Many ISHR activities towards achieving our Society’s stated mission, “To promote the discovery and dissemination of knowledge in the cardiovascular sciences on a world-wide basis through publications, congresses and other media”, are reliant on the support of external sponsors. In this regard, we have been very fortunate indeed to receive continuous sponsorship from SERVIER towards publishing *Heart News and Views* since 1999, in the form of an annual unrestricted educational grant. SERVIER’s dedication to scientific endeavor is reflected not only by the company’s investment in research (as much as 25% of turnover, one of the highest figures in the pharmaceutical industry) but also by a policy of friendly cooperation with the international research community, including the ISHR. In this issue, we would like to take the opportunity to thank SERVIER, and Dr Laurence Alliot (SERVIER’s Director of Medical Affairs) in person, for their unwavering support, in sponsoring our newsletter as well as a variety of ISHR meetings and awards. These are undoubtedly difficult times for the world economy, including for the pharmaceutical industry, which makes us appreciate even more the true value of such loyal support.

The unique position of the ISHR is as an international organization linking basic cardiovascular scientists. Our triennial meetings are a high point in the calendar, where all the Sections come together to have excellent and intense discussions about our latest research in progress. We particularly aim to choose locations which benefit each Section in turn, and to have a geographically diverse range of speakers in each symposium. In the years between these events, the Sections keep the ISHR ideals alive in their own yearly meetings. However, each Section operates against a different background at home where they compete or cooperate with national societies. Basic science is already at a disadvantage compared to clinical cardiology conferences when seeking sponsorship. As the number of meetings grows, and the pool of sponsors gets smaller and less munificent, the Sections fight to find the best way to preserve their solvency as well as identity.

In this article I would like to discuss the challenges that face the European Section (ISHR-ES) particularly, and one initiative that is still in its experimental stage – the “Frontiers in Cardiovascular Biology” (FCVB) meeting. I always feel that the ES is microcosm of the International society, because of the number and variety of constituent...
Our biggest challenge has always been the relationship with the European Society of Cardiology (ESC). This behemoth now hosts the largest cardiology meeting in the world, with over 30,000 participants at each annual conference in the last decade. The ESC annual conference itself is clearly at the opposite end of the spectrum from the ISHR section meetings, with its clinical focus and busy, crowded atmosphere. It is enjoyed by our clinician scientists but rather overwhelming for young scientific Ph.D. students. The ESC has also generated a number of specialist societies of which some, like the Heart Failure Association and various Working Groups, have many common interests and common members with the ISHR. Once again, we have a tradition of joint meetings and sessions with these societies. The question about the unique identity and purpose of the ISHR-ES within this network is one that continually exercises us.

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In this issue we introduce a new series of articles entitled “Section Beat”. These articles will be written by the Officers of the seven ISHR Sections, and will address current challenges and successes experienced by the Section leadership. The goal is to provide a forum to augment sharing and communication between our Sections.

We are privileged to begin our series with a thoughtful article by Prof. Sian Harding, Professor of Cardiac Pharmacology at the National Heart and Lung Institute, Imperial College, London, and Past-President of the European Section. Dr Harding has written an insightful commentary on the complex relationship between basic science research societies in Europe, and the role of the ISHR-ES in this milieu.

We are grateful to Dr Harding for this thought-provoking look at basic research in Europe, and we look forward to similar informative articles from the leaders of our other Sections as the series continues.

Leslie Anderson Lobaugh
Editor HN&V

In a further effort to give basic science a prominent role, the ESC set up in 2004 the Council on Basic Cardiovascular Sciences (CBSC), and has provided it with a budget to “enhance the importance of basic science to clinical cardiology”. Members again include the ISHR as well as other similar non-ESC Sister Societies such as the EVBO,
and the Working Groups of the ESC such as Cellular Biology and Electrophysiology. In all, 14 societies and Working Groups are represented. This Council has put in place initiatives like the CBSC Poster Reception, to draw scientists together at the ESC annual meeting in an evening event, and the Summer School, where trainees spend intensive time with senior scientists as a way to develop their careers. A further vision that developed during many hours of discussion was the possibility for a pan-European basic cardiovascular science meeting. Many of the Working Groups and Sister Societies, like the ISHR-ES, had a similar ideal structure to ISHR for their own meetings: science in progress, rather than didactic summaries; a central role for trainees to share a platform with established scientists; lengthy poster slots; time for discussion and networking in an informal atmosphere. Many already held joint meetings between themselves and many were struggling with similar financial and logistic problems to the ISHR.

The first “Frontiers in Cardiovascular Biology” meeting experienced some successes then, and cautious optimism for future meetings

So, the idea of “Frontiers in Cardiovascular Biology” was born. It was to be a forum in which the newest and best developments in basic science were presented; where integrative interests united cardiac and vascular researchers and where novel technologies were brought in to be applied to cardiovascular research. It would operate to the ideal structure described, and all points would be decided by a Committee with representatives of every Working Group and Sister Society. The ESC Board was encouraging and pledged the help of their impressive management structure. For the first meeting, all agreed to minimize the identities of their individual societies: suspending their usual yearly meetings and attempting to find new speakers and integrative subjects. It is fair to say that the ISHR-ES were leaders in the commitment to FCVB. In 2010, the year planned for the first FCVB, our International Congress was in Kyoto in early May. The ISHR-ES, like all Sections, was to sponsor symposia and hold their Section events at this meeting.

