A few years ago, in 2002, after surgery had been completed, a group of primary care physicians rolled up their sleeves to spruce up the decor and rewire the premises of a redundant school in the commune of Erpe-Mere in a Flemish-speaking area near Brussels, Belgium. This extraordinary scene took place under the supervision of a young trainee cardiologist who, to get a major new research project up and running, had temporarily taken his mind off a PhD study of arterial stiffness and put his clinical training on ice. A few months earlier, Ernst R. Rietzschel, MD, primary investigator of the Asklepios Study, Department of Cardiovascular Diseases, Ghent University, Ghent, Belgium, had set out to present a 30-minute talk on his PhD study to a group of primary care physicians serving Erpe-Mere and the adjacent commune of Nieuwerkerken. He never could have envisaged that his professional life would soon change so dramatically.

The “30-minute talk” became a 4-hour session, during which it transpired that these particular primary care physicians, members of the local association of primary care physicians, Asklepios (named after the Greek demigod of medicine), felt keen to collaborate on a research project that might help prevent cardiovascular disease. These primary care physicians (headed by Luc Cooman, MD, Peter Cassiman, MD, and Piet Van Damme, MD) genuinely wanted to improve the management of their own patients, but they also feared that routine work without a research element would bring on professional burnout. They told Dr Rietzschel that if he could come up with the idea, the protocol, and the money, they could provide the patients, the manpower (89 primary care physicians are now involved), and the means to carry out the work. Undaunted by what he calls “the dream,” Dr Rietzschel conceived the idea of the Asklepios Project, which has involved a 2-year baseline study of the status of the cardiovascular systems of 2524 healthy people 35 to 55 years of age (median age, 46 years) and long-term follow-up to monitor the onset of disease and how their systems evolve pathophysiologically.

Besides carrying out a classic epidemiological survey, the researchers have performed novel, noninvasive, biomechanical assessments of cardiac and arterial functions and their interactions. The use of applanation tonometry has allowed high-fidelity recording of arterial (and often carotid) pressure traces, which the researchers can then combine with echocardiographic flow data. The combination of these fundamental haemodynamic variables makes it possible to model and better characterise the cardiovascular system. The determination of peripheral blood leucocyte telomere length as a possible marker for biological age represents another novelty.
To date, the Asklepios Study Group has published ≈18 articles, 13 of them last year. In setting up the project, Dr Rietzschel accepts that he had what he calls “several strokes of luck,” all stemming from the existing facilities of Ghent University.

First, his chief of service, Thierry C. Gillebert, MD, PhD, did not think he was reaching for the sky, but he gave him his full support and added his echocardiographic know-how, with Marc De Buyzere, MSc, acting as a scientific and practical adviser.

Then, he had the good fortune to draw on the expertise of cardiologist Guy G. De Backer, MD, PhD, FAHA, head of the Department of Public Health, and Dr De Backer’s collaborator, Dirk De Bacquer, PhD, a biostatistician from the same department.

Dr Rietzschel knew also that to gain detailed knowledge of haemodynamics, he would need the help of Patrick Segers, PhD, head of the Cardiovascular Mechanics and Biofluid Dynamics Research Unit—a part of the Institute of Biomechanical Technology. In this remarkable unit, engineers familiar with measuring pressure and flow levels in metal pipes and the like have, for many years, applied their considerable experimental and mathematical skills to the messier scenario of the human body.

What he calls his “final stroke of luck” came when he mentioned to his wife, Inge Van Pottelbergh, MD, an endocrinologist, that to stage subjects in the study, he may never have seen a carotid artery, but when they see a white piece protruding—even a child can guess it’s plaque! When people see these things on their own echo images, they say things like, ‘Well, I guess I’ll have to quit smoking.’ Whether such effects are long term or not, we don’t know.”

Dr Rietzschel believes that the real value of these studies lies in their ability to show each individual the status of his or her own cardiovascular system, whereas cardiologists tend to talk in terms of statistics, which, of course, refer to populations. He comments, “Individuals are individuals, and everyone tends to think they are on the [favourable] tail of the distribution!”

