



Sir John Robert Vane (1927–2004)

Sir John Robert Vane was born on 29th March 1927, in the family of several children, at Tardebigg, Worcestershire (England); died on 19th November 2004 in London. In 1982 he was awarded, together with Sune Bergstrom and Bengt Samuelsson of the Karolinska Institutet in Stockholm, the Nobel Prize for achievements in their research on prostaglandins. Many universities in the world bestowed on Sir John the title of *doctor honoris causa*; the title received from the Jagiellonian University in Krakow was the first honorary doctorate in his life. Sir John was the foreign member of the Polish Academy of Sciences and Polish Academy of Sciences and Arts, and commander of the Order of Merit for the Republic of Poland. He was a founder and the first director of the William Harvey Research Institute in London.

His death brought an end to the romantic, stimulating era in history of experimental medicine, studied with such names like Claude Bernard, Louis Pasteur, Oscar Langendorff, Paul Ehrlich, Napoleon Cybulski, Marcell Nencki, Henry Dale, Sir Howard Florey, Albert Szent Gyorgy, Harold J. Burn, Sir Hans Krebs, John Gaddum, Janusz Supniewski and many others. These names became the symbol of the epoch which believed in global biological Script of Existence. This attitude justified addressing the Nature with questions, meaning – in practice – carrying out of the simplest experiments to obtain clear answers: “yes” or “no”. This is why the scientists of that epoch not only discovered unknown facts, not only they were authors of new hypotheses and theories; they also invented new, sometimes perversely simple research methods.

For example, Sir John invented “the Vane’s bioassay cascade”, one may say: a new way to tease the Nature with subversive questions. The method consists in biological designation of active substances (such as adrenalin, serotonin, histamine, angiotensin, bradykinin or prostaglandins), which might occur in

a nutritive fluid (for example: Krebs’ buffer, or blood) superfusing drop by drop several smooth muscle organs, suspended in air downwards in the bioassay cascade. When one of these biologically active substances appears in the fluid, organs in cascade perform a dance of contractions and relaxations (some organs stay still). This answer of the cascade, “the setting of ballet steps”, is characteristic for each one of known biological mediators. However, when the cascade shows an unknown dance setting – a bell is ringing – a new, hitherto unknown biological mediator has been discovered. In this way we discovered prostacyclin; nobody knew it existed until the Vane’s cascade showed a record, which did not match dance setting of any known biological mediators, especially none of the known prostanoids.

The Vane’s method was – and still is – used in the systems *in vitro* (e.g., Krebs’ buffer perfused isolated guinea pig lungs), or *in vivo* (e.g., blood-superfused cascade of detector-organs in dog’s extracorporeal circulation). This method was, for Sir John and some of his collaborators and pupils, a tool to accomplish crucial discoveries in medical sciences. These comprise: discovery of the role of histamine and peptides in releasing of adrenalin and noradrenalin from suprarenal glands, discovery of the importance of catecholamines in acute myocardial infarction, discovery of the mechanism of antiinflammatory and anti-thrombotic activity of acetylsalicylic acid (aspirin), and of some other non-steroid antiinflammatory drugs (e.g., naproxen), discovery of the mechanism of action of steroid antiinflammatory drugs, i.e. hydrocortisone and dexamethasone, on the release of arachidonic acid from cell membrane phospholipides, discovery of unstable intermediary products (RSC) in the biosynthesis of prostaglandins, discovery of prostacyclin, discovery of metabolic function of lungs, discovery of coupled release of prostacyclin and nitric oxide from vascular

endothelium, of the role of superoxide anion in selective destruction of nitric oxide free radical – and many others.

An important achievement was the discovery of a new group of drugs applied in arterial hypertension, so-called angiotensin-converting enzyme inhibitors (ACE-I). First, Sergio Ferreira found in the venom of a viper *bothrops jararaca* a peptide that intensified biological action of bradykinin (bradykinin potentiating factor, BPF). Quite soon later, Mick Bakhle observed that BPF – in perfused guinea pig lungs – inhibits conversion of angiotensin 1 to blood vessel-contracting angiotensin 2, meaning that BPF “additionally” acts as ACE-I. This important discovery was made at John Vane’s laboratory, with the use of his classic cascade. As for John Vane, his merit was his persistent demand from the American chemists of the Squibb pharmaceutical firm to perform chemical synthesis of orally active compounds derived from the proline-rich structure of venom peptide BPF/ACE-I. Sir John believed that these compounds might become the drugs effective in the treatment of arterial hypertension. He was right again. In fact, the first such drug from the ACE-I group was captopril and Sir John’s expectations found confirmation in clinical practice.

Even more, newer lipophilic ACE-I – like chinapril, perindopril or ramipril (“The Three Musketeers”) not only exert hypotensive activity, but they also improve endothelial dysfunction, showing their properties of BPF. This is because – as we proved – their second function is due to their ability to accumulate bradykinin within endothelium, and that triggers the release of prostacyclin and nitric oxide. It is why nowadays clinicians administer these drugs to patients not only with arterial hypertension but also with coronary insufficiency, stroke and diabetic retinopathy.

