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European Perspectives in Cardiology



Spotlight: Michel Burnier, MD, FASN



“Involved in the Clinical Development of the First Angiotensin-Converting Enzyme Inhibitors After Captopril and in the Early Development of Blockers of the Renin-Angiotensin System”

Michel Burnier, professor of medicine and head of the Service of Nephrology and Hypertension, University Hospital of Lausanne, Lausanne, Switzerland, talks to Mark Nicholls.

To tackle cardiovascular risk, Michel Burnier, MD, FASN, professor of medicine and head of the Service of Nephrology and Hypertension, University Hospital of Lausanne, Lausanne, Switzerland, says further investment in research is needed to understand the mechanisms that lead to hypertension. He also highlights the importance of preventive measures, education, and monitoring drug compliance.

Professor Burnier's research has been a great passion during his career, and his research interests include the renal mechanisms of hypertension and the pathogenesis of disease progression in chronic kidney diseases, with a special emphasis on the role of sodium and salt in controlling blood pressure. He has also worked on the clinical pharmacology of new antihypertensive drugs in humans, with a special emphasis on drugs affecting the renin-angiotensin system, and on the importance of drug compliance. He says, “Several reasons led me to these topics: I was puzzled by the lack of knowledge on them, I have always been fascinated by the complexity of the regulation of blood pressure and renal function, and I have been personally affected by a chronic kidney disease.”

Born in 1953 in Aigle, Switzerland, Professor Burnier grew up in Valais, Switzerland. He completed his medical studies at the University of Lausanne. After early research and training in internal medicine in the Department of Medicine, University Hospital of Lausanne, he spent 2

years in the Division of Nephrology of Professor Robert W. Schrier, MD, at the University of Colorado Health Science Center, Denver, CO. He says, “My stay in the United States was a very important step in shaping my career. It enabled me to gain autonomy and independence in research. This was a crucial time that I could dedicate to research, and this was really the basis of my personal development once I returned to Switzerland.”

Professor Burnier reflects that his early training in the lab of Professor Hans R. Brunner, MD, who was head of the Division of Nephrology and Hypertension, University Hospital of Lausanne, and who became a key mentor, helped in the development of his career. Professor Brunner's work on the renin-angiotensin system led Professor Burnier to focus his MD thesis on interactions between the renin-angiotensin system and vasopressin and the sympathetic nervous system,¹ which led to a research award from the Faculty of Medicine at the University of Lausanne.

Professor Burnier says, “The hypotheses were that these systems contributed differently to the control of blood pressure, and that one system could counterbalance the absence of another one in case of blockade.”

Further research for Professor Burnier followed from this early work on the clinical development of the second generation of angiotensin-converting enzyme inhibitors (enalapril, lisinopril) in collaboration with Professor Jerome Biollaz, MD, from the Division of Clinical

On other pages...



Awards: European Society for Clinical Investigation Award for Excellence in Biomedical Investigation

Professor Laszlo Nagy, MD, PhD, head of the Debrecen Clinical Genomics Center, University of Debrecen, Debrecen, Hungary, talks about this award, which he received in 2008. **Page f119**



Awards: International Society for Heart Research, European Section/Servier Research Fellowship

Marta Roccio, PhD, postdoctoral fellow, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, talks about this award, which she received in 2007. **Page f120**



Professor Burnier (right) with Dr Qing Wang (left) and his key mentor, Professor Brunner (centre), at the meeting of the European Society of Hypertension in Glasgow, Scotland, in 1996. Professor Burnier says, "I have always been impressed by Professor Brunner's capacity to listen and support young fellows. He was a very positive person promoting the personal development of each individual working in his division and also pushing to go ahead with new ideas and hypotheses. He taught me all the important values of research—honesty, hard work, critical assessment of all observations, and essentially the respect of individuals. He was very supportive and provided me with the opportunity to gain competence in nephrology." Photograph courtesy of Professor Burnier.