Did Dr Rietzschel, not yet a qualified cardiologist, feel daunted by the prospect of coordinating so large a team? He replies, “Not really; we just got on with it. Also, in my early cardiology training, I had spent a year at the Cardiovascular Centre, OLV Aalst Hospital [Aalst, Belgium], under Erik Andries, MD, and Paul Nellens, MD, who have propelled this [provincial] centre to international status and shown me that ‘dreaming’ is allowed. Though later on, with hindsight, at certain moments, we sometimes thought, ‘What the hell have we started?!’ Getting the database clean after we had entered all the baseline data was one of the roughest patches. There was no output [of results] when people were expecting it.”

Erpe-Mere and Nieuwerkerken exist as virtual suburbs of Brussels, and most of their 25000 inhabitants either commute to the city or work in the many light industrial companies based in the area. One priority involved finding premises in the vicinity where the researchers could examine patients and enter them into the trial; this led to the redundant school mentioned above. The researchers decided to open the centre (see Figure) between 8 AM and 10 PM, to prevent skewing the data toward those who might find it easier to attend during the working day.

For a nominal fee of €50, the primary care physicians undertook to oversee an inclusion visit, a follow-up examination, and clinical follow-up until the next examination cycle. Dr Rietzschel and a nurse, Frida Brusselmans, performed all baseline measurements. He says that although patients initially seemed sceptical about “something that was free,” they became extremely enthusiastic, especially during the echocardiography examinations. “We allowed them to look at the images, and then we explained how the heart works, and the cardiovascular system. They asked questions, and we showed them various parts of the equipment we were using—tubes containing deposits of DNA, and the like. It was very successful educationally. You should never underestimate the intelligence of people. Someone may never have seen a carotid artery, but when they see a white piece protruding—even a child can guess it’s plaque! When people see these things on their own echo images, they say things like, ‘Well, I guess I’ll have to quit smoking.’ Whether such effects are long term or not, we don’t know.”
The European Society of Cardiology (ESC) created Working Group 20 as a working group on hypertension. The ESC discussed the idea with the European Society of Hypertension (ESH), and they jointly created this Working Group on Hypertension and the Heart. “The group became a kind of bridge between the ESH and the ESC,” says Robert Fagard, MD, PhD, FESC, professor of medicine at the hypertension department, University of Leuven, Belgium.

As chair of the group, Professor Fagard has a background as an ex-officio member of the council that governs the ESH. “With many of these ESC working groups, there is no society in Europe, so they are ‘the society.’ But hypertension already had the ESH, so the working group has developed a straight collaboration with the ESH and works on many joint initiatives, such as guidelines, meetings and congresses, and educational initiatives, rather than duplicating these activities,” he says. ESH educational activities include summer schools for young doctors, advanced master classes, and educational meetings in hypertension, and ESH recognises specialists and centres of excellence in hypertension.

Professor Fagard continues, “There is a society specifically for hypertension because it is a multidisciplinary condition involving specialists such as nephrologists and endocrinologists as well as cardiologists. We have to be careful that one of these societies does not take hold of hypertension, so hypertension has a society of its own.” But the working group doubtlessly has succeeded in promoting greater cooperation between the ESC and the ESH.

The phrase “spare time” hardly has a place in Dr Rietzschel’s vocabulary, but when he can grab a moment, he likes to follow his passion for black-and-white photography—the hard way. In what he calls “a moment for oneself,” he locks himself into a dark room and processes plates exposed by peering into old-fashioned, large cameras of wood and brass, with a black cloth over his head. Also a passionate traveller, particularly in the Arctic region, he has made several visits to Baffin Island in northern Canada, part of the Nunavut territory of the Inuit people.

Barry Shurlock is a freelance medical writer.

European Society of Cardiology Working Groups: Hypertension and the Heart

“We Have to do a Better Job at Preventing and Controlling High Blood Pressure”

Robert Fagard, MD, PhD, FESC, chair of the European Society of Cardiology Working Group on Hypertension and the Heart, ex-officio member of the council of the European Society of Hypertension, and vice president of the International Society of Hypertension, talks to Ingrid Torjesen, BSc, about his work.

