Pioneers in Cardiology:
Salvador Moncada,
MD, PhD, FRS

Dr Salvador Moncada has spent the last 35 years doing research that has completely changed the way that vascular disease is understood. Although he has spent his entire career in laboratory-based biomedical research, Dr Moncada originally trained to be a clinician. He graduated from medical school in El Salvador in 1970, then was promptly deported for political reasons.

“The situation was very unstable and the student movement was very active against what was basically a dictatorship. I knew I was going to have problems, but these are the things that you have to do and you take the risk. Actually, you often risk being killed, so in a way I was lucky,” he explains.

After he was deported, Dr Moncada spent a year in Honduras while he tried to organise further training. He decided to come to Europe rather than pursue a career in the US, as his family were Eastern European Jews who had emigrated to South America in 1937. On the suggestion of a teacher from El Salvador who had been in London 10 years previously, he contacted Sir John Vane, FRS (who later won the Nobel Prize in Physiology or Medicine in 1982 for his work on aspirin), at the Royal College of Surgeons. Dr Moncada was accepted by Sir John as a PhD student in 1971.

When he arrived in London, Dr Moncada was thrown into the middle of a research project looking into the mechanism of the action of aspirin and how it achieves its analgesic and antiinflammatory effects. “I was lucky to arrive at the time at which the hypothesis as to how aspirin might work was being developed in the department, so I was immediately plugged into the experiments that led to that discovery. I got into lab work, and it was so exciting that after 6 months I had forgotten that I had to register as a doctor. I practically abandoned medicine,” he explains. “I’ve spent the last 35 years of my life just doing research.”

Just a few months after his arrival in London, Dr Moncado was part of the team that published 3 papers describing how aspirin-like drugs inhibit prostaglandin biosynthesis. And when Sir John accepted a job as research director of the Wellcome Research Laboratory in London, Dr Moncada formed part of the small team that went with him.

At Wellcome, he was made head of a small group working on inflammation, but after attending a meeting in Florence on his way back from a short stay in El Salvador, Dr Moncada decided to look into the effects of aspirin on platelets instead. Within a few months his team had demonstrated that the well-known antithrombotic properties of low-dose aspirin are mediated by its effects on platelets, rather than by any effect on the endothelium.

It was when he turned his attention to the vessel wall that Dr Moncada made his next discovery. His team was looking for evidence that the endothelium produces the proaggregating and vasoconstrictor substance thromboxane A2 (TXA2), but what they found was that the vessel wall was making a substance that was the exact biological opposite of TXA2, in that it was a vasodilator and had antithrombotic properties. “We had serendipitously stumbled onto the discovery of

Dr Moncada modestly says that he and his colleagues “stumbled on the discovery of prostacyclin,” and later formulated it for therapeutic use.
prostacyclin,” Dr Moncada says (see Figure). The team then spent several years formulating prostacyclin so that it could be used therapeutically. “It was difficult because it is unstable. But we eventually succeeded in making it in small vials,” he remembers. The drug, for which Dr Moncada holds the patent, is used in transplant and bypass patients to drastically reduce blood pressure and has revolutionised the treatment of primary pulmonary hypertension.

Dr Moncada’s next project was to pin down the identity of the mysterious endothelium-derived relaxing factor (EDRF), a substance produced by the blood vessel wall that causes surrounding smooth muscle tissue to relax, thus dilating the artery and increasing blood flow. Robert Furchgott, MD, professor of pharmacology at the State University of New York Downstate Medical Center, NY, had discovered its existence in 1980, but in 1986 the chemical identity of the substance was still unknown. “Others had already spent 6 or 7 years trying to find out what it was, so I decided to have a go,” Dr Moncada recalls.

In 1986 he attended a scientific conference at the Mayo Clinic in Rochester, Minn, at which Dr Furchgott and Louis Ignarro, PhD, professor of pharmacology at UCLA, independently reported experiments suggesting that EDRF might actually be nitric oxide or a derivative of it. “Everybody else looked at them with total disbelief, but I got very excited by the idea,” Professor Moncada says.

When he returned to London, he bought a bottle of nitric oxide and started trying to make solutions of it. “It was very difficult because nitric oxide is almost water insoluble. But in the end, we managed it, and there it was: The behaviour of that substance was very similar to authentic EDRF produced by endothelial cells.” In 1987 Professor Moncada’s team published the first paper identifying EDRF as nitric oxide. They also described how it is made from the amino acid L-arginine. The ramifications of this finding have been huge. Around 60 000 papers on nitric oxide have been published since the one by Dr Moncada’s team, and the chemical is now known to be a key signalling molecule that plays a major role in neuronal communication and immune response, as well as in blood vessel modulation.

However, despite being the first to biologically identify nitric oxide, discover its synthetic pathway, and develop a widely used bioassay for measuring it, Dr Moncada was not included in the group of scientists who in 1998 were awarded the Nobel Prize for the discovery that EDRF was nitric oxide. “Nobel Prize or not, the work is there, as I think the scientific community knows,” he says.

