Report from the XXVIII European Section Meeting (May 28-31, 2008)

‘Future ages will wonder at us, as the present age wonders at us now’
Pericles, General of Athens c. 495–429 BC

Athens provided a wonderful location for the European Section meeting, offering an intriguing blend of novel science with historical interlude in a city rich in ancient history. A healthy balance of cardiovascular research and cultural events ensured that the attendees enjoyed a stimulating visit to the capital of this ancient civilisation. Modern medical practice originated from Hippocrates and Asklepieios, and from the evidence presented in Athens, modern cardiac science is flourishing in keeping with their ethic and energy.
On arrival at Athens International Airport, the visitor is immediately struck by the dynamism of modern Athens thriving after the 2004 Olympic Games. Investment in modern infrastructure continued to be apparent as one was whisked smoothly from the airport to the city centre in the modern metro system which would be the envy of any major world city. Few ‘underground’ train systems can claim to be educational, but travelling on Athens’ subway allowed glimpses of ancient sites uncovered during its construction, with detailed descriptions for the passengers waiting at each station platform. Megaron Athens International Conference centre, the location of the XXVIII meeting, is an impressive modern venue for a scientific meeting, and upon our arrival both the clinical efficiency and generous hospitality of our hosts became apparent. Basking in the early summer Mediterranean sun, Athens ensured a welcoming and comfortable stay for all the delegates visiting from near and far.

The conference started with a pre-symposium meeting addressing Thyroid Hormones and the Heart, providing an intellectual appetiser before the main course ensued the following day. The conference was opened in grand style in the beautiful surroundings of the Great Hall of the National and Kapodistrian University of Athens. This 19th century building has formed the heart of the modern University since its conception in 1837, and upon arrival delegates were provided with a welcome pack including a copy of the Hippocratic Oath (in Greek and an English translation) and a CD of Hellenic Poetry and Music. The President of Greece, Dr Karolos Papoulias was in attendance, and although he did not address the audience, his presence was certainly felt with a plethora of security guards and flash photography. The meeting co-chairman, Professor Dennis Kokkinos, provided a stimulating and balanced review of the Hippocratic Oath, its place in the evolution of the discipline of Medicine, and its context in modern medical practice. The choir from Athens University Department of Music provided a relaxing interlude, and Professor Denis Noble from Oxford University was presented with the ES/ISHR Medal of Merit with an entertaining and humorous laudatio provided by Professor Guy Vassort. Few cardiac research scientists can speak the number and diversity of languages in which Professor Noble has lectured! The recipient of the 2007 ES/ISHR Servier Fellowship, Dr Marta Roccio, presented her work on phenotyping cardiac progenitor cells, and Dr Francesca Rochais was awarded the new 2008 ES/ISHR Servier Fellowship. Professor Evangelia Kranias delivered an interesting Keynote Lecture highlighting her combined genotype-phenotype approach to heart failure, and introducing a number of new proteins into the central playing field of cardiomyocyte calcium cycling. Her lecture was preceded by a moving tribute by Lucie Carrier to Ketty Schwartz, who devoted her life to a distinguished career studying heart and skeletal muscle biology, and sadly passed away last December. We all retired to the courtyard of the Great Hall and had an opportunity to relax and enjoy the warm Athenian evening atmosphere, catching up with old friends and new over a glass of wine.

The scientific programme interspersed abstract presentations with overviews by leaders in the field, and, as usual, covered a diverse range of topics in cardiac research. Unfortunately, it is still not possible to attend all the sessions, but highlights for me included delineation of the paracrine hypothesis for bone marrow progenitor cell-mediated cardiac repair, a review of I f current and pharmacology, and novel viewpoints on ryanodine receptor regulation. The scientific programme was punctuated by plenty of breaks for mingling, informal scientific discussion and poster viewing. Over 250 posters were presented during the conference, and, as usual, the diversity and inquisitive scientific methods on display were testament to the strength of scientific research in Europe (and beyond) in 2008. Presenters were put through their
paces by moderators and delegates, and provided new ideas in addition to consolidating or questioning old hypotheses.

Professor David Eisner delivered the 2008 Keith Reimer Lecture with his usual entertaining demeanor, using classical music and Shakespearian poetry to highlight the problems of love, despair, catecholamines and arrhythmias. He reviewed his major contribution to the understanding of SR and transsarcolemmal calcium cycling, and described how disrupting the tight regulation of this system can underpin arrhythmogenesis via abnormal calcium release. The Young Investigators competition followed with the usual high standard and wide scope of topics. Mirna Chahine won the award for her presentation regarding the differential nuclear import of signaling in vascular smooth muscle cells after LDL stimulation.