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The ESC Working Group on Hypertension and the Heart has 140 members, including a nucleus of 10 specialists. Professor Fagard says, “Its major aim is to promote and develop knowledge on the epidemiology, prevention, pathophysiology, diagnosis, and treatment of hypertension and hypertension-related cardiac organ damage, which will allow the improvement of treatment of hypertension and hypertension-related cardiovascular diseases.” However,
because members do not pay a fee, the working group has limited finances. It cannot, therefore, organise studies, so it focuses on stimulating research and taking part in education.

“We try to organise sessions on hypertension and the heart at existing meetings, because we don’t have the funds to set up our own meetings, and, in any case, there are already so many meetings,” Professor Fagard says. The working group holds sessions at the annual meetings of both the ESH and the ESC and at meetings of other organisations, such as the ESC Association of Cardiovascular Prevention and Rehabilitation, and it contributes to meetings of national hypertension societies. The working group also took part in the recent update of the ESH and ESC guidelines for the management of hypertension.1

Professor Fagard first became attracted to cardiology while a resident in internal medicine in the early 1970s. “It was not so much invasive cardiology but more preventive cardiology that interested me,” he says, “so I became involved in 2 aspects of cardiology—hypertension and cardiac rehabilitation.”

His career reflects these interests. He spent a year in Jackson, Miss, studying hypertension, with Herbert Langford, MD, and Arthur Guyton, MD, in physiology. He later completed 2 PhDs in Belgium—one in medicine and hypertension and the other in physical exercise and sports medicine. Along with his commitments to hypertension, Professor Fagard still holds responsibility for cardiac rehabilitation at the University of Leuven.

Professor Fagard sees the suboptimal control of blood pressure as the major challenge in hypertension; he believes that doctors deserve some of the blame for this because they do not act aggressively enough to manage their patients’ blood pressure. “We know the epidemiology of hypertension, we know the environmental causes of hypertension, we know how it can be prevented, and we know how we can treat it—but every study shows the control of blood pressure is suboptimal everywhere in the world,” he says. “We have to do a better job for prevention, and we have to do a better job for treating hypertension and controlling blood pressure. That is a worldwide problem.”

This predicament particularly affects developing countries, where up to 30% of people have hypertension but few receive treatment for the condition. As vice president of the International Society of Hypertension and chair of the International Society of Hypertension Low and Middle Income Countries Committee, Professor Fagard has the responsibility of facilitating improved knowledge about hypertension among doctors in developing countries, to improve management of the condition. He organises teaching seminars for such doctors, mainly those in Africa. The first one took place in Maputo, Mozambique, in September 2006.2

Around 30 doctors attend each event. “These young, interested, and enthusiastic doctors from about 10 nations are really leading the way in their countries, and we hope that there will be some effect,” Professor Fagard says. In addition to the teaching sessions by mixed European and African faculty, they have the opportunity to present and discuss their own research at these meetings. “When you talk to people in Africa, they don’t have enough medication for the treatment of hypertension, and pharmaceutical companies have, in general, not much interest because of the lack of resources, so it is a challenge,” he explains. “Nevertheless, a number of pharmaceutical companies from my country and some at the international level do support our African hypertension seminars.” The financial constraints on doctors in developing countries obviously lead to limited access to modern drugs, and thus doctors in these countries must rely on generic versions of older therapies, which can vary in quality. “But,” says Professor Fagard, “this should not be a stumbling block. We know that black people will respond better to diuretics and to calcium channel blockers than Caucasians, so if the cheaper drugs are okay, that should be fine.”

Professor Fagard is now trying to get the hypertension societies to work together on the seminars. “We already work with the International Forum for Prevention and Control of Hypertension in Africa, mainly for the local organisation, and with the World Health Organisation and the World Heart Federation, but it would be good to have seminars organised by the International Society of Hypertension and the European Society of Hypertension,” he says. “That is what I have been trying to achieve as an ex-officio member of the council of the ESH and being president of the ESC working group. ESH has supported the seminars in the past, but, from 2009 on, ESH has agreed to be a co-organiser.”

