the Nuffield Institute for Medical Research with Geoffrey Dawes (FRS 1971). During this time he and Daphne had two daughters, Nicola and Miranda. In 1953 the whole family moved to New Haven, Connecticut, where he took up a post as Assistant Professor at Yale University in the Department of Pharmacology under the chairmanship of Arnold Welch. This was a happy and formative time in his life, both socially and academically. He stayed there until 1955, when he returned to England as Senior Lecturer in Pharmacology at the Institute of Basic Medical Sciences, which was eventually located at the Royal College of Surgeons building in Lincolns Inn Fields, London. The head of the Department of Pharmacology was initially Bill (later Sir William) Paton (FRS 1956), who was succeeded by Gus Born (FRS 1972); both were leading pharmacologists who created an exciting and productive working environment. John and Gus, who had known each other in Oxford, established a friendship that was to last for the rest of John’s life. He became Professor of Experimental Pharmacology in 1966.

It was while John was at the Royal College of Surgeons that he developed what could be regarded as one of his greatest scientific achievements: the blood-bathed superfusion bioassay technique. The method of pharmacological bioassay had been modified by B. Finkelman in the 1930s and J. H. (later Sir John) Gaddum FRS in the 1950s, both of whom pursued the idea that a biological tissue could be superfused rather than bathed in a physiological solution, thereby increasing the sensitivity of the bioassay. In the early 1960s John further modified the bioassay system so that different tissues, each in a separate organ bath, could be suspended one above the other in a cascade, so that the superfusion fluid flowed over each of the tissues in turn. By doing so he developed a system by which the differential sensitivity of three or four tissues gave a unique pattern or ‘fingerprint’ for each substance investigated. Most importantly, this permitted the immediate detection of previously unrecognized biologically active agents. This appealed to John’s nature because he was always impatient to find out whether his ideas were correct. He also realized that, instead of a physiological solution, blood obtained directly from an animal could be used in an extracorporeal circulation circuit for the instantaneous monitoring of the fate of active materials and the inactivation of an infused substance across a particular vascular bed. These developments were powerful tools of discovery and he used them very successfully (1)*.
One important use of the blood-bathed bioassay technique was to study the way in which vasoactive substances are handled by the circulation. This led him to propose that the lungs are metabolically active organs involved in maintaining a homeostatic control over the concentration of certain ‘local hormones’ or autacoids such as bradykinin and 5-hydroxytryptamine. Other mediators such as histamine and adrenaline were found to pass through the lungs unchanged and were termed ‘circulating hormones’, whereas angiotensin I was actually converted into the active angiotensin II in the lung. Depending on its site of release or formation, and on the target organ, a hormone could be further classified as ‘venous’, ‘pulmonary’ or ‘arterial’. This was a major contribution, which spawned a great deal of research around the world.

In 1964 a Brazilian pharmacologist, Sergio Ferreira, came to work at the Royal College of Surgeons at the recommendation of Mauricio Rocha e Silva, the discoverer of the vasodilator bradykinin. Sergio had been working in Brazil with an extract from the venom of the snake Bothrops jararaca that potentiated the circulatory effects of bradykinin; he had therefore called this factor bradykinin potentiating factor (BPF). The bringing together of BPF and the blood-bathed organ technique was to result in a finding which was to change the approach to the treatment of hypertension, namely that BPF inhibited the conversion of angiotensin I to angiotensin II. John realized that the kininase that was responsible for the inactivation of bradykinin—and which was inhibited by BPF—was the same enzyme that converted angiotensin I to angiotensin II (angiotensin-converting enzyme or ACE); this suggestion was soon confirmed by experiments in his laboratory. At this time he was acting as a consultant to the pharmaceutical company Squibb in New Jersey, where Arnold Welch, his old colleague from Yale, was Director of R&D. Some of John’s contacts at Squibb set about isolating, purifying and synthesizing one of the peptides from the venom extract and showed that it prevented the angiotensin-induced elevation of blood pressure. Sergio Ferreira, working independently, also characterized the various peptides in BPF. Both groups showed that the isolated peptides were potent inhibitors of ACE and prevented the angiotensin-induced elevation of blood pressure. Furthermore, when given to patients with hypertension, the peptides from the venom reduced the blood pressure. These experiments led to the development of ACE inhibitors as anti-hypertensive drugs; these have proven to be a very successful therapy in patients with hypertension and chronic heart failure. Interestingly, one side-effect of these drugs is a tendency to cough, which may be attributable to the prevention of the breakdown of bradykinin.