Two cultural lectures started the days’ intellectual stimulation, and reflected the philosophy of the host city. Professor Denis Noble discussed the ‘Music of Life’ and integrating multilayered systems biology to suggest that perhaps our genes are prisoners rather than the governors. This provided an antidote to the ‘Selfish Gene’ hypothesis, and (with musical metaphors, live music with French guitar, and a recital of O Sole Mio) introduced a novel perspective on life and biology. On Friday we were treated to a historical tour around the Asklepieia, the hospices of Asklepios in Ancient Greece, by Professor Stephanos Geroulanos. The Asklepieia were the first medical centres, combining medical care with rehabilitation and religious support, and there were over 400 centres throughout Greece extending back to 1600BC. Prof. Geroulanos also gave us a flavour of medically-related art from Ancient Greece, which included some eye-wateringly graphic pieces.

The evenings were an opportunity to appreciate some of Athens’ most famous monuments. The Gala dinner was held in a restaurant in the foothills of the Acropolis, overlooking the floodlit Parthenon. As an enduring symbol of ancient Greece and of Athenian democracy, the Parthenon is one of the world’s greatest cultural monuments and was a truly awe-inspiring backdrop to a wonderful dinner. Professor Sian Harding welcomed all the delegates as the incoming President of the ES-ISHR, and provided the younger scientists with a useful template letter to reject the editorial rejection letter.

Friday evening provided an excursion to Cape Sounio on the southernmost tip of the Attica Peninsula, where the Temple of Poseidon stands on the promontory overlooking the Aegean Sea. Legend states that this is the location where Aegeus, king of Athens, threw himself off the cliff into the sea in the mistaken belief that his son, Theseus, had been killed by the Minotaur. The temple is a Doric-style peripteral temple with many columns still preserved, despite the graffiti from Lord Byron et al, and was referred to as Holy Sunium, the headland of Athens, in Homer’s Odyssey. After enjoying the view from top of the headland, we dined on the beachfront with a breathtaking sunset across the sea. Traditional Greek dancers provided entertainment during the meal, and it ultimately proved too much for many delegates to resist participation on the dance floor.

Saturday concluded the scientific programme, with translational aspects of cardiac science, a series of excellent presentations showcasing the best of Greek science, and the award of the Young Investigator and Poster prizes.

The organising committee should be commended for such a stimulating and well-structured conference. In particular, Professor Cokkinos deserves special mention for his tireless efforts in organising and hosting the meeting, the success of which was the result of his energy and enthusiasm.

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Dear Colleagues,

In this column I would like to address an issue that I regard as vital for our Society, namely, that of unity. The structure of the ISHR is rather unusual among scientific societies, with an “International” Section and seven regional Sections (Australasian, Chinese, European, Indian, Japanese, Latin American, and North American), each of which has its own separate governance and holds its own separate meetings. The relationship between the regional Sections and the International Section, and among the regional Sections themselves, has fluctuated over the years, undermined by uncertainty and punctuated by parochialism, competition, and, at times, outright tension. This is a problem that most other cardiovascular societies don’t have, because they are not truly international. In this sense, it is the price we must pay for being the only truly international society devoted to cardiovascular research. With members spread over five continents, it is inevitable that local issues take priority and the concept of being an “international” body may become nebulous or downright forgotten.

Many of us are aware of past instances of misunderstandings and friction between a regional Section and the International Section. In my mind, this has been one of the major problems that have plagued our Society. Although the causes can be debated, it is difficult to dispute that the consequences have been nefarious for all involved. Fortunately, the dark times of regional–international tension seem to be finally over. Thanks to a number of changes in both the regional and the International Section, we have entered an era of détente, in which acrimony has been replaced by harmony. The World Congress in Bologna was the most tangible demonstration of this new world order. In an unprecedented show of unity, the European, Japanese, and North American Sections all held their annual meetings in Bologna, and the Australasian and Latin American Sections sponsored symposia at the Congress. This was the first time in my memory that regional meetings were so fully integrated with the World Congress – an ecumenism that has doubtlessly benefited the Society in many ways (vide infra). The big question in 2007 was: will this last? The vast majority of the colleagues with whom I spoke in Bologna and afterwards expressed fervent hope that the spirit of unity that permeated Bologna 2007 would not be just a meteor.