Professor Fagard concludes, “Maybe what we try to do in Africa is a drop in the ocean, but I think that it has to be done, and, hopefully, our efforts will contribute to some extent to the control of hypertension in this neglected continent.”

References


Ingrid Torjesen is a freelance medical writer.
Pioneers in Cardiology:
Sir James Black, MB, ChB, FRS, FRCP

The Nobel Prize Winner in Physiology and Medicine, 1988

Sir James Black talks to Mark Nicholls about his life and the research that led to his Nobel Prize, including his work on β-blockers, which revolutionised the treatment of heart disease.

The chance to establish a new physiology department from scratch at Glasgow University, Scotland, in 1950 set Sir James Black, MB, ChB, FRS, FRCP, on a course that would eventually transform the treatment of angina, heart disease, and heart failure.

Born the son of a coal mining engineer in Uddingston, Scotland, on June 14, 1924, James Whyte Black emigrated to Singapore in 1947 after graduating from St Andrew’s University, Scotland, where he had received his medical degree the previous year. He intended to earn enough to pay the debts he had incurred as a student. Working as a senior lecturer in physiology at the University of Malaya, Kuala Lumpur, he pursued research, though he admits he did so without the benefit of supervision. Sir James says, “Needless to say, in my research efforts—trying to study the pressure–flow relations of intestinal blood flow—my ambition was greater than my skills, and I more or less lost my way.”

In 1950, Glasgow University took over the Glasgow Veterinary College, with the mandate to modernise. “I was very lucky to get the chance to build up a new department of physiology from scratch,” he says. “With my superb workshop and brand-new research equipment, I became a honey pot for a few university bees.” These included cardiac surgeon George Smith, FRCS, who had trained with Claude Beck, MD, in Baltimore, Md. Sir James explains, “In the 1940s and 1950s, all the therapeutic strategies, pharmacological as well as surgical, were directed towards trying to increase blood flow to hearts that were crippled by narrowed coronary arteries. Dr Beck had pioneered an operation to try to increase blood supply to the heart in which he brought the omentum through the diaphragm and stitched it to the surface of the pericardium that was scarred with a carrot grater.”

“However,” explains Sir James, “Dr Smith had the idea to try oxygen delivery to the heart using hyperbaric oxygen.” Using a specially built pressure chamber, he exposed anaesthetised dogs to atmospheric oxygen or oxygen at 1 or 2 atmospheres pressure of pure oxygen. Sir James adds, “He used ventricular fibrillation induced by tying the anterior descending coronary artery as a surrogate for a massive heart attack. He found that 2 atmospheres of oxygen had a huge effect in reducing the induction of ventricular fibrillation. I knew, of course, that haemoglobin was fully saturated with oxygen at the normal pressure of one-fifth atmosphere of oxygen, so that the increased capacity of blood oxygen at 2 atmospheres had to be entirely due to dissolved oxygen in plasma. I knew enough chemistry to know that oxygen has a low solubility in water. I was able to calculate that the blood oxygen could only have increased by 15% to 20%.”

Sir James recognised that physical training lowered the resting heart rate to 60 beats per minute or less by reducing the cardiac sympathetic drive. He points out, “Reducing the circulation in this way slowed the average transit time of blood through the capillaries, thus increasing the extent of oxygen diffusion to tissues at zero energy cost. This benefit shows up as an economical overall increase in the arteriovenous oxygen difference.”

With this background, Sir James says, “The questions raised by Dr Smith’s results were that if such a small increase in the supply of oxygen is so effective, would an equivalently small decrease in the cardiac demand for oxygen also be effective, and could that be achieved pharmacologically? And, consequently,” he asks, “would antiadrenaline drugs be effective for treating angina?”