Dr Moncada is currently researching the role of nitric oxide in the regulation of cellular bioenergetics, research that could lead to treatments for conditions such as septic shock and chronic inflammation. “We are also toying with the idea of starting to work on cancer,” he says.

Dr Moncada lives in London with his wife, Princess Maria-Esmerelda of Belgium, and his two children. Although he visits Honduras regularly, he considers London his home. “I’ve lived in London longer than anywhere in the world, and I don’t have plans to move anywhere else, as long as I can keep doing my research here,” he says.

Emma Baines is a freelance medical writer.

Hypertension in Pregnancy:
A Russian Initiative

Olga Tkacheva, PhD, MD, is professor of medicine at Moscow State Medico-Stomatological University, Russian Federation, and chair of a recently formed national working group on arterial hypertension in pregnancy. She talks to Monika Polak, PhD.

Hypertension in pregnancy is one of the most significant medical problems currently facing healthcare services in the Russian Federation, and a problem that is far from solved, according to Dr Olga Tkacheva. Last year, the Russian Scientific Society of Cardiologists (also known as the Society of Cardiology of the Russian Federation)1 founded a new section to address the issue of cardiovascular disease in pregnancy. Four specific working groups were set up within the section to focus on arrhythmias, heart valve disease, metabolic disturbances in pregnancy, and, of course, arterial hypertension.

Dr Tkacheva explains, “Hypertension in pregnancy is one of the leading causes of maternal and perinatal mortality and morbidity in Russia. About 20% of pregnancies are affected, compared with around 1 in 10 in Western Europe.”

The management of pregnant women affected by hypertension has not changed for many years, she says, because there has been little progress in understanding its causes, and an evidence base for the introduction of new therapies has been lacking. Moreover, in Russia there are many interpretations of terminology, classification, diagnostic criteria, and treatment in this area of medicine. This results in a lack of coordination in thinking and in practice. For example, the pregnancy-specific syndrome (which occurs after 20 weeks’ gestation and includes an increase of blood pressure accompanied by proteinuria) may be referred to by several different terms, such as gestosis, nephropania, and pre-eclampsia. This helps to explain why it is sometimes difficult for doctors to exchange information accurately.

The arterial hypertension working group believes that one of the causes of the high prevalence of hypertension in pregnancy in Russia is doctors’ interpretation and opinions concerning the diagnostic criteria. Dr Tkacheva says, “Cases with a blood pressure below 140/90 mmHg would usually be classified as normotensive. However, some doctors will make a diagnosis of hypertension if there is an increase

1 Russian Scientific Society of Cardiologists.
in blood pressure from the prepregnancy baseline of 30 mm/Hg systolic or 15 mm/Hg diastolic, even if the pressure does not reach 140/90.” She acknowledges that not all the causes of hypertension in pregnancy are known. “This,” she adds, “necessitates further study of the pathogenesis, diagnosis, and treatment of the condition.” It is important that the working group, which consists of about 20 members, unite the different specialities involved in the care of women during their pregnancy. These specialities include cardiology, obstetrics, and even paediatrics.

The working group has set itself 3 main aims. The first aim is to produce national recommendations on hypertension in pregnancy; the second is to organise educational programmes, conferences, and symposia for clinicians to improve knowledge and thus practice; and the third is to foster international cooperation. “That is very important for us because it gives us the opportunity to exchange information and experience,” Dr Tkacheva says.

In addition, there will be an active programme of research. The members of this programme will be scientists from different Russian scientific and clinical institutions. The programme will examine the mechanisms of how hypertension develops in pregnancy, including endothelial dysfunction and the role of inflammation and inflammatory mediators. It will also assess the role of metabolic syndrome in hypertension during pregnancy and in the postnatal period. Among the parameters to be recorded will be the mother’s weight and lipid profile, the presence of insulin resistance, and serum levels of C-reactive protein, leptin, and other proinflammatory markers.

Dr Tkacheva subscribes to the published view that metabolic syndrome is a common route to preeclampsia and atherosclerosis.1,2 She is also keen to further develop the idea that pregnancy is a stress test for life.4 “We have investigated women for 10 to 15 years after delivery, those who had hypertension diagnosed during pregnancy. We have a great interest in the prognostic value of hypertension in pregnancy for later life,” she says.

Enthusiastic support for the new working group comes from the highest echelons of medical expertise in Russia. Both Rafael Oganov, PhD, MD, professor of cardiology at the Russian Academy of Medical Sciences and chief research officer of the Myasnikov Institute of Clinical Cardiology, and Vladimir Kulakov, PhD, MD, president of the Russian Scientific Society of Obstetricians and Gynaecologists and chairman of the Joint Scientific Council on Obstetrics and Gynaecology of the Russian Academy of Medical Sciences—the “great specialists,” as they are known—are backing the initiative.

Dr Tkacheva anticipates that the management recommendations will be published about a year from now. International cooperation is greatly valued, not only because it helps to inform the proposed recommendations but also because it enables the working group to look forward to new goals in this area of cardiology.