By the early 1970s the ‘Vane cascade bioassay technique’ was regularly used by everybody in his laboratory to investigate a variety of topics. It was found that the inflammatory mediators known as the prostaglandins were released from tissues that were disturbed or traumatized in any way. There was also the intriguing discovery, made with Priscilla Piper, of an ephemeral substance released from the lungs during anaphylaxis that was recognized for its ability to contract rabbit aortic strips and was therefore given the acronym RCS for ‘rabbit aorta contracting substance’ or, as John used to say, RCS for Royal College of Surgeons. The release of this material was inhibited by aspirin-like drugs. Interestingly, when RCS was discovered there was no known connection between it and the prostaglandins.

In the early 1970s John began a series of experiments with the blood-bathed organ technique to investigate the effect on pulmonary blood flow of prostaglandins released from the...
lungs. He noticed that aspirin infused into the hyperventilated dog not only reduced the associated hypotension but also inhibited the release of prostaglandins. This led him to the idea that the mechanism of action of aspirin was to inhibit prostaglandin biosynthesis. He tested this by adding arachidonic acid (from which prostaglandins are synthesized via an enzyme known as cyclo-oxygenase) to lung tissue and monitoring the effect of aspirin and other aspirin-like anti-inflammatory agents on prostaglandin formation.

By this time I had obtained an MD and came to do a PhD with John at the Royal College of Surgeons. At John’s instigation, Sergio and I began to study the effects of aspirin-like drugs on the release of prostaglandins from the dog spleen, confirming and extending his observation. Independently, Bryan Smith and Jim (A. L.) Willis, also in the Department of Pharmacology at the Royal College of Surgeons, demonstrated the effects of aspirin on prostaglandin synthesis in human platelets. The results of these three sets of experiments were published simultaneously in 1971. The importance of this finding, undoubtedly John’s major contribution to biomedicine, cannot be overstated. Besides clarifying the mechanism of action of a drug widely used as an analgesic and anti-inflammatory agent for almost 100 years, it pointed the way to potential applications in a range of different diseases and opened avenues of research and drug discovery that are still being explored more than 30 years later. Notably, between 1974 and 1975 RCS was identified as thromboxane A₂, which is also released from platelets and has powerful platelet-aggregating properties. This led to the unravelling of the mechanism of the now well-established anti-thrombotic properties of aspirin and to the successful use of low doses of the drug in the prevention and treatment of cardiovascular diseases. John used to comment that the experiments of 1969 on RCS had already indicated the mechanism of action of aspirin, because the responses of the tissues detecting prostaglandins were also reduced after treatment with aspirin—a fact that they had originally overlooked.

John remained at the Royal College of Surgeons for 18 years, during which time he performed the most productive work of his life and gathered around him a group of students and research workers from all over the world. One of his colleagues from this time, Joe Collier (Collier 2004), said of John:

He taught us how to work, teach, write, learn and even how to conduct ourselves as scientists. He was ever curious, a wonderful communicator with a deep understanding of the process (and business) of research, able to analyse problems, find the pivotal issues and offer (usually novel) solutions.

He was heavily involved with the British Pharmacological Society and held many positions there. He was the first Meetings Secretary (1968–70), the General Secretary from 1970 until 1973 and Foreign Secretary in 1982; he was elected to Honorary Membership in 1985. He greatly enjoyed the tradition of writing amusing summaries of what happened in the scientific sessions of the meetings of the Society. These records became known as the Social Minutes and are still read out at the dinners of the Society’s meetings. John’s quick wit was evident in his after-dinner speeches and is illustrated by the following anecdotes. At one BPS meeting Bill Paton introduced the concept of the rate theory of drug action, in which interaction with the receptor releases a quantum of pharmacological response, like striking a piano key. He contrasted this to the occupation theory, where the pharmacological effect continues as long as the receptor is occupied, as with an organ key. After much discussion, John asked Paton if in future we should be using piano baths rather than organ baths. On another occasion John brought to an end a prolonged debate about whether the prostaglandins were
only important in disease by pointing out that aspirin doesn’t cure a headache if you don’t have one!