Pharmacology, University Hospital of Lausanne. This resulted in Professor Burnier's first article in clinical pharmacology, and the beginning of "a long story on the development of blockers of the renin-angiotensin system with future studies on angiotensin receptor blockers and renin inhibitors."²

Professor Burnier explains, "I was involved in the clinical development of the first angiotensin-converting enzyme inhibitors after captopril, and participated in the early development of blockers of the renin-angiotensin system, with new therapeutic concepts evolving rapidly, not only in hypertension, but also in heart failure and chronic renal failure. This was a fantastic opportunity for me to develop my career, and all future research developments had their base in these early studies."

In the 1990s, Professor Burnier carried out the first study on the renal impact of drugs affecting the renin-angiotensin system.³ He considers this work to be among his most important, and says, "This study not only described for the first time the renal consequences of angiotensin II receptor blockade, but also demonstrated the uricosuric effects of losartan independently of the blockade of AT₁ (angiotensin-1) receptors."

"Salt Sensitivity of Blood Pressure is Due in Part to an Inability of the Renal Proximal Tubule to Handle Sodium"

During the early 1990s, Professor Burnier collaborated with Professor Biollaz to develop a technique to measure renal sodium handling more precisely in patients using the

technique of endogenous lithium clearance.⁴ The article demonstrated for the first time a misadaptation of the handling of sodium in the proximal tubule in hypertensive patients as well as in patients with white coat hypertension. Professor Burnier says, "With this approach, I developed the concept that salt sensitivity of blood pressure is due in part to an inability of the renal proximal tubule to handle sodium. Several studies were conducted to confirm this hypothesis, and we are still working on this aspect. These studies brought me to work on sodium and salt consumption as a determinant of blood pressure and hypertension. Our group became one of the reference centres for the investigation of the renal handling of sodium in humans. The work we did on developing the technique of endogenous lithium enabled us to create many international collaborations."

Professor Burnier also carried out experiments in this field with Professor Bernard Rossier, MD, from the Institute of Pharmacology, who worked on the epithelial sodium channel, which they cloned in Lausanne.

Since 2000, Professor Burnier and his team have collaborated with Professor Fred Paccaud, MD, PhD, and Professor Murielle Bochud, MD, PhD, from the Institute for Social and Preventive Medicine at the University of Lausanne. Professor Burnier says, "We have initiated several large epidemiological studies in the fields of hypertension and nephrology. These studies aim to understand the relationship between genetic parameters, salt consumption, renal function, and blood pressure." This work was conducted in the Seychelles with Dr P. Bovet, in Lausanne, and in collaboration with Professor Jan Staessen, MD, PhD, from the University of Leuven, Leuven, Belgium. The resulting article examined the association of CYP3A5 genotypes with blood pressure and renal function in African families.⁵ Professor Burnier says, "This study emphasises the importance of having a complete phenotype to study populations. Several other studies have been conducted since on the genetics of renal function and blood pressure." In 2007, Professor Burnier and Dr Bochud won the Sanofi Aventis Cardiovascular Research Award in Switzerland for their work on the genetics of hypertension.

Professor Burnier believes that it is essential to maintain the link between clinical practice and academic research. While working in the outpatient department of the university hospital, he realised drug compliance was an important issue in the management of hypertension for his



Team 2011. The clinical research team of the Service of Nephrology and Hypertension, University Hospital of Lausanne, Lausanne, Switzerland. From left to right: Professor Burnier, Dr Daniel Teta (who works on nutrition in chronic renal failure), Dr Menno Pruijm, Dr Bruno Vogt, Carole Zweigacker, Linda Guihard, Murielle Bochud, Dr Olivier Phan, Dr Olivier Bonny (who is working on renal stones and renal genetic diseases), Dr Marc Maillard, Dr Aline Chappuis, Dr Valentina Forni, Sylvie Tremblay, and Dr Grégoire Wuerzner. Missing from the photo: Dr Delaviz Golshayan (who works on tolerance in transplantation), Dr Anne Zanchi (who works on glitazones and the kidney), and Dr Qing Wang (who performs experimental studies on hypertension, cardiac hypertrophy, and the role of the inflammasome). Drs Vogt and Pruijm are leading the project on renal oxygenation using blood oxygen level-dependent magnetic resonance imaging. Professor Bochud and Drs Pruijm and Chappuis are conducting the genetic studies on hypertension and the Swiss Salt Study. Drs Wuerzner and Forni are conducting studies in hypertension and drug adherence. Drs Phan and Maillard are working on vascular calcifications in renal failure. Photograph courtesy of Professor Burnier.