For this initiative to succeed, we must eliminate the possibility of it being a small, untried venture that no one would care about. The ES Council has been very concerned as to whether the identity of the ISHR-ES can survive such infrequent and traditional meetings, and that is a real risk. On the other hand, the strong anchor provided by the International ISHR is a protection against the changing fortunes of the Sections. The next FCVB meeting is in London in March/April 2012 and as Conference Chair I am in a good position to uphold the interests and ideals of the ISHR members, even if our identity appears to be diminished.

One particular hurdle for the FCVB is the periodicity of the meetings, which are planned for alternate years. For a society with a regular annual meeting, the loss of one year in two still allows for continuity of its own schedule. For the ISHR-ES, with the additional International meeting, we have a situation where 3 years can pass before a conventional stand-alone Section meeting. The ES Council has been very concerned as to whether the identity of the ISHR-ES can survive such infrequent and traditional meetings, and that is a real risk. On the other hand, the strong anchor provided by the International ISHR is a protection against the changing fortunes of the Sections. The next FCVB meeting is in London in March/April 2012 and as Conference Chair I am in a good position to uphold the interests and ideals of the ISHR members, even if our identity appears to be diminished.

Can this initiative survive, and can it fulfill its aim to reduce the number of meetings by supplying its constituent societies with everything they need? When the Societies/Working Group representatives discussed this with their members they realised that some things must change. The ban on other society meetings during the year should be lifted, and the individual identities of the societies should be allowed to increase in prominence. We decided not to expand the size too greatly, in case we spoil the friendly atmosphere.

Professor Sian Harding
Past-President of the European Section
London, UK
A Lesson from the HeLa Cells

Today’s newspaper said that in January of this year it was 60 years since HeLa cells were descended from a 30 year old female patient with cervical cancer at the Johns Hopkins University Hospital. Dr George Gey first succeeded in establishing a human cell line from these cells, named HeLa cells after the patient, Henrietta Lacks. Before this coup, many investigators had tried to culture human cells; however, they did not succeed. HeLa cells were distributed widely to investigators around the world, and to date, a total of 50 million tons of HeLa cells have been cultured and more than 65,000 papers have been published about research done on HeLa cells. It is also well known that HeLa cells were used by Jonas Salk to test the first polio vaccine in the 1950s.

In normal human cell cultures, cells can be passaged to their Hayflick limit, but the cells died thereafter with an incremental shortening of telomeres. Many people misunderstand that HeLa cells are proliferative because of their cancer cell origin. Unfortunately, primary culture of cancer cells often fails, especially with cells of epithelial origin. This is a surprise for cardiologists and vascular biologists, since the primary culture of either cardiomyocytes or vascular smooth muscle cells is not difficult. In contrast, for oncologists, it is well known that primary culture of cancer cells is not possible in most cases, and thus, subcutaneous transplantation in immunodeficient mice (xenograft tumor) is necessary to propagate cancer cells.

Recently, however, my colleagues at our institute have succeeded in the primary culture of colorectal cancer cells (PNAS 2011, online http://www.pnas.org/content/early/2011/03/22/1015938108.full.pdf+html). The secret of the art lies in maintaining the cell-cell contact during cell preparation. In the conventional primary culture of cancer cells, the cells are dissociated into single cells and immediately dispersed on a culture plate, as most isolated cancer cells rapidly die through apoptosis when cultured in suspension. In contrast, the organoid fraction, clusters of the tumor cells that form spherical structures during overnight suspension, turned out to be entirely composed of cancer cells. We named this spheroid fraction “cancer tissue-originated spheroids (CTOS).” CTOS are composed of EpCAM positive cells, and do not include contaminating fibroblasts, vascular smooth muscle cells or macrophages. CTOS grow to 40 – 500 µm in diameter and passage is possible by mechanically breaking the spheroid into small pieces. CTOS can generate xenograft tumors in immunodeficient mice. It is amazing that CTOS preserve the characteristics of the parent tumor even after a number of passages. In CTOS, cell-cell contact is tightly connected with E-cadherin. Antibodies against E-cadherin can dissociate CTOS into individual single cells, in which apoptotic signaling, e.g. caspase-3 and PARP, is quickly activated and apoptotic cell death is induced, mimicking “anoikis” often observed in the cells detached from a matrix. This indicates that cell-cell contact is crucial for cancer cell survival, and this may be an essential condition for survival of the epithelial cells.

Myocytes and vascular smooth muscle cells are of mesoderm origin. In these cells, E-cadherin is minimally expressed and cell-cell contact is not tight. Myocytes and vascular smooth muscle cells are contracting or migrating, and this plasticity may be a characteristic of these cells. Malignant tumors derived from smooth muscle are called sarcoma. It is interesting that sarcoma cells can be cultured in isolated cell form. Given the hypothesis that cancer cells of epithelial origin cannot survive in isolated conditions as single cells, whereas mesoderm derived cells can survive even under isolated conditions, we can understand that cancer cells need cell-cell contact for survival as a cluster of the cells. HeLa cells may have lost the characteristics of epithelial cells, probably due to genetic alterations associated with papilloma virus infection. HeLa cells opened a new era of culturing cancer cells but in return lost a very important characteristic: the cell-cell communication of epithelial cancer cells. Cancer is the most dreadful killer of elderly people, comparable to cardiovascular disease. A lesson from the HeLa cell and CTOS will provide us with a new paradigm for cell culture of cancer and teach us the biological significance of cellular community.