Let us not forget that many elderly people owe to Sir John their every day ingestion of aspirin at low doses (50–150 mg) for protection against myocardial infarction. To many others, physicians administer ACE-I in aim to control arterial hypertension or to prevent atherosclerotic or diabetic angiopathies.

Sir John studied chemistry (University of Birmingham), but having finished his studies he at once declared that he would engage in anything except chemistry. Thus he happened to come across an outstanding British pharmacologist, Harold J. Burn of the Oxford University. It was his strange way to becoming the top British pharmacologist, although he himself used to say that the label “pharmacologist” does not say the

whole truth about his vocation, as – above all – he feels himself an “experimentator”, a person who – using invented by himself experimental systems – asks the Nature his personal questions. He joked that his appreciation of the journal “Nature” was connected with its title suggesting what should be published inside.

Collaborators and pupils knew well Sir John’s several original sayings and a specific choice of quotations from other authors, matching his personal attitude towards Science.

He had a special respect for William Harvey, the Court Physician to the King Charles Stuart the First. William Harvey was the author of the most famous medical dissertation of all times: “*De motu cordis et sanguinis in animalibus*” (1628). So it is symbolic that John Vane crowned his scientific career and activity founding the William Harvey Institute in that very place in London (Charterhouse Square) where his great countryman worked and discovered the central role of the heart in blood circulation. Nowadays, the John Vane Centre has been erected besides this Institute.

According to Sir John, the attributes of a good scientist were readiness to instantaneous change of any conception in view of undeniable facts and intellectual curiosity to continue research on a new way superimposed by these facts. He considered perseverance an important condition of research success, but he did not deny the importance of the element called “an ounce of luck”, although he preferred to describe this element with an English-Hindu” term “serendipity”, more applying to imagination.

It is worthy to pay attention to Sir John’s relations with our country. For the first time he visited Poland in 1963, invited by the Division of Medical Sciences of the Polish Academy of Sciences and it was then that he demonstrated his new “cascade” research technique, a year after he had invented it, while dr. Janina Staszewska-Barczak (presently Woolley) offered him the assistance. Later she, her colleague dr. Krystyna Herbaczyńska-Cedro (from the Institute of Experimental Medicine of the Polish Academy of Sciences, in Warsaw) and the Warsaw cardiologist dr. Leszek Ceremużyński were engaged in scientific cooperation with Sir John, in Warsaw, and in the Department of Pharmacology of the Royal College of Surgeons in London. In 1967, Sir John started his collaboration with the Chair of Pharmacology of the Medical Academy (presently Jagiellonian University Medical College) in Kraków and in the next years nine researchers of that Chair (dr. dr. Emilia Mikoś, Aldona Dembińska-

Kieć, Ryszard Korbut, Marek Radomski, Artur Zembowicz, Waldemar Radziszewski, Maciej Trybulec, Tomasz Świerkosz, and myself) had a chance to work with John Vane. Most of us were staying several times in laboratories under Sir John's direction working there for a period of a few weeks to the whole year, not only in the Royal College of Surgeons, but also in the Borrough Wellcome Research Laboratories and the William Harvey Institute. In those very hard times for Poland we received also from Sir John generous and precious help, as test kits, reagents and laboratory equipment.

At first, big two-cylinder brass Palmer's kymographs, factory-mounted on heavy, oak tables came by sea to Gdynia, beautiful monsters remembering the beginning of the 20th century. Then, at the Warsaw Airport, we collected modern, chromium-glistening six-channel polygraphs, donation from the Wellcome Trust, offered to us by Sir John's pledge, not speaking about meters of silicone piping, polyethylene cannules and bathes, electronic transducers and the Gustav Born's blood platelet aggregometers made by Zygmunt Sabikowski. In this way John Vane simply enabled us to continue in Kraków research, which we carried out with him in London. Only those who remember pitiful standards of equipment of the Polish biological laboratories of sixties and seventies of the last century

are able to duly appreciate Sir John's generosity and help and understand our feelings of deepest gratitude.

From the moment of funding in 1992 in Kraków of JMRC (Jagiellonian Medical Research Centre) till 2003, Sir John was taking part in our annual International JMRC Symposia. He delivered unforgettable lectures and participated vividly in discussions on the results of research of young scientists, especially those from Poland, Czech Republic, Slovakia, Hungary, Ukraine, Belarus and Lithuania. Sir John's personality attracted many excellent scientists from Europe, USA and Japan who came to Kraków to participate in our meetings and who became – and are – our "friends in science", among them Jack McGiff, Robert Furchgott, Kenneth Wu, Garry FitzGerald, Randy Sprague, Fujio Numano, Rod Flower, Jim Parratt, Renia and Jack Botting, Sir Arnold Burgen, Eric Anggaard, Paola Patrignani, Flavio Cocceani, Jean-Pierre Dupin, Michael Mulvany, Gunther Stock, Sylvester Vizi, Valeria Kecskemeti, Radoslav Stoika, Valery Kozlovski, Frantisek Kolar, Ivan Stepuro, Zygmunt Mackiewicz, and many, many others.

In our memory John Vane will forever stay as a symbol of an unforgettable epoch in history of Science, our friend and protector, and – above all – our Guide to "the Nature's beautiful gardens".

Ryszard Jerzy Gryglewski