patients. He developed research programmes to promote strategies to improve the monitoring of drug compliance and to support drug compliance in collaboration with pharmacists and the medical industry.

He explains, “The work in clinical pharmacology and the development of new drugs in hypertension was the trigger for my work on drug compliance. It became apparent that noncompliance was a major issue in the management of patients with chronic silent diseases, such as hypertension or chronic kidney disease. This is the main reason I developed the concept of measuring drug compliance in clinical practice using electronic monitors to support long-term drug compliance.”

Professor Burnier believes the team’s 2001 article in the *Journal of Hypertension*⁶ was crucial in demonstrating the importance of poor compliance in hypertensive patients with so-called resistant hypertension. He says, “The study emphasises the importance of measuring drug compliance in clinical practice in order to take good clinical decisions.”

“I Am Very Proud to See the Personal Development of My Collaborators”

As head of the service of Nephrology and Hypertension since 2004, Professor Burnier says, “My role is to promote research while maintaining a high quality of care in our nephrology and hypertension division.” He endeavours to apply the principles he learned from Professor Brunner—to “give everybody a chance to expand and develop him or herself either in the clinic or in research and at best in both domains.” He is keen to promote new careers in hypertension and nephrology and to develop an enthusiasm for research in all his staff, including physicians, nurses, and technicians. Alongside his clinical and research work, Professor Burnier teaches nephrology at the University of Lausanne, and enjoys explaining in a “simple and accessible way” a topic that is often perceived as a complex system.

Together with Professor Bernard Waeber, MD, chief of the Division of Clinical Pathophysiology at the University Hospital of Lausanne, Professor Burnier teaches students



Professor Burnier on a family walk on the Aletsch glacier in Valais, Switzerland. Professor Burnier lives in St L  gier, ~20 km from Lausanne. He is married to Marie-France, and they have 3 daughters. He says, "I must emphasise that my wife has been instrumental in the development of my career. Without her continuous support and understanding, it would have been impossible to reconcile an academic career and a family life. My present work implies a lot of travelling, and my family life has certainly suffered from these inconveniences." Away from medicine, his interests include music, reading, and playing basketball, although he adds, "My wife would say that my major interest besides medicine is medicine. It is almost a full-time job." Photograph courtesy of Professor Burnier.

about new therapeutic concepts in hypertension that have evolved since the early 1980s. He particularly enjoys the postgraduate teaching for physicians. He says, "It is a real pleasure to teach the new concepts to physicians and to be confronted with their questions and problems arising from their daily practice. Our clinical research has been nourished by the physicians' questions, and that is why we have developed a very practice-oriented clinical research."

Professor Burnier has always been happy with his work as long as he has been able to "ask questions and to organise studies to answer these questions." He says, "I spent a fantastic time in the United States entirely devoted to research, but I also enjoy the present very much. Today, I try to develop new careers, and I am proud to see the personal development of my collaborators who are becoming more competitive in research and have acquired the virus of research. I am glad that I can transmit to them all the enthusiasm and values I have received from my mentor."

A number of factors are challenging, in particular the financing of research. He explains, "Public funds are difficult to obtain, particularly for the development of clinical research. I have been lucky because Professor Brunner introduced me to his network of drug companies, with which we always had an excellent relationship. Institutional support is rather limited, and I fear that it will become more difficult in the future. I am increasingly concerned by the

administrative hurdles. I fear they will discourage young fellows." Professor Burnier's work is financed through industrial contacts, with 30% to 40% of the funds coming from the Swiss National Research Fund.