Masatsugu Hori, M.D., Ph.D.
President ISHR
Richard Bing was a man of great vision and many talents. Born in Germany on October 12, 1909, he died on November 8, 2010 at the age of 101, and his unique talents gave rise to obituaries in both The New York Times and The Los Angeles Times. Although I have had the privilege of training under two Noble Prize winners and knowing two more, none have been as multi-talented as Richard. He was scientist, cardiologist, musician and novelist, all rolled into one. He once weighed up careers in Academic Medicine versus Music and reluctantly put music into second place. His novelettes appeared much later. His early academic fame came from his discovery in 1954 that fatty acids are the major fuel of the human heart as shown by the trans-myocardial extraction of cardiac fuels using his new technique of coronary sinus catheterisation. Among his many other academic achievements, he also pioneered studies of nitric oxide and blood flow in the human heart.

His leading role in the early evolution of what was to become the International Society for Heart Research deserves emphasis. In 1967, Richard chaired a group of eminent clinical and laboratory cardiovascular workers who met at Schloss-Lieberg in Germany to discuss the impact of the rapidly expanding new knowledge of the heart muscle, including its metabolism. Of those who were there, Bajusz, Jennings, Rona and Schwartz among others helped to start up the International Study Group for Research in Cardiac Metabolism. There were two proposed sections, North American and European. I was then working in the Chain lab in London, and was invited to the nascent European Section meetings in Dubrovnik in 1968 and later on the shores of Lake Garda, in Gargnano, Italy, in 1969. Richard Bing was nominated and elected as the first president of the International Study Group for Research in Cardiac Metabolism (ISGRCM) in 1969.

Being born in Germany and having studied Medicine in Switzerland and thereafter migrating to the USA, he had the ideal broad background to bring together the views of the European and American Sections. In the next year, 1970, he presided over the first International Meeting held in Stowe, Vermont. He continued to guide the Study Group till 1973 when he gave the Presidential Address to the European Section, then meeting in Freiburg. He was badly heckled, and then in a few swift replies, he verbally put the heckler in his place. He was elected as Lifetime President of the Study Group organization which in 1978 became the International Society for Heart Research (ISHR) at the meeting in New Delhi. There he played a recording of part of his Requiem Mass to the general acclaim of all. Overall, Bing produced more than 300 works for chamber ensemble, orchestra and chorus, working closely with the composer Carl Orff (The New York Times).

An important step in the evolution of the ISHR was the creation of a new Journal. In 1969, I was invited to be Co-Editor with Richard. Thus, the Journal of Molecular and Cellular Cardiology was born with its first issue in 1970. With Bing as Senior Editor and Sir Hans Krebs coming in later as Chief Consulting Editor (both escapees from Nazi Germany), articles flowed in and the journal flourished. Bing saw the big picture; I saw the detail and the combination worked.

Much more recently, and in his 90s, Richard appeared to value my opinion on his novelettes as they appeared. “Fifteen Lives and the Cat’s Story” was sent to me in 2004 with the inscription: “To my friend Lionel”. These stories, each in a different way, bore a relationship to Bing’s progression as physician and scientist, and his new avocation as a writer. Writing was his fourth career, upon which he successfully embarked in his late 80s and 90s, the other three careers being Scientist, Cardiologist, and Musician. For many years he wrote a column entitled “Past Truth & Present Poetry” for Heart News and Views, the news bulletin of the International Society for Heart Research. In his Finale in 2010 at age 101, he summarized the achievements and several disappointments of his life: “Foremost there were the pleasures of living, of seeing the world’s beauty, its lakes, mountains, stars, laughter and tears”. What an all-rounder he has been.

Richard was always creative, whether in metabolism of the heart or choral music or novels, thus being by far the most multi-creative person I ever had the privilege of knowing and working with.

Lionel Opie

Professor of Medicine and Director Emeritus of the Hatter Institute for Cardiovascular Research
University of Cape Town
Robert B. Jennings, M.D.

Inaugural Recipient of the ISHR Distinguished Leader Award (2009)

Dr. Jennings is Emeritus James B. Duke Professor of Pathology at Duke. He retired from the chair of Pathology at Duke in 1989 and continued active experimentation until he closed his laboratory in 2000. He has published several recent papers on work done earlier but never written up.

Dr. Jennings’s association with the ISHR began in the late 1960s when he became a member of a committee named “the International Study Group for Research in Cardiac Metabolism” formed by George Rona, Richard Bing, and Eörs Bajusz. This committee was formed as a reaction to the emphasis placed by the American Heart Association on hemodynamics and electrocardiography. Metabolism, mechanisms of contraction, genetic diseases, ultrastructure, ischemic injury, Ca overload, etc. were all uncommon topics in AHA publications and generally were not discussed at heart meetings. This committee arranged meetings in Europe and the USA where investigators with similar scientific interests could meet and discuss their work. Eventually, under the leadership of Naranjan Dhalla, Lionel Opie, and Richard Bing, the International Association of Heart Research was formed as a loosely organized Society composed of scientists from around the world who met to discuss cardiovascular research topics of interest to them. In 1973, the Society held an excellent meeting in Freiberg, Germany arranged by Albrecht Fleckenstein. In 1978, the Society held a meeting in New Delhi following the World Congress of Cardiology in Tokyo. At this meeting, Jennings became the President-Elect of the ISHR.