It was not. I am pleased to report that a similar arrangement will be followed at the 2010 World Congress in Kyoto. Last year, the North American, Japanese and Australasian Sections announced that they will hold their 2010 regional meetings in Kyoto. Last May, the European Section decided to follow suit, and I wish to applaud their wise, enlightened, and forward-looking decision. Thus, in 2010 all major ISHR Sections will hold their meetings in conjunction with the Kyoto World Congress. In another significant step forward for our Society, Masatsugu Hori, organizer of the Congress, has wisely decided to make Section-sponsored symposia an integral part of the Congress rather than separate satellite meetings, which will further boost Congress attendance (i.e. attending both a Section meeting and the World Congress will not increase total travel time).

Why is it so important that Section meetings be held in conjunction with World Congresses? The benefits are obvious. From the World Congress’ standpoint, this arrangement markedly increases attendance, making it possible to achieve that critical mass of delegates and speakers that is necessary to produce the scientific and social impact required for a meeting to be memorable. (It is self-evident that if regional meetings are held simultaneously with, or in close chronological proximity to, the World Congress, the participation of delegates and speakers in the Congress will be decimated; as a consequence, its scientific program will be damaged and the ability of participants to interact with other scientists will be curtailed.) Because networking is one of the main benefits of a scientific meeting, it is important that
our World Congresses be an opportunity for delegates to meet all, or almost all, of their fellow ISHR members, as well as non-ISHR members. I am certain that those of you who attended the World Congress in Bologna found it to be an unforgettable scientific and cultural experience. This would not have been possible if, say, half of the delegates and speakers had attended separate Section meetings instead of the Bologna Congress.

On the other hand, Sections also benefit handsomely from holding their meetings during the World Congress. The high scientific quality, the critical mass of scientists, the fervor and excitement that characterize a World Congress represent unique experiences for the Section members who attend. (I still have fond memories of past World Congresses; in retrospect, I can say that these have been my most meaningful experiences with the ISHR.) There can be no doubt that a successful World Congress benefits the entire Society and, therefore, all of the Sections. Size does matter; none of the Sections can put together a program comparable to a World Congress in scope, depth, and richness of content. Furthermore, the World Congress highlights and leverages what I regard as one of our major strengths. That is, we have the advantage over other cardiovascular societies that, by virtue of our international nature, we can hold World Congresses in attractive venues that are not accessible to most other cardiovascular organizations. As a result, our World Congresses are characterized by a wonderful mix of outstanding science and exciting social programs. This is rather unique. For example, one would be hard pressed to find another cardiovascular society that can boast a meeting with a scientific and cultural value comparable to, say, the 2007 Congress in Bologna. It is self-evident that a successful World Congress motivates delegates to renew their membership in, or to join, the ISHR, thereby benefiting the Section to which they belong. In short, outstanding World Congresses are one of the major benefits that a scientist gets for being a member of an ISHR Section.

In addition, combining Section meetings with the World Congress benefits the Society as a whole, for the World Congress is the only time when we all get together. Being in the same place at the same time reinforces the idea that we do belong to the same society. It allows interaction and exchange among Sections that otherwise would not even see each other. This is critical to foster a feeling of cohesion. If we don’t do this, our sense of belonging to one society will quickly evaporate.

In view of the above, the International Section has taken unprecedented steps to facilitate the merging of World Congresses with Section meetings. Recognizing that young investigators are not only the future of cardiovascular science, but also the future of the ISHR, we have launched a new initiative aimed at promoting their participation in the Kyoto Congress and their involvement in the Society. Specifically, I have proposed, and Council approved, a dramatic expansion of the Trainee Travel Award Program, whereby in 2010 the International Section will distribute one hundred Trainee Travel Awards, each for US$ 1000, to support attendance at the Kyoto World Congress by students/Fellows. For the recipients of these awards, the cost of traveling to Kyoto should not be higher than what it would have cost to travel to a Section meeting in their own region. This program will enable many young investigators to enjoy an unforgettable scientific and cultural experience that otherwise would not be accessible to them. Such an initiative fulfills two of our core missions: our commitment to support young investigators and our efforts to help all ISHR Sections to hold their meetings during the World Congress. I am well aware that some ISHR members cannot afford traveling to a World Congress. However, this slight decrease in attendance is more than offset by the extraordinary opportunity that is offered to Section members to experience a unique meeting and, in the case of Travel Award recipients, to do so at a relatively modest cost.