Professor Burnier is a council member and treasurer of the European Society of Hypertension, president of the Swiss Society of Nephrology, vice-president of the Swiss Society of Hypertension, and a fellow member of the American Society of Nephrology. He also participates in the French societies of nephrology and hypertension and sits on the editorial board of several journals.

Professor Burnier advises people who want a career in cardiology to "be determined and to decide early what they really want to do." He says, "Today, too many young fellows hesitate between clinical work and research. In our country, it is crucial that fellows dedicate time and effort to research, either clinical or experimental. This should be done early, possibly before clinical training. Thereafter, it is important to remain focused." He adds that it is important to build a specific research line and to follow it, as well as spend time in another country to be "confronted with different ways of doing medicine."

In the future, Professor Burnier plans to focus on the development and consolidation of the nephrology and hypertension service and to fight to maintain high standards in clinical research in cardiovascular medicine. With the development of new drugs in cardiovascular medicine decreasing, he says, "It seems that these days we have to do the best with what we have, and this why drug compliance and education of patients and physicians are so important for the management of cardiovascular diseases."

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Awards: European Society for Clinical Investigation Award for Excellence in Biomedical Investigation



“We Identified Some Lipids That Could Activate the Transcription Factor Peroxisome Proliferator-Activated Receptor Gamma, and Some Are Associated With Oxidised Low-Density Lipoprotein”

Laszlo Nagy, MD, PhD, professor of biochemistry and molecular biology, University of Debrecen, Debrecen, Hungary, head of the Debrecen Clinical Genomics Center, and International Scholar of the Howard Hughes Medical Institute, talks to Jennifer Taylor, BSc, MSc, MPhil.

The 2008 European Society for Clinical Investigation Award for Excellence in Biomedical Investigation (a cash prize of €10,000 for personal use) was presented to Laszlo Nagy, MD, PhD, professor of biochemistry and molecular biology, University of Debrecen, Debrecen, Hungary, head of the Debrecen Clinical Genomics Center, and International Scholar of the Howard Hughes Medical Institute, for his work on the molecular mechanisms in macrophage differentiation and foam cell formation, a critical step in atherosclerosis.

In 2 back-to-back articles in *Cell* in 1998, which have received >1000 citations each, Professor Nagy and his collaborators at the time, Professor Peter Tontonoz and Professor Ron Evans, showed that the transcription factor protein, peroxisome proliferator-activated receptor (PPAR) gamma, is expressed in macrophages and its activity is increased during foam cell formation.^{1,2} He also identified some of the targets, for example, the scavenger receptor CD36, which brings in low-density lipoprotein. He explains, “The reason it was so significant was that we identified some of the lipids that could activate the transcription factor to carry out its function, and some of these lipids are associated with oxidised low-density lipoprotein, which is believed to be one of the driving forces of atherosclerosis. The key is that the metabolic functions brought about by a lipid-activated transcription factor and macrophage component of the immune system have been linked.”

Professor Nagy has also linked PPARgamma to a unique immune function called lipid antigen presentation.³ The finding stimulated interest because he showed that PPARgamma is present and active in dendritic cells, where it regulates a set of molecules that help the dendritic cell to present lipid antigens, as opposed to protein antigens, and that initiates a unique and separate immune pathway.

Eligibility and Selection Criteria, and Award Procedure

The European Society for Clinical Investigation (<http://www.esci.eu.com>) was established in 1967 for clinicians and scientists with an interest in the mechanism of disease. The awards are restricted to biomedical investigators under 45 years of age of any nationality but residing in Europe at the date of the application deadline. The work must have clear relevance to the understanding, diagnosis, or treatment of

human disease, and a significant part of it must have been performed in Europe.

The recipient of the award is required to give a lecture on his or her work at the annual scientific meeting of the European Society for Clinical Investigation and to submit a review article to the *European Journal of Clinical Investigation* summarising the work for which the award has been given. Professor Nagy attended the annual meeting in spring 2008, which was held in Geneva, Switzerland, and gave a plenary lecture on the role of lipid-activated transcription factors regulating macrophage and dendritic cell function. His review article summarised research by himself and others on how macrophages and their intricate regulatory circuits lead to changes in gene expression, how the genome is regulated, and how this can contribute to foam cell formation and ultimately to atherosclerosis.⁴ He was later invited to join the journal's editorial board.