It was clear that the Society could prosper only if it had bylaws to govern its operations and the relationships between the international sections of the Society. Using the bylaws of the International Society of Nephrology as a model of how to organize a confederation of international societies, Dr. Jennings prepared a draft of bylaws for the ISHR. Howard Morgan helped write and edit the final version, and in 1980 the bylaws were presented and approved at the Moscow Congress of the ISHR. Since that time, the Society has been functioning in an orderly fashion. The Secretary General of the Society is the most critical officer because most actions take place through this office. This individual is responsible for holding the Sections together and for keeping the ISHR-International operating between triennial congresses.

Following the new bylaws, Dr. Jennings served as President for only two years and as Past-President for three years. He continues to be active on a variety of Committees, has arranged symposia at various Congresses and attended many of the Congresses of the Society. In Kobe in 1993, he was awarded the Peter Harris Distinguished Scientist Award for excellence in cardiovascular research. In 1996, he was named Chairman of the newly formed Finance Committee of the Society. A finance committee became necessary when Drs. Dhalla, Morgan and Makoto Nagano raised US$300,000 to support

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The ISHR Distinguished Leader Award is an award of high distinction that is conferred annually, beginning in 2009, to an individual who has made sustained outstanding contributions to accomplishing the mission and advancing the objectives of the ISHR.

The selection of the recipient is made solely on the basis of a distinguished and consistent track record of major contributions to the Society, such as leadership roles, activities, and initiatives that have benefited and promoted the ISHR by overcoming problems, developing new programs, and expanding the reach and impact of the Society at the Section and/or the International levels.

Candidates are nominated by current Section Presidents and President of the Int'l-ISHR. Details of the competition are available on the ISHR website (www.ishrworld.org) under the ISHR Awards tab.
EDWARD G. LKATTA, M.D.

2010 RECIPIENT OF THE ISHR DISTINGUISHED LEADER AWARD

Dr LKATTA is the founder and Director of the Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health. He also holds adjunct appointments as Professor, Department of Physiology, University of Maryland School of Medicine, and Professor, Cardiology Division, Johns Hopkins School of Medicine.

Dr Lakatta was recently awarded the prestigious 2011 Distinguished Leader Award of the International Society for Heart Research (ISHR) at XX World Congress of the ISHR in Kyoto, Japan for his sustained and outstanding contributions to advancing the objectives of the Society. Over the years, Dr Lakatta has been both a leader and advocate for the ISHR. He served for many years on both the International Council and the North American Section Council, and chaired the Scientific Program Committees for the successful ISHR World Congresses held in Rhodes, Greece (1998) and Brisbane, Australia (2004). In addition, he has published more than 50 papers in the Society journal, the Journal of Molecular and Cellular Cardiology. During his career, Dr Lakatta has placed particular emphasis on mentoring early-career scientists both in his laboratory and in the context of career development activities of the Society.

Dr Lakatta has made a sustained 30-plus-year commitment to a broad-based research career. His studies range from molecules to humans, including translation of novel findings into the clinical realm. The overall goals of his research program are 1) to identify age associated changes that occur within the cardiovascular system and to determine the mechanisms for these changes; 2) to determine how aging of the heart and vasculature interacts with chronic disease states to enhance the risk for CV diseases in older persons; 3) to study basic mechanisms in excitation-contraction coupling and how these are modulated by surface receptor signaling pathways in cardiac cells; 4) to elucidate mechanisms of pacemaker activity in sinoatrial nodal cells; 5) to elucidate mechanisms that govern cardiac and vascular cell survival; 6) to establish the potentials and limitations of new therapeutic approaches such as changes in lifestyle, novel pharmacologic agents or gene or stem cell transfer techniques in aging or disease states.

Dr Lakatta is recognized as both nationally and internationally as an expert in cardiovascular research. He has authored over 350 original publications in top peer-reviewed cardiovascular journals, written over 200 invited reviews/book chapters, and delivered over 300 invited lectures. He is a member of multiple scholarly societies and journal editorial boards. Based upon his accomplishments, Dr Lakatta has received numerous awards, among which are the Allied Signal Achievement Award in Aging, the Novartis Prize in Gerontology, and the Irving Wright Award of Distinction of the American Federation for Aging Research (AFAR).
Adelaide once again provided a picturesque backdrop for the ISHR Australasian Section Annual Scientific Meeting held jointly with the Cardiac Society of Australia and New Zealand (CSANZ). Discussions on the latest trends in cardiovascular research were complemented by lovely food and wines native to the region showcasing the best South Australia has to offer. A comprehensive high calibre scientific programme featuring international and national world class speakers from a range of fields, poster wine-and-cheese sessions, and challenging mini-oral (3 min!) presentations, ensured a successful, highly informative meeting.