Returning to the broad issue of the regional-international Manichean ambivalence of the ISHR, how should we approach it? We must always keep in mind that our primary goal is to serve the ISHR members in the best possible way we can. This, in my mind, must be our overriding principle that takes precedence over anything else. To achieve this goal, it is my view that the ISHR needs both strong regional Sections and a strong International Section. We must realize that both contribute enormously to the Society. Regional Sections play a crucial role because they are the natural “home” for investigators in a specific country or continent. Nothing can replace this grassroots organization and activity. Sections offer many opportunities for scientific exchange, interaction, and involvement that would not be feasible at the international level. Their relatively small meetings have a distinctive personal “feeling” and offer a quaint, familiar
atmosphere that is highly conducive to networking. On the other hand, the International Section provides a number of important services to the Sections and the membership at large, including an outstanding journal, memorable World Congresses, a well-organized website with many features, a splendid portfolio of awards that now includes three named lectures and five prizes for every stage of an investigator’s career, one of the best newsletters I have seen in my professional experience, awards for best posters at Section meetings, and more. I believe ISHR members need a varied menu that includes both the relatively small Section meetings (300-500 attendees) and, once every three years, a larger Congress (2,000-3,000 attendees). Thus, both the regional and the International Section serve the needs of the membership.

To summarize, we are one Society, not seven different Societies, and it is essential that all Sections work together to support the ISHR as a whole. If each Section holds separate meetings during World Congress years, the World Congresses will inevitably deteriorate and lose their appeal. This would be a disaster, for the World Congress is the flagship product of the ISHR; it is what defines us as a major international Society that is on a par with the American Heart Association, the European Society of Cardiology, the Japanese Circulation Society, and other bodies. If the World Congress declines by losing attendance and speakers, the ISHR declines with it, and all Sections suffer. Conversely, strong World Congresses help to energize the entire Society, and therefore, the Sections as well. The experience of 2007 eloquently attests to the benefits of combining Section meetings and World Congresses. We must not undo what has been accomplished in Bologna. We must not go back to the dark days of competition between Section meetings and World Congresses. So, let us commit to carrying on the legacy of Bologna. Let us make 2007 the start of a new era for the ISHR.

Ultimately, the vitality and success of the ISHR will require both vibrant Sections and a strong International Section, working together toward common goals. When we are divided, nobody wins, and all lose. That unity equals strength has been recognized for ages across many diverse cultures. China is replete with old adages extolling the virtues of unity. “United we prevail, divided we fail”, “More bells, louder sound; more candles, brighter lights”, and “More firewood, higher flame” are but a few examples of a large anthology. I am told there are similar proverbs in India as well. The Italian homologue is the saying “L’unione fa la forza” (“Unity strengthens”). And on the other side of the Atlantic, the official motto of the State of Kentucky is “United we stand, divided we fall”.

I ardently hope that the praxis of combining Section meetings and World Congresses will become permanent, and that Bologna 2007 will pass in history as the beginning of a new covenant for the ISHR. We have no other choice, for unity is critical to our very survival as a viable cardiovascular society.

As always, I welcome your comments and/or suggestions at rbolli@louisville.edu.

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President, ISHR
Beginning in 2009, the ISHR International Council will sponsor a Poster Award to be presented at Section meetings* and the World Congress. These awards will be given in addition to Section-sponsored poster awards and other young investigator awards that are currently offered at ISHR meetings.

**Purpose of the Prize**
The purpose of the Poster Award is to call attention to the exceptional research presented in ISHR meeting poster sessions, and to recognize outstanding young investigators whose posters demonstrate both excellence in research and clarity of presentation.

**Nature of the Prize**
The ISHR International Poster Award will be presented at the annual meetings of dues-paying ISHR Sections (*currently the North American, European, Japanese, Latin American and Australasian Sections) and the triennial World Congress. The winners will receive a certificate, a $300 prize and a ribbon to be displayed on the poster during the meeting.

**Procedure for Application and Selection**
1. By intent, the Poster Award is targeted at young investigators, notably students and Fellows. Because of international differences in the definition of “Fellow”, eligibility for the award is limited to those within 6 years of their terminal degree (*e.g.* M.D. or Ph.D.).

2. Only ISHR members in good standing (as determined by their Section Secretary) will be eligible for the Award.

3. Applicants must be the first or last author of the abstract presented, and must be present at the meeting to be eligible.