Professor Nagy believes that the award has helped him obtain funding from other sources because most European funders want to support scientists who have been recognised nationally and internationally. He says, “I think in smaller countries like Hungary, where the scientific establishment is a little bit inbred, outside recognition counts a lot.” He adds, “My university was pleased and used it as a publicity opportunity. I have been invited to talk about this to local and national newspapers.”

Professor Nagy is now on sabbatical at the Salk Institute in San Diego, CA, where he is learning new technologies to further his research on macrophages and dendritic cells.

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Awards: International Society for Heart Research, European Section/Servier Research Fellowship



“I Was Looking for Personal Grants That Would Allow Me to Work More Independently”

Marta Roccio, PhD, postdoctoral fellow, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, talks to Jennifer Taylor, BSc, MSc, MPhil.

Marta Roccio, PhD, postdoctoral fellow, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, received the International Society for Heart Research, European Section/Servier Research Fellowship in 2007. It provided €20,000 to cover her salary for 1 year of an 18-month postdoctoral fellowship.

A biologist by training, Dr Roccio completed her PhD on basic cancer research, cell biology, and signal transduction in the Department of Physiological Chemistry, University Medical Center Utrecht, Utrecht, the Netherlands. She then moved to the Department of Experimental Cardiology, at University Medical Center Utrecht as a postdoctoral fellow. She says, “I was looking for personal grants that would allow me to work more independently.” During the postdoc she worked with Pieter Doevendans, MD, PhD, professor and chief of cardiology at the University Medical Centre Utrecht (see <http://circ.ahajournals.org/cgi/reprint/117/6/f3>) and Marie-Josè Goumans, PhD. Professor Doevendans’ lab focused on the isolation and characterisation of human cardiac progenitor cells, and Dr Roccio had no specific background in the field when she applied for the fellowship.

The International Society for Heart Research, European Section/Servier Research Fellowship grant supports a cardiovascular research project within a European research group for a period of up to 1 year. It enabled Dr Roccio to investigate the role of chromatin modification on the differentiation of human cardiac progenitor cells towards the endothelial and cardiac lineage. She explains, “The currently used differentiation protocol is not ideal for in vivo clinical applications. We proposed to use compounds already used in the clinic for other applications, namely, histone deacetylase inhibitors, to modify and possibly induce myogenic differentiation.” These compounds were previously shown to induce differentiation in mouse embryonic stem cells.

The final data from the postdoctoral fellowship have yet to be published, but Dr Roccio has published findings from some of the preparatory work showing that it was possible to isolate cardiac progenitor cells from human fetal hearts as well as from adult human heart biopsies.¹

She and her fellow researchers previously expanded and differentiated cardiomyocyte progenitor cells in vitro into cardiomyocytes and endothelial cells and published their findings in 2008.² That same year, Dr Roccio published a review on the field of cardiac stem cells and cardiac regeneration.³

Eligibility and Selection Criteria, and Award Procedure

Dr Roccio says that the application process for the Research Fellowship was “very easy.” To meet the eligibility criteria, she had to be <35 years of age and a member of the International Society for Heart Research, European Section at the time of the application (see <http://www.ishr-europe.org>). It was stipulated that her doctoral thesis should be completed before the International Society for Heart Research, European Section annual meeting and that she should be available to attend. “The fellowship gave me the opportunity to join the annual meeting, all expenses covered, and to present the project plan in the opening ceremony,” she says. “1 year later, at the completion of the grant, I was invited by Servier in Paris, France, to give a presentation about my work and treated at one of the best restaurants in town.” When Dr Roccio’s project was completed, she was invited to the International Society for Heart Research, European Section annual meeting to present her findings to a broad international audience. She has now moved to Lausanne for a second postdoc.

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