The prestigious RT Hall Lecture was delivered by Kenneth Chien (Massachusetts General Hospital Cardiovascular Research Center). Ken inspired us with his entertaining talk titled “How to make a heart: towards regenerative cardiovascular stem cell therapeutics”, in which he discussed challenges associated with the translation of stem cell biology into stem cell therapy. Shaun Jackson (Monash University) delivered the Basic Science Lecture, titled “Impact of disturbed blood flow on platelet thrombus formation”, presenting an overview of recent advances in our understanding of how platelets aggregate to form thrombi through the restructuring of membrane tethers.

We were particularly delighted to have two prominent ISHR scientists from the US contribute to the Basic Mechanisms stream. Roberta Gottlieb (San Diego State University) gave us an overview of autophagy in cardiovascular biology and disease, while John Solaro (University of Illinois College of Medicine) offered insights into the chemomechanical workings of sarcomere contraction. These talks complemented the impressive program of presentations by Australasian researchers, covering a range of topics including cardiac stem cell biology, sarcomere and cytoskeletal dysfunction, mitochondrial transduction, cardiomyocyte calcium stores, cardiomyocyte growth and death, and cellular substrates of arrhythmia and failure. Both John and Roberta took time out of their busy schedules to offer advice to students and early career scientists in a workshop focusing on a strategic approach to publishing papers and navigating the journal review process.

The ISHR Australasian Section places great emphasis on providing opportunities for early career scientists to present their research. This year’s ISHR Student Investigator finalists were Karina Huynh (Baker IDI Heart and Diabetes Institute), Lavinia Tran (Monash University), Yang Liu (Baker IDI Heart and Diabetes Institute) and Kanchani Rajopadhyaya (University of Adelaide), who all gave excellent presentations and were grilled with questions by the supportive and enthusiastic audience. Congratulations to Kanchani for her winning presentation titled “Endothelin-1-mediated vasoconstriction involves rapid and sustained protein kinase C and Rho kinase activation: potential therapeutic strategies for management of microvascular vasoconstriction”. Perhaps the most social of the student presentations were the poster sessions, which were held in the evenings over cheese and some very special South Australian wines. The judges...
once again had a difficult time choosing a winner from an overall high quality field, but after some spirited debate they ruled in favor of Bryan Wai’s (University of Melbourne) poster titled “E/e’ is an independent predictor of heart failure admission in patients with type 2 diabetes mellitus”. Congratulations to Bryan and all who presented. The final format on showcase at this year’s conference (and in this author’s opinion, the most terrifying) was the mini-oral presentation sessions. The mini-oral format encourages presenters to communicate their research concisely and effectively, a skill that is essential in modern research. This year’s top student communicators were Kimberley Mellor (University of Melbourne) for her talk “Autophagy is upregulated in hearts of insulin resistant mice” and Kate Weeks (Baker IDI Heart and Diabetes Institute) who presented “Cardiac-specific deletion of Foxo1 causes heart dysfunction in mice”. Congratulations to all the winners and our sincere thanks to ISHR Councilor Igor Wendt for once again taking on the challenge of organizing the judging and awarding of student prizes – and thank you to the team of judges who assisted with this important task.

We had a new prize category this year, Postdoctoral publication prize for the best original research paper published during the first 5 postdoctoral years, awarded to Freya Sheeran (from Salvatore Pepe’s group at the Murdoch Children’s Research Institute, Melbourne, Australia). Her publication: Diminished NADPH trans–hydrogenase activity and mitochondrial redox regulation in human failing myocardium (Biochim Biophys Acta 2010; 1797: 1138-48), is the first to quantitatively demonstrate nicotinamide nucleotide transdehydrogenase expression and activity in the human heart and its dysfunction in chronic human heart failure.

A lively Annual General Meeting (AGM) was held on Friday night, at which Lea Delbridge (President), David Saint (Secretary) and Julie McMullen (Treasurer) summarised the Australasian Section’s activities over the past year. The AGM was followed by a magnificent dinner at the Balcony Restaurant in the Strathmore hotel. Dinner at the Strathmore is fast becoming a tradition for Adelaide meetings!

Finally, a vote of acknowledgement and appreciation to all involved on the Local Organizing and Scientific Program Committees led by Omar Farouque and Jonathan

(continued on page 11)
The Latin American Section of the International Society for Heart Research (ISHR) held its XVIII meeting on the campus of the School of Medicine of the University of La Plata. The aim of the organizing committee was to offer basic scientists, clinical cardiologists, fellows, interns and students a meeting of the highest possible scientific quality and to encourage the active participation of the young members of our section.

This year’s meeting was really unique in many ways. Firstly, because we had truly regional attendance. We had delegates not only from Buenos Aires and La Plata, but also from the provinces of Cordoba, Santa Fe, Mendoza, and from neighboring countries such as Chile, Brazil and Uruguay. Secondly and sadly, the day before the meeting, the death of the Ex-President of Argentina, Néstor Kirchner, was announced, and the country was in National Mourning. This was not a simple obstacle for the organizing committee, given that the National University of La Plata, where the meeting would take place, was officially closed. Fortunately, after several hours of expectation and extreme stress, the Dean of the School of Medicine, Dr Jorge Martinez, agreed to take extraordinary measures and enabled the facilities and personnel in order to allow the meeting to take place as planned, a gesture for which we are very grateful.