Sir James knew that drugs could block the effects of adrenaline. Medical professionals had known about ergot alkaloids for more than 50 years, mainly because of the work of Henry Dale, MD, FRCP. Sir James says, “In the late 1920s and 1930s, medicinal chemists, mainly in Fourneau’s lab in Paris, made huge strides in synthesising simple phenylethylamine- and benzodioxane-related molecules that had antiadrenaline properties in animal experiments. In the late 1930s, antiadrenaline drugs (also known then as sympatholytics) such as dibenamine were studied in man, and their most dramatic effect was seen on blood pressure. There was little effect on blood pressure in horizontal subjects, but, on standing, the blood pressure fell dramatically, leading to dizziness and even to fainting, and this was associated with tachycardia.” Sir James continues, “There was also progress in the synthesis of adrenaline-like, sympathomimetic, drugs. Isoproterenol, the N-isopropyl
analogue of adrenaline, had been found to lower blood pressure, increase heart rate, and dilate the bronchi. Clinically, it was introduced for the acute relief of asthma.”

Sir James recalls that in 1946, pharmacologist Raymond P. Ahlquist, MD, had rationalised the pharmacology of dibenamine and isoproterenol and proposed the revolutionary idea that 2 kinds of receptors existed for adrenaline; he symbolised these as α- and β-receptors. The vasoconstrictor actions of adrenaline occurred in response to activation of α-receptors, and the stimulation of heart rate and dilation of bronchi occurred in response to activation of β receptors.

“In terms of Ahlquist’s hypothesis, dibenamine (and Fourneau’s antiadrenalinés) acted by blocking the α-receptors, thus unmasking the β-receptor activity of adrenaline, and isoproterenol acted by stimulating the β-receptors without activating the α-receptors,” says Sir James.

After reading about Ahlquist’s work, Sir James knew how to test his hypothesis about treating angina pectoris—invent a β-blocker. In 1958, Imperial Chemical Industries, based in the United Kingdom, employed him as a pharmacologist and gave him “an eager young medicinal chemist,” John Stephenson, to work with him. Sir James says, “Just as Fourneau and colleagues succeeded in modifying sympathomimetic phenylamines and converted them to sympatholytics, we started with isoproterenol and tried to do the same.”

In 1959, Neil C. Moran, MD, showed that dichloroisoproterenol blocked the effects of adrenaline on ventricular contractions, measured with a strain gauge arch, and suggested that it blocked β-receptors. Later, Sir James and Mr Stephenson made some dichloroisoproterenol and observed its properties as a very powerful stimulant of heart rate, using an isolated guinea pig perfused heart preparation. “Some months later,” says Sir James, “I replaced the spontaneously beating isolated heart with an electrically stimulated guinea pig ventricular muscle preparation. Recording the force of these ventricular contractions with a strain gauge, I found that dichloroisoproterenol would now block the effects of adrenaline—just like Dr Moran. That was the key.” He continues, “Stephenson went from dichloro substitution of the benzene ring to a betanaphthyl ring to produce our first β-blocker—pronethalol. The rest is history.”

He notes that in having classified pronethalol and propranolol as β-blockers, all the subsequent development of the clinical use of these drugs has come through the work of clinical investigators. In 1964, Sir James joined the British subsidiary of Smith Kline & French Laboratories, where he stayed until 1974. From there, he spent 4 years as head of the Department of Pharmacology at University College, London, England, and from 1978 to 1984 he served as director of therapeutic research at the Wellcome Research Laboratories in Kent, England, before taking a post at King’s College of Medicine and Dentistry in London. Sir James joined the Royal Society of London in 1976 and received its prestigious Mullard Award in 1978. He received the Albert Lasker Clinical Medicine Award in 1976 and became Sir James Black when he received his knighthood in 1981. In 1988, he received the Nobel Prize in Physiology and Medicine, which recognised his outstanding contribution to medicine.

Away from his work, Sir James enjoys reading, music, and the arts. He received one of the Royal Society’s 2004 Royal Medals “for his work in both academia and industry, pioneering a new era of rational drug discovery.” The award citation continues, “His work has played a major influence in elevating British pharmacology and pharmaceutical research to its current eminent international stature.”

Sir James now serves as emeritus professor of analytical pharmacology at King’s College, and he works at the James Black Foundation at the Denmark Hill Campus in London. The Princess Royal opened the centre that bears his name and specialises in research in cardiology and gastroenterology in January 2007 (see Figure).

Mark Nicholls is a freelance medical writer.