4. Applicants must indicate their desire to compete for the Award when submitting their abstract to the meeting. Meeting organizers will maintain a list of eligible posters.

5. The number of Poster Awards offered at a given meeting will be determined by the number of posters presented at that meeting. One Award will be given for every 100 posters; at the larger meetings where multiple poster sessions are held, this is expected to equate to one Award per day of poster presentation.

6. Posters will be evaluated by a small panel of senior investigators, selected and chaired by a member of the ISHR International Council who is in attendance at the meeting. The Secretary General will be responsible for providing the names of the judges to the meeting organizer.

7. Poster presentations will be judged on the basis of:
   - Excellence and significance of research
   - Clarity of visual and verbal presentation

8. Council members will declare any conflict of interest (or close relationship with any candidate) and the voting mechanism will be adjusted accordingly.
The treatment of human illness has a selfish motivation: disease menaces not only the patient but also the therapist, including the physician and other professionals. All of us fear our own vulnerability: “there but for the grace of God [go I].” The greater the menace, the greater the effort to conquer it. The treatment of heart failure represents one of the great advances of modern medicine. Here, I describe some of our current knowledge of heart failure, and tell the story of one of the pioneers, Ernest Starling.

During the last fifty years, heart failure has grown to epidemic proportions; it is a frequent cause of hospital admissions. Hospitals and medical schools have created new departments for its study, societies have been founded, and new journals are being published. Seventy-five years ago when I was a medical student, we learned that heart failure causes edema, dyspnea and ascites, and that the kidneys play a predominate role. I also remember listening to heated discussions: whether high and low output failure are related; is high output failure a “white raven?” Since then we have learned that heart failure is a multi-system disease affecting ergoreceptors in skeletal muscles, the sympathetic nervous and renin-angiotensin systems with possible parasympathetic withdrawal. Instead of “backward” and “forward” heart failure, we now distinguish between systolic and diastolic heart failure. These two groups have some common clinical features, although they have different mechanisms. Diastolic heart failure has become of particular clinical interest, since it afflicts at least half of the patients with heart failure. The characteristic of diastolic heart failure is normal ejection fraction; at its basis are changes in the contractile elements of the heart muscle, leading to malfunction of the heart, stiffness, and lack of plasticity. Echo-Doppler has enabled us to explore diastolic failure through measuring mitral inflow velocity, isovolumic relaxation time, and mitral inflow propagation velocity. In medical school we have learned that when heart muscle stiffens, less volume is needed to cause a disproportionate pressure rise in the cardiac cavities. Now we know that stiffness of the ventricular muscle causes diastolic dysfunction. In 1958, Kako and I studied the role of contractile elements, publishing experiments on isolated actomyosin fibers from failing human hearts; we found that they showed diminished contractility. Now, the spotlight has turned on specific components of the contractile system, especially Tigrin (Connectin), the third myofilament system in the sarcomere. Its stiff isoform predominates when the heart muscle is overloaded. It is likely that increased collagen turnover also contributes to cardiac stiffness. In my medical school days, treatment of heart failure was restricted to digitalis leaf and oxygen. Since then, a series of discoveries have paved the way to current treatment regimens, beginning with ganglionic blocking agents and vasodilators. Then came the discovery of orally active angiotension-converting inhibitors, beta-blockers, and loop diuretics, the latter thanks to the pioneering work of Karl H. Beyer, who called the discovery of chlorothiazide a classic example of designed discovery. The use of angiotensin-inhibitors and beta-blockers has become one of the significant advances in modern medicine. Treatment with angiotensin-inhibitors is based on the work of Skeggs, who defined the renin-angiotensin system and discovered ACE, the converting enzyme, leading to the development of potent inhibitors. Bristow et al have shown that beta-adrenergic blockade selectively attenuates adrenergic drive to the failing heart.

At a time when pathophysiology of heart failure was primarily concerned with pressure, volume and flow, the British physiologist, Ernest Starling (1866–1927), together with Patterson, discovered the law of the heart. It states that “the mechanical energy set free on passage from the resting to the contracted state depends on the area of the chemically active surface, i.e. on the length of the muscle fibers” or, the output of the heart depends on its diastolic filling. Starling was aware of similar results previously obtained by Otto Frank, Professor of Physiology in Munich, on the perfused frog heart. [I was a student of Frank in Munich, who was feared because he could not tolerate mediocrity amongst medical students]. In his original report, Starling plotted the venous pressure against the cardiac output, with the axes the wrong way. Henderson, in his book on Starling, ascribes this error to “unfamiliarity.” Maybe the great man simply made a mistake, which escaped the eyes of the editor of the Journal of Physiology. It seems to happen to the best of us!