THE INDUSTRY YEARS

In 1973, John was offered the position of Group R&D Director for the Wellcome Foundation—a job that involved the responsibility for more than 1000 scientists. John found a resistance to the idea of his entering into industrial science among a few of his friends, who perhaps felt that good science can be conducted only in academia. However, he was influenced in his decision to accept the job by the fact that Sir Henry Dale FRS (PRS 1940–45), a physiologist whom John greatly admired, had been a previous Director of Research at Wellcome. Although he never regretted his move to industry, his new role brought about a distancing from direct involvement in the research that was his passion, and many times he complained privately about missing the pleasure of being close to the bench where the action is. He took with him to Beckenham a nucleus of colleagues from the Royal College of Surgeons. This expanded into a Prostaglandin Research Department, of which I was the head. It was in this department that prostacyclin, a potent vasodilator and platelet anti-aggregating substance, was discovered and its pharmacology investigated. Prostacyclin was later developed as a drug by the Wellcome Research Laboratories and, in collaboration with the Upjohn Company in the United States, a programme for the synthesis and development of analogues was established.

During his time as worldwide R&D Director of the Wellcome Foundation a very productive research atmosphere developed between Beckenham and the laboratories in North Carolina. This was largely due to the similar philosophies and friendship of John and Pedro Cuatrecasas, who was head of Wellcome R&D at Research Triangle Park in the USA from 1975 onwards. Both believed in bringing bright scientists together and letting them exchange ideas freely, encouraging them to work hard on what interested them most. This was a successful approach, and during John’s time as Group R&D Director he oversaw the discovery and development of new drugs such as atracurium (a short-acting muscle relaxant), lamotrigine (an anti-convulsant used in epilepsy) and acyclovir (an antiviral active against herpes virus).

Together with Bengt Samuelsson (ForMemRS 1990) and Sune Bergstrom (both from the Karolinska Institute at Stockholm, Sweden) John was awarded the Nobel Prize in Physiology or Medicine in 1982. The Nobel committee cited him for ‘discoveries concerning prostaglandins and related biologically active substances’. In 1984 he was knighted in the New Year’s honours list for services to pharmaceutical science. He acted as Vice President of the Royal Society from 1985 until 1987.

THE WILLIAM HARVEY YEARS

In 1986, when John left the Wellcome Foundation, he founded the William Harvey Research Institute at St Bartholomew’s Hospital Medical College. Under his direction the institute, which was dedicated to inflammation and cardiovascular research, grew to about 120 people with a grant income of more than £3 million per year.
John went back to research and continued to pursue his interest in mediators in the cardiovascular system. He began to work on the vasoconstrictor substance—endothelin—produced by the vascular endothelium. Together with a new group of bright collaborators he studied the metabolism of endothelin and characterized its receptors in various tissues. They also performed studies on nitric oxide and investigated its interactions with prostacyclin.

In the early 1990s it became known that cyclo-oxygenase exists as two isoforms: COX-1, which is constitutive and generates prostaglandins involved in physiological mechanisms, and COX-2, which was initially thought to be expressed only during inflammation and to generate the prostaglandins that participate in this process. John and others suggested in 1993 that the anti-inflammatory actions of aspirin-like drugs are due to the inhibition of COX-2, whereas the unwanted side-effects such as irritation of the gastric mucosa are due to the inhibition of COX-1 (2). This hypothesis was tested by John’s research group, who later showed that there is a strong correlation between the inhibitory activity of the different drugs against COX-1 and gastrointestinal damage in man. It was therefore suggested that selective inhibitors of COX-2, if developed, would have anti-inflammatory effects without the side effects of gastrointestinal ulceration, bleeding and platelet dysfunction that characterize the use of the classical non-steroidal anti-inflammatory drugs. Over the next 10 years or so the pharmaceutical industry committed substantial resources to the development of such compounds, leading to the introduction in 1999 of the first selective COX-2 inhibitors, namely celecoxib and rofecoxib. The compounds (known as coxibs) proved to possess analgesic and anti-inflammatory activity and have somewhat less adverse gastrointestinal effects than the non-steroidal anti-inflammatory agents. However, they did not inhibit the formation of thromboxane A₂, which is a product of COX-1 in the platelets; furthermore, studies showed that oral administration of coxibs to human volunteers substantially inhibited prostacyclin biosynthesis. This led to the suggestion that, in the vasculature, a COX-2-like enzyme was the predominant source of prostacyclin and therefore inhibition of COX-2 might increase the risk of thrombosis in predisposed individuals. Indeed, clinical trials in patients with arthritis and pain suggested that treatment with the coxibs results in an increase in cardiovascular side effects; this provoked a great deal of controversy and led to the withdrawal from the market of rofecoxib (Vioxx). In 2002 John wrote a considered perspective on the subject of the coxibs in which he questioned whether this class of drug was, after all, any improvement on aspirin (3).