This year’s scientific program was also unique. We had four symposia each with four invited speakers, and at the end of each symposium there was a presentation of a selected abstract on the topic of the symposia, given by a young investigator. The symposia were thematically diverse, ranging from calcium and arrhythmogenesis, to the heart as a source and target of the endocrine system, and from mitochondrial metabolism in heart disease to the more autochthonous theme of Chagasic myocarditis. There were also three sessions of oral presentations of abstracts and a special session for the Young Investigator Award (YIA) competition. These sessions were very fruitful because they provided a great opportunity for young researchers and fellows to present their work, often for the first time, to a large and qualified audience. We were delighted to see that lively, stimulating and provocative discussions were a common feature of all these sessions. The YIA deserves a special mention: Seven abstracts were presented and the judges (Drs Nidia Basso (Buenos Aires), Paulina Donoso (Chile) and Rosana Bassani (Brazil)), found all of them to be of exceptional scientific quality. In the end, the judges unanimously agreed that the work titled “TRH promotes myocardial damage in rodents”, presented by Dr Mariano Schuman, was most deserving of this year’s prize.

Other highlights of the meeting were the opening and closing lectures, delivered by our special guests, Drs Xander Wehrens and Brian O’Rourke. Xander enlightened us with his talk on the novel roles of junctophilin in the heart, and Brian revealed new mitochondrial mechanisms that underlie sudden death. This year’s meeting was also innovative from the technological point of view. For the first time we held a real-time video conference with Dr Burns Blaxall from the University of Rochester Medical Centre. Burns gave an exceptional talk on new strategies to target heart failure.

The social events of the meeting were no less important. These included a welcome cocktail where we enjoyed, in a relaxed atmosphere, the taste of a traditional Argentinean Malbec wine elegantly
combined with local delicatessen, and a closing ceremony were the winner of the YIA prize was announced and we had the enormous pleasure of hearing the Tango Orchestra called “Pure Strain” (which, we are proud to say, is led by a member of the LAISHR, Dr Eduardo Escudero).

We are extremely happy because we believe that this year’s meeting of the Latin American Section was truly outstanding and met all of its goals, as outlined in the bylaws of the ISHR. The meeting was extremely busy - there were over 150 attendees, new members were added to the roster, there was a vibrant forum for discussion of cutting edge cardiovascular science, and our most important initiative, to encourage the participation of young investigators, was accomplished and exceeded our expectations.

We look forward to organizing the next annual meeting of the LAISHR to further position our society as the most important cardiovascular basic research association in Latin America, and to give our members a fertile environment for learning, discussing and promoting cardiovascular science. We also wish to remind all members of the ISHR that in 2016, the World Congress of the ISHR will be held in Buenos Aires. We look forward to being your hosts and giving you the “Buenos Aires Experience.”

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**Dr Martin Vila Petroff**
Chairman, 18th Annual Meeting of the Latin American Section
President ISHR, Latin American Section
La Plata, Argentina

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(continued from page 9)

**THE AUSTRALASIAN SECTION**

Kalman – especially recognizing the major input from Lea Delbridge and Julie McMullen, our ISHR council delegates. Many hours of planning work turned into an exciting meeting that was over in a flash.

David White
Kate Weeks
Helen Kiriazis

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You are welcome to join us at the 2011 ISHR AUS-Section Meeting (joint meeting with CSANZ)

August 11-14, 2011
Perth Convention & Exhibition Centre
Perth, Australia

Details can be found at:
www.csanz2011.com
It was an immense honor and opportunity for me to be awarded the prestigious ISHR-ES/SERVIER Research Fellowship in May 2009 in Nice. In 2008, after my post-doctoral fellowship at Johns Hopkins Univ Sch of Med (Cardiology), I joined the Dept of Clin Med, Cardiovascular and Immunological Sciences directed by the late Prof Chiariello, at Federico II Univ, Naples, Italy. The ISHR Fellowship provided essential support that allowed me to continue with my career in Italy, and in September 2010 I started my own lab in the Div of Cardiol directed by Dr Maurea at the National Cancer Inst, Sen. Pascale Foundation, Naples, Italy. Thanks to the ISHR-ES/SERVIER Fellowship, I continued my studies of nitroxyl (HNO) as a modulator of myocardial function, characterizing possible sources of HNO in cardiac myocytes, further dissecting its actions on specific targets in the EC-coupling machinery. Our studies formed a core piece of data for a patent submission, and were the basis for the development of a new HNO donor, CXL-1020 (synthesized by the recently founded company, Cardioxyl Pharmaceuticals, Durham, NC), which preliminary studies have shown to be effective in both normal and failing murine myocytes. Cardioxyl is pursuing the clinical application of a novel HNO donor for treating human heart failure, and has tested their pharmaceutical in humans, completing initial Phase IIa studies.

Nitroxyl (HNO/NO−) is the one-electron reduction product of NO. Under physiological conditions it is present in its protonated form, HNO. Even though the first HNO donor, Angeli’s Salt (AS), was synthesized by the Florentine chemist Angelo Angeli more than 100 years ago, HNO has not been extensively studied (unlike NO). It has been shown that HNO can be generated in vitro by a variety of cellular systems. For instance, nNOS can generate HNO in the absence of its cofactor, BH4, or under nitrosative and oxidative stress 9.