The law of the heart is graphically expressed in left ventricular function or Starling curves, plotting volume output against inflow pressure. The relevance of the Starling curves in heart failure has been vehemently argued, like a theological dogma was disputed in the early middle ages. One of the disputes was whether the curves of the failing heart have a descending limb. Some investigators have answered in the negative and have
Ernest Starling died on board alone without family and friends.

What of the future treatment of heart failure? In medicine and science there is never an end point of knowledge, nor an end for the search for a cure. The search goes on and there are signs that new modes of treatment may become available, such as phosphodiesterases and renin inhibitors. For those of us with heart failure, this is good news. To quote Starling, “In physiology, as in all other sciences, no discovery is useless, no curiosity misplaced or too ambitious, and we may be certain that every advance achieved in the quest of pure knowledge will sooner or later play its part in the service of man.”

References


Richard J. Bing, M.D.
KETTY SCHWARTZ, who died on December 25, 2007, was one of the most emblematic figures of cardiac and muscular research in the second half of the 20th and beginning of the 21st century. Her sensitivity, firm kindness, wisdom, natural authority, and the beauty and warmth of her superb blue-eyed gaze will remain in the memories and hearts of all those who had the chance to work with her, even if only for a few days or hours on one of the many boards and committees she participated in. I had the chance to work with Ketty for 13 years thanks to Bernard Swynghedauw, the head of the Inserm Unit 127 in 1979, who assigned me to her group to prepare my Master in Science thesis. Actually, my plan at that time was to have a one year break in my clinical training, but Ketty’s overwhelming charisma made it happen differently! I finally found myself as a post-doc on Ketty’s team and, in 1985, I was offered the position of full time researcher assistant! I left Ketty’s group at the beginning of the nineties and even though, as a former clinician, I was happy to return to clinical cardiology much later, the years that I spent with Ketty were undoubtedly the richest of my career.

Ketty was born on November 29, 1937 in Boulogne-Billancourt, a western suburb of Paris, in a family of emigrants running away from Nazi persecution. Probably upon the advice of her family, who wanted her to have a good social situation, she studied at the Paris Faculty of Pharmacy and received her diploma in 1960. She worked as a resident in pharmacy in Paris public hospitals (1959-1964), an experience that probably engendered her orientation towards a career dedicated to public and state service rather than private practice. At the end of her internship, she was recruited as a full time researcher for the Centre National de la Recherche Scientifique (CNRS), where she remained a member her whole life; first as a Research Assistant, then as a Head of Research and finally as a Director of Research, even though she spent most of her time working for the benefit of Inserm, either as a researcher or at Inserm’s highest administrative levels.

One of Ketty’s early mentors predicted that, as a bright scientist, she would not spend more than 10 to 15 years working on the same subject in the same place. This proved to be true. Ketty started her scientific career at the Laboratory of Biochemistry of the CNRS Center for Surgical Techniques at the Broussais Hospital in Paris where she worked on heart and liver preservation and the detection of rejection. During the mid seventies, she was invited by Bernard Swynghedauw to join him in creating a new Inserm unit dedicated to the biochemistry of cardiac remodeling and progression to heart failure. Initially located at the Faculty of Medicine, rue des Saint-Pères in the Latin quarter, the group moved in 1978 to a new building at Lariboisière Hospital near Gare du Nord to create the Inserm Unit 127. Owing to the development of new sophisticated immunochemical and electrophoretic techniques, this collaboration initiated a series of important discoveries; including the heterogeneity of cardiac myosin and the redistribution of cardiac and skeletal muscle myosin isoforms during development and in response to new functional requirements. At that time, Ketty’s group included Anne-Marie Lompré, two technicians and me, plus one or two pre-graduate students. Ketty’s dedication to bench research and her commitment to her team created a unique environment; including both an open exchange of ideas that led to progress in research, and a maternal atmosphere that imparted the important values of life: honesty, hard work and discipline.