There has already been some contact with other European clinicians with an interest in hypertension in pregnancy. Representatives of the working group took part in the 15th World Congress of the International Society for the Study of Hypertension in Pregnancy in Lisbon, Portugal, in July. “This meeting provided good opportunities for discussion and debate,” says Dr Tkacheva, “and I am keen to maintain an international presence at forthcoming congresses.”

Most of all, the working group wishes to encourage international cooperation and interest in its work to help reduce the burden of hypertension in pregnancy in Russia. Enquiries and contact from those who are practising or researching in this area of cardiology are welcomed by Dr Tkacheva, whose e-mail is tkacheva@rambler.ru.

Monik Polak is a freelance medical writer.

References


The opinions expressed in Circulation: European Perspectives in Cardiology are not necessarily those of the editors or of the American Heart Association.
History of Cardiology:
Paul Louis Duroziez, MD

Dr Paul Louis Duroziez’ descriptions of aortic incompetence and mitral stenosis resulted in the terms Duroziez’ sign and Duroziez’ disease. Diana Berry relates his story.

Paul Louis Duroziez was born in 1826 in Paris where, as an adult, he studied at the Faculté de Médecine. He spent some time at l’Hôpital des Enfants Malades, and during the years 1849 and 1850 he was an extern under Jean Baptiste Bouillaud, MD, a professor at l’Hôpital de la Charité in Paris.

In 1856, Dr Duroziez was made clinical chief at la Charité in Dr Bouillaud’s service, and he remained in this post until 1858. It was in 1861 that Duroziez’ important paper, The Double Intermittent Murmur Over the Femoral Artery as a Sign of Aortic Insufficiency, was published. The murmur he described later became known eponymously as Duroziez’ sign. In the same year he wrote a paper, “Pure Narrowing of the Mitral Valve,” elucidating the clinical characteristics of a pure type of mitral stenosis, a condition that later became known as Duroziez’ disease.

Duroziez was deeply interested in diseases of the heart, an organ that he considered to be a “separate being endowed with a male half, the left ventricle and a female half, the right ventricle.” He saw the male half as being more active and regular, calm, and stable and the female half as contrastingly nervous and disorderly. In his work on this perceived duality, Duroziez referred to the 4 cardiac cavities as comparable to “four horses fastened to the same chariot,” such an arrangement allowing for “an easy break in equilibrium and resulting badly combined movement.”

In his 1861 work that established Duroziez’ sign, he pointed out the valuable information offered by the femoral arteries which are “readily compressed” and “offer the same advantages as the radial arteries.” Duroziez went on to describe the “shock or thrill” felt on compression of the femoral artery and how auscultation revealed “a sound of unique blowing character, a simple intermittent blowing murmur,” and added that the character of that murmur is influenced by blood changes, artery size, condition of the vessel wall, and the force of aortic contraction.

Duroziez stated that sustained compression of the artery and gradual release will, in a patient with chlorosis (a form of anaemia), at times produce “a continuous humming murmur” and at other times “a double murmur.” However, the intermittent double murmur occurring in certain other cases is rather different. This had been described in aortic insufficiency many times, but Duroziez did not feel it had been given its deserved significance. He pointed out that the murmur occurring in arterial diastole had been mentioned by everyone, but few had noted the murmur’s occurrence during systole. The simple murmur results from a powerful ventricular contraction, but the more subtle second murmur is produced by the systole of the lower limb arteries and, as it is less powerful, its production is facilitated by arterial compression.

Duroziez described how the double murmur may be produced either by use of the stethoscope or manually. The artery is completely compressed by pressure from the stethoscope, which at a given moment will elicit the double murmur. When the second murmur is more readily produced, it is possible to place the stethoscope on the artery without pressure. Pressure is then gradually applied manually above and below the stethoscope. Pressure above produces the first murmur, and pressure below, the second. Duroziez felt the double intermittent murmur to be of interest as a diagnostic tool. He also believed that the reflux of blood explained some of the symptoms occurring in aortic insufficiency and the sudden deaths that were occasionally observed.

In one of the concluding remarks of his paper, Duroziez stated that “the double intermittent femoral murmur occurs in typhoid fever, chlorosis, lead intoxication, but only temporarily, as it is soon replaced by continuous murmurs.”

Duroziez was elected President of the Société de Médecine in 1882, having been an active member for some 30 years. His marriage in 1861 to Mademoiselle Rohan, whose grandparents had been guillotined during the French Revolution, produced four children, but sadly the eldest, his only son, died of scurvy which developed during the siege of Paris in 1870. This was at the time of the Franco-Prussian war, during which Duroziez served in the French army as an ambulance physician and surgeon major of the Fourteenth Infantry Battalion.

About 2 years before his death, Duroziez was made Chevalier of the Légion d’Honneur. He is described by Ralph H Major, MD, as “a general practitioner, a remarkably keen observer, a simple and gentle man who sought no honour or preferment but whose name was honoured throughout the medical world.”

Diana Berry is a freelance writer and medical historian.

References

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