Nitroxyl Enhances Heart Function in vivo
We showed that AS was able to improve contractility in vivo, lowering preload as well. Specifically (Fig 1A-B), the pressure-volume (PV) loops showed that the end-systolic pressure-volume relation (ESPVR) was shifted to the left, with an increase of the end-systolic elastance (Ees, a parameter of cardiac contractility), and a parallel decrease of the left ventricular end-diastolic dimension (LVEDD), throughout the whole infusion time 11. These effects were independent from beta-blockade, but redox sensitive, since they were blunted by the concomitant infusion of N-acetyl cysteine (NAC), and importantly, were also present in failing hearts, which are well known to be desensitized to beta–agonists 10.

Nitroxyl is a Modulator of Myocardial Function in Normal and Diseased Cardiac Myocytes

Figure 1
Nitroxyl increases contractility and relaxation in vivo and in vitro. (A) Representative PV-loops in a conscious dog showing the effect of HNO infusion. (B) Ventricular contractility (Ees, slope of the left ventricular pressure-volume relation) rose rapidly and markedly and remained elevated throughout drug infusion. Also, there was a rapid decline of left ventricular preload (LVEDD, left ventricular end-diastolic dimension) that remained elevated throughout drug infusion. (C) Dose-response effect of AS/HNO and DEA/NO on cell shortening. *p<.001 vs control, **p<.0005 vs control. (D) AS/HNO effects on myocyte relaxation (time to 50% relaxation).
Nitroxyl Enhances Contractility in Isolated Normal Mouse Myocytes

To establish whether HNO directly primed myocyte contractility, we infused freshly isolated normal murine cardiomyocytes with AS. AS significantly increased contractility in a dose dependent manner, and this effect was not reproduced by equimolar doses of an NO donor (DEA/NO), that we used to discriminate between HNO and NO effects (Fig 1C). Also, since nitrates can be generated from the decomposition of AS, we tested sodium nitrite (NaNO2) at comparable doses, which showed no impact on myocyte contractility. Also, HNO exerted lusitropic effects, shortening myocytes relaxation time (Fig 1D). AS exerted its effects independently from cAMP/PKA and cGMP/PKG pathways, but such effects were redox sensitive, and were blunted after incubating the cells with the reducing agent GSH.

To further dissect AS mechanisms, we recorded single RyR2 in lipid bilayers: the addition of AS produced a dose dependent activation of the open probability of the channel, and this effect was blunted upon addition of the reducing agent DTT. Together with such activation of the RyR2, we observed concomitant faster kinetics of SERCA2a with HNO, with a general enhancement of Ca2+ cycling. As a result, Ca2+ sparks frequency and Ca2+ transients were increased with AS in a dose-dependent and redox-sensitive manner. Interestingly, Ca2+ cycling in the SR was improved with AS, without the recruitment of extracellular Ca2+ through the L-type Ca2+ channels.

We then tested whether activation of SERCA2a by HNO required the presence of phospholamban (PLN), and, if so, whether the HNO-induced increase in pump activity resulted from modifications of thiols (cysteines) in the trasmembrane domain of PLN. We found that HNO did not change Ca2+ transient amplitude, Ca2+ transient decline, or caffeine-induced SR Ca2+ release in myocytes isolated from PLN−/− mice (kindly provided by Dr Kranias, Univ of Cincinnati, OH, USA). However, in PLN−/− myocytes AS could produce a blunted, but significant, increase in fractional shortening, likely due to the previously described HNO-evoked myofilament Ca2+-sensitizing effects. We also showed that SERCA2a activation by HNO is PLN-dependent: SERCA2a coexpressed with PLN lacking cysteines could not be activated by HNO, pointing to thiol reactivity with HNO and potential disulfide bond formation.

Is Nitroxyl Endogenously Generated?

In vitro data show that HNO can be generated by heme protein-mediated peroxidation of hydroxylamine (NH2OH, a molecule produced during catalytic turnover of NOS). We hypothesized that cardiomyocytes utilize H2O2 (an endogenous signaling molecule) to oxidize NH2OH in the presence of heme proteins (i.e. myoglobin) to generate HNO, effectively enhancing cardiac function. Neither H2O2 nor NH2OH alone produced a significant change in myocytes fractional shortening (FS). Conversely, when added together (10 minutes), they significantly increased FS and Ca2+ transients. In TAC hearts, echo measurements showed significantly enlarged LVES diameter and FS decrease. Moreover, TAC myocytes displayed β-adrenergic desensitization, with a modest increase in FS and no change in relaxation after 2.5nM ISO. In contrast, the positive inotropic/lusitropic action of CXL-1020 was fully preserved in TAC cells: FS increased by more than 100%, and time from peak shortening to 50% relengthening (t to bl, an index of relaxation) significantly increased.