The mid eighties was the time of the eruption of molecular biology in cardiovascular research, and Ketty was the first within the French scientific cardiovascular community to sense the importance of this methodological revolution as a means to speed up research progress. The new techniques were rapidly incorporated into her investigative armament, resulting in important contributions in the areas of natriuretic peptides and Ca\(^{2+}\)-ATPase of the sarcoplasmic reticulum (SR), including the first report of the decreased expression of SR Ca\(^{2+}\)-ATPase in the failing human heart. Interestingly, as predicted by her mentor, Ketty never spent much time over-exploiting the results of her research. When the first paper reporting an important new result was published, her mind had already moved to another idea, another question on the path of knowledge. This brought her naturally to the track of human genetics and to her desire to contribute to deciphering gene defects responsible for a number of cardiac and skeletal muscle familial diseases. Indeed, Ketty had always been interested in comparative physiology and pathophysiology, and her work on cardiac muscle was paralleled by similar work on skeletal muscle. In this respect, I remember discussions we had during the late eighties regarding the possible pathophysiology of the Syrian Hamster cardiomyopathy and, in fact, global myopathy, in which we proposed...
hypotheses about alterations in force transduction between adjacent myocytes and myocyte degeneration long before the discovery of defects at the delta-sarcoglycan gene.

Eventually, Ketty’s involvement in the Scientific Council of the Association Française Contre les Myopathies (AFM) since 1986, her close friendship with the head of the Association, Bernard Bara-taud, and two important scientists in the field of skeletal muscle development and disease, François Gros and Michel Fardeau, and her desire to devote her research activity to the service of patients and their families, combined to convince her to leave the field of cardiac remodelling for that of the genetics of heart and skeletal muscle diseases. During the early nineties, this decision rapidly culminated in the main project of her scientific and professional life: the creation of an institute dedicated to striated muscle physiology and pathophysiology from bench to bedside, with a special focus on the care of young patients and their families. She left Lariboisière and first joined the Inserm unit of Michel Fardeau at the Fer à Moulin, a research site close to Pitié-Salpêtrière Hospital, before being housed in the basement of the cardiology building of the hospital owing to the support of Michel Komajda and his interest in the pathophysiology of human cardiomyopathies. This started an era of very fruitful collaboration between Ketty and clinical cardiologists, allowing France to participate successfully in the race to the discovery of disease loci, genes and mutations, not only in the field of cardiomyopathies but also in that of channelopathies owing to her close collaborator, Pascale Guicheney. Because Ketty always knew that identifying new mutations is nothing without understanding the downstream pathophysiological mechanisms, she maintained a constant interest in experimental models; for example, she closely followed the work of Lucie Carrier and Gisèle Bonne in the areas of myosin binding protein C and lamins, respectively.

After many years of waiting, Ketty and her group finally left the cardiology building in 1996 to enter the brand new Institut de Myologie. At this stage of her career, Ketty’s responsibilities were, of course, far beyond those of a group leader, and she demonstrated outstanding skills as an institute manager in developing fruitful interactions between basic scientists, clinicians, and research administrators resulting in a number of multidisciplinary research teams devoted to cardiac and skeletal muscle diseases in France and abroad. In addition, Ketty brought together patients and their families for a new constructive dialogue and partnership with researchers, physicians and people in charge of public health. On the scientific side, in keeping with her mentor’s prediction and always in an attempt to serve the patients more directly, Ketty focused her interest on biotherapies. She firmly supported a number of researchers and fostered several institutional initiatives in this area. She was personally involved in the organization of the first cell therapy trial in patients with myocardial infarction that involved a number of basic scientists and clinicians, including Jean-Thomas Vilquin and Philippe Ménasché to cite but a few.

After two terms on the Board of Governors of the Inserm (1993-1996 and 2002-2005), her public career culminated in the position of Director of Research at the French Ministry of Research (2001-2002), where she exercised great influence on French research policy through her strong will and outstanding capacity to find simple and pragmatic solutions to the often complex problems of French research. Ketty also played an important role in the growth and success of several international organizations, most notably the International Society for Heart Research (ISHR). She served as a council member (1987-1995), and as the president of the European Section (1992-1998), and, along with Bernard Swynghedauw and other colleagues, she organised several memorable ISHR meetings in France. The ISHR was something like a family for Ketty, in which she cultivated very strong and durable friendships with, for instance, Jutta and Wolfgang Schaper, Tom Ruigrok, and a number of Israeli colleagues. Israel had a very special place in her heart, and she made numerous trips to Israel during the past ten years to counteract attempts to boycott Israeli academics. Ketty also served as the associate editor of the Journal of Molecular and Cellular Cardiology (1985-1992) and of Circulation Research (1992-1999).

In addition to her personal scientific contributions, Ketty undoubtedly participated in several major transitions in cardiovascular research in France and elsewhere. There was the era before Ketty, and we are now in the era after Ketty, and we all can see the important place she occupied both scientifically and in our hearts. One of the reasons for this is that, despite all of her responsibilities, Ketty always remained totally available for any of her fellows or colleagues who needed her advice or support. In this advice, Ketty always favoured attitudes that she had developed for herself: freedom, responsibility, creativity, and risk-taking. With Ketty’s death, I and some others have lost a mother figure and a mentor, others have lost an inspiring colleague, and we all have lost an invaluable friend.

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The Joint Annual meeting of the Indian Section of the ISHR, the International Academy of Cardiovascular Sciences (Indian Section) and the Heart Failure Society of India was held at the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, from February 29th to March 2nd 2008 under the chairmanship of Prof. KK Talwar. Prof. Madhu Khullar and Dr Yashpal Sharma were the organizing secretaries of the meeting. The meeting was attended by 250 delegates from all over the globe, and included invited talks by speakers from the USA, Canada, Japan, UK, the Netherlands and Israel.

The meeting featured a series of lectures in the fields of cardiomyopathy, cardiovascular genomics, interventional cardiology, heart failure, metabolic syndrome, molecular cardiology and preventive cardiology. The scientific program was comprised of 16 sessions and 60 invited talks on a wide range of topics in cardiology. The meeting was an amalgam of clinical and basic cardiovascular research and provided a platform for the interaction of cardiologists and basic scientists. The main topics of the conference were cardiomyopathies, genomics, rheumatic heart disease and heart failure. The role of herbal drugs in cardiovascular medicine was also part of the program. The scientific sessions provided opportunities for young investigators to present their research work and interact with the renowned faculty in their respective fields. Young investigators presented nearly 60 abstracts at the poster session and 20 oral presentations at the awards session. The Society initiated two awards to encourage scientific excellence by rewarding young scientists who have distinguished themselves for their contributions to cardiovascular research.

Heart Failure was the main theme of the meeting and various aspects of etiology, pathophysiology and therapeutics were discussed in several sessions. Dr Shainberg (Israel) spoke on metabolic aspects of heart failure. Dr Akira Matsumori (Japan) discussed the significance of Hepatitis C virus in cardiomyopathies in Japan and various other continents including Pakistan and some parts of Europe. Dr IS Anand (USA) highlighted the role of anemia in heart failure, while Dr S Sarkar (India) presented a new transgenic model of heart failure that mimicked human heart failure, and Dr NS Dhalla (Canada) discussed the benefits of treatment of congestive heart failure by antiplatelet agents. Dr PK Singal (Canada), International coordinator for this meeting, highlighted the role of drug-induced heart failure and its prevention, and Dr Narasimhan (India) presented a brief review on the role of device therapy in heart failure. Finally, Dr GS Chattwal (Germany) presented results on targeted diagnosis of Streptococci capable of causing rheumatic fever.

The session on Molecular Cardiology focused on new and exciting findings in the areas of stem cell therapy in dilated cardiomyopathy, A-kinase anchor protein AKAP121 in cardiac hypertrophy and...
autophagy of cardiomyocytes in ischemic cardiomyopathy. A symposium on “Metabolic syndrome and cardiovascular diseases” included talks on the role of G protein-coupled receptors in diabetic vascular complications (Dr P Ramarao, India), comparative efficacy of chromium complex supplementation (Dr S Jain, USA) and the beneficial effects of non-selective beta blockers on the diabetic heart (Dr B Turan, Turkey). Dr Ravinder S Kohli (USA) gave new insights into comprehensive management of metabolic syndrome.

Talks presented in sessions on “Hypertension” and “CAD” discussed the genetic determinants and interactive effects of gene polymorphisms on the risk of hypertension and CAD, respectively. Dr N Mahapatra (India) described chromogranin as a novel biomarker of essential hypertension. Deficiency of Vitamin B12 compounded by abnormalities in homocysteine metabolism which might further elevate risk of CAD was highlighted by Dr S Sengupta (India). In addition, topics including preventive measures for ischemic heart disease, ethics in cardiovascular research, myocardial ischemia and angiogenesis, and the role of myocardial lymph-angiogenesis and its pathophysiology in heart diseases were covered in the scientific sessions.

The NS Dhalla Award for outstanding work by young scientists in the area of basic cardiovascular research was awarded to Mr Shamim Ahmad and Ms Bhoomoika Goyal for their presentations entitled “Decreased expression of titin