In 1991 John and a colleague, Erik Anggard, set up a pharmaceutical company, which they called Vanguard Medica Ltd (now Vernalis) to develop compounds that pharmaceutical companies were not interested in proceeding with for reasons other than toxicity. This company was floated on the Stock Exchange in 1996.

In the late 1990s John retired from full-time directorship and became Honorary President of the Institute, retaining an office there. In 2000 the institute merged with Queen Mary College, University of London, but kept the title of the William Harvey Research Institute. John became Honorary President of the William Harvey Research Foundation, a charity with the objective of raising money for the institute.

**Character**

Although essentially a shy man, John was charismatic and approachable, and he had a special talent for creating an all-encompassing friendly atmosphere where intense work was combined
with the most enjoyable social occasions. He was a generous host, with a taste for good food and wine, and he and Daphne greatly enjoyed having parties at home and in their beautiful garden. People from all over the world joined his research groups and were made to feel welcome—in many cases this led to lifelong friendships. In particular he developed a strong connection with Poland. From the 1960s onwards many Polish scientists came to work in his laboratory, and he made regular visits to the country, bringing much-needed scientific reagents and equipment, attending conferences and maintaining friendships. His last visit there was in May 2003, when he attended a scientific meeting in his honour in Krakow and was awarded the Cross of Merit of the Polish Republic in recognition of his contribution to Anglo-Polish scientific collaboration.

During the years we worked together, some of our most productive discussions and interesting ideas came at John and Daphne’s home in our after-lunch or pre-dinner conversations, or when we travelled together on long flights to attend meetings. He loved to travel and, in its day, he was a frequent user of Concorde. From 1973 onwards he made regular trips to the Caribbean island of Virgin Gorda, where the family had a house. He was a keen snorkeller and loved underwater photography. These holidays also provided an opportunity to keep in touch with friends from his days at Yale.

John was an ingenious, hands-on pharmacologist, able to generate meaningful hypotheses almost effortlessly. He was a gifted speaker and writer, a motivator and a teacher to several generations of pharmacologists. He had a great understanding of biological processes and a keen eye for the behaviour of the tissues in his beloved bioassay. One of his favourite phrases to students reporting back to him with results that they did not understand was ‘the tissues never lie’—it is the interpretation that can fail. He said of himself, ‘My life and times with enzymes and mediators have been a fascinating detective story; finding previously undiscovered pathways and interactions that have led to important new concepts and drugs.’

He became a target of animal liberationists and spoke out fearlessly against their activities. He was a supporter of the Research Defence Society, whose aim is to promote understanding of the use of animals in scientific research. In addition to the Nobel Prize in 1982 he received many other greatly deserved honours and accolades, including the Royal Medal of the Royal Society.

He had successful heart surgery in 1992 and then a further operation in 2002. His recovery from the second procedure was marred by fractures of the hip and he died in hospital from pneumonia on 19 November 2004.