Nitroxyl Enhances Contractility in Isolated Failing Myocytes

We then assessed whether HNO retains its positive inotropic/lusitropic action in failing myocytes. We isolated myocytes from sham-operated mice and from mice subjected to 9 weeks of transverse aortic constriction (TAC). In sham myocytes, the new HNO donor CXL 1020 (Cardioxyl Pharmaceutical, 50µM) significantly increased FS as much as the β-agonist isoproterenol (ISO, 2.5nM). Relaxation was also equally accelerated by HNO and ISO. Consistently, Ca2+ transients increased, with a faster Ca2+ decay. In TAC hearts, echo measurements showed significantly enlarged LVES diameter and FS decrease. Moreover, TAC myocytes displayed β-adrenergic desensitization, with a modest increase in FS and no change in relaxation after 2.5nM ISO. In contrast, the positive inotropic/lusitropic action of CXL-1020 was fully preserved in TAC cells: FS increased by more than 100%, and time from peak shortening to 50% relengthening (t to bl, an index of relaxation) significantly increased.
diminished. Accordingly, Ca^{2+} transients also increased and Ca^{2+} t to bl was shortened after CXL-1020 (Fig 3). Thus, HNO donors, such as the agent CXL-1020, display full positive inotropy and lusitropy in failing myocytes with altered β-adrenergic signaling 14. This further supports the use of HNO donors as promising pharmacological agents in the treatment of heart failure (HF).

**Concluding Remarks**

Many signaling pathways that are essential for the heart to cope with increased physiological demand or decreased cardiac function are down-regulated in HF 3. Moreover, although NO and other nitrogen-derived species are useful for unloading failing hearts, they may dampen β-stimulated increases in contractile reserve 6. Inotropic agents that use intracellular cAMP levels to leverage myocardial performance (i.e. β-agonists and phosphodiesterase inhibitors) are deleterious in the long-term. Given chronically, they alter intracellular Ca^{2+} homeostasis, making the heart prone to potentially fatal arrhythmias. Accordingly, their use in HF is currently limited to palliative care or as a bridge to transplantation or mechanical assist device implantation. Still, the failing heart requires functional support. Unfortunately, recent clinical trials employing the most promising Ca^{2+} sensitizer, levosimendan, were accompanied by increased mortality 5.

Nitroxyl enhances contractility and accelerates relaxation in normal and failing myocardium in vivo and in vitro, without the requirement of cAMP/PKA signaling or the recruitment of extracellular Ca^{2+}. Rather, HNO modifies critical cysteines in key EC-coupling proteins, enhancing Ca^{2+} cycling in the SR and inducing myofilaments Ca^{2+} sensitization. Such an agent should be ideal for the treatment of HF, at least acutely or in sub-chronic terms. Conversely, for a thorough exploration of the effects of HNO in a chronic setting we must wait until reliable long-lasting HNO donors are available for use in animal models of HF. Ongoing clinical trials are being conducted (clinicaltrials.gov NCT01096043, 7).

![Figure 3](image)

**Figure 3**

Comparison of ISO and CXL-1020 inotropic effects on fractional shortening and Ca^{2+} transients in isolated cardiomyocytes from sham and TAC animals. (A) ISO effects are blunted in TAC-induced HF. (B) CXL-1020 effects are preserved in TAC-induced HF.

**References**


13. Tocchetti CG et al. Nitroxyl (HNO) modifies cysteine residues in phospholamban to increase (continued on page 15)

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**Carlo Gabriele Tocchetti** (Naples, Italy) was the winner of the ISHR-ES/SERVIER Research Fellowship 2009 at the XXIX European Section Meeting (Nice, France; May 2009).
injured myocytes exhibited striking disruption of their architecture within a few seconds of the onset of reperfusion (contraction band necrosis), and were later shown to accumulate large quantities of calcium phosphate in the mitochondria. The source of the calcium was the plasma reperfusing the tissue.

In 1975, Jennings retired from the chairmanship of Pathology at Northwestern and became Chairman of Pathology at the Duke Univ. Med. Ctr (Durham, NC), where he continued his work on ischemic injury but added cardioprotection to the topics under study. Since reperfusion therapy was now a common clinical procedure, his group studied the factors involved in myocyte salvage after prolonged periods of ischemia. They showed that there was a wavefront of ischemic injury progressing from the subendocardium to the subepicardium and that most of the myocytes salvaged by reperfusion were in the midmyocardium and subepicardial myocardium. They also established the parameters required to estimate whether or not a therapy was protective. Dr Jennings, along with collaborators Chuck Murry and Keith Reimer, showed that a brief episode of ischemia followed by reperfusion protected the myocardium against a prolonged period of ischemia. This was termed preconditioning with ischemia, which is the strongest form of cardioprotection identified to date.

Finally, Dr Jennings and his group established the biochemical and ultrastructural features associated with the transition to irreversibility in the dog heart. These features include very low ATP and destruction of the adenine nucleotide pool with accumulation of adenosine, inosine, hypoxanthine and xanthine in the tissue together with marked acidosis secondary to the accumulation of lactate. From the ultrastructural point of view, irreversibility is associated with small breaks in the sarcolemma generally located in the region of the attachment complexes between the Z band and the sarcolemma. In addition, the cytoskeletal protein, vinculin, is lost from the complexes at about the same time that the disruption occurs.

Dr Jennings has delivered numerous named lectures around the world and has received a number of awards such as the Distinguished Achievement Award of the Society of Cardiovascular Pathology and the Distinguished Alumnus Award of the Northwestern University Medical School, both in 1996. In 2004, he was awarded the AHA Discovery Channel Award, and in 2005 he was awarded the Medal of Merit of the International Academy of Cardiovascular Sciences. He won the Gold-Headed Cane Award of the American Society of Investigative Pathology in 2007, and at the 2009 Annual Meeting of the American Section of the ISHR in Baltimore, MD, he was the inaugural recipient of the Distinguished Leader Award of the ISHR.
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