**Honours and Awards**

*Named lectures*

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<th>Year</th>
<th>Lecture/Event</th>
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<tbody>
<tr>
<td>1968</td>
<td>Gaddum Memorial Lecturer, British Pharmacological Society</td>
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<td>1972</td>
<td>Giarman Memorial Lecturer, Yale University</td>
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<td>1973</td>
<td>Smith Kline and French Lectureship, Vanderbilt University</td>
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<td>1974</td>
<td>Royal Society Review Lecture, the Royal Society</td>
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<td>1975</td>
<td>Windsor C. Cutting Lecture, Stanford University</td>
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<td>1977</td>
<td>Smith Kline and French Laboratories Lectureship in Allied Health Sciences for 1977, University of Edinburgh</td>
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<td></td>
<td>The Walter C. MacKenzie Lecture, University of Alberta</td>
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1978  Carl Vernon Moore Lectureship, Washington University
   Rennebohm Lectures, University of Wisconsin
   Cass Memorial Lecturer, University of Dundee
   Cross Memorial Lecture, London
1979  Saal van Zwanenberg Lecture, Groningen
   Charles E. Dohme Memorial Lectureship, Baltimore
   Shirley Johnson Memorial Lecture in Pharmacology, London
   Sixth Otto Krayer Lecture in Pharmacology, Harvard Medical School
1980  Dale Lecture, Society for Endocrinology
   Foundation Lecture, British Society for History of Pharmacy
1981  Lilly Lecture, Royal College of Physicians of Edinburgh
1983  Francis Fraser Lecture, British Postgraduate Medical Federation
   Windsor C. Cutting Lecture, University of Hawaii, John A. Burns School of Medicine
1984  Schorstein Memorial Lecture, London Hospital Medical College
   Stephen Paget Memorial Lecture, Research Defence Society
   George Pincus Memorial Lecture, Worcester Foundation for Experimental Biology
   Schueler Lecture, Tulane Medical Center
   Wade Foundation Lecture, University of Southampton, Faculty of Medicine
1986  Chauncey D. Leake Lectureship in Pharmacology Lecture, Tufts University
   Cecil L. Brown and H. Martin Friedman Lectures, Rutgers University
1988  Mark Nickerson Lecture, McGill University
1989  7th Edward C. Franklin Memorial Lecture, New York University
1991  The William Withering Lecture, Royal College of Physicians
   G. B. West Memorial Lecture, University of East London
1993  Huffington Lecture, University of Texas
   Croonian Lecture, the Royal Society
1995  Chancellor’s Award Lecture, Louisiana State University

Medals, prizes and awards

1977  Baly Medalist, Royal College of Physicians
   Albert Lasker Basic Medical Research Award
1979  Joseph J. Bunim Medal, American Rheumatism Association
1980  Peter Debye Prize, University of Maastricht
   Nuffield Lecture and Gold Medal, Royal Society of Medicine
   Feldburg Foundation Prize, Feldburg Foundation
   Ciba Geigy Drew Award, Drew University
1981  Dale Medalist, Society for Endocrinology
1982  Nobel Prize in Physiology or Medicine, Nobel Foundation
1983  Galen Medallist, Worshipful Society of Apothecaries
   Medal, Biological Council
1984  Knight Bachelor
   Louis Pasteur Foundation Prize, Louis Pasteur Foundation
1986  Pythagoras Prize, Calabria
1988  Freeman of the City of Scranton, Pennsylvania
   Stilo Award, Calabria
1989  Freeman of the City of Taipei, Taiwan
Honorary degrees

1977  Doctor of Medicine, Copernicus Academy of Medicine
1978  Doctor of Science, Rene Descartes University
1980  Doctor of Science, Mount Sinai Medical School
1983  Doctor of Science, Aberdeen University
1984  Doctor of Science, New York Medical College
       Doctor of Science, Birmingham University
       Doctor, University of Surrey
       Doctor of Science, Camerino University
1986  Doctor of Science, Catholic University of Louvain
       Doctor of Science, University of Buenos Aires
       Doctor of Medicine and Surgery, Florence
1993  Doctor of Pharmacy, University of Milan
1995  Doctor of Medicine, University of Vienna
1997  Doctor of Science, University of London
1998  Doctor of Medicine and Surgery, University of Verona
1998  Doctor of Medicine, University of Silesia

ACKNOWLEDGEMENTS

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REFERENCE TO OTHER AUTHOR


BIBLIOGRAPHY

The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2006.0027 or via http://www.journals.royalsoc.ac.uk.

(3) 2002 Back to an aspirin a day? Science 296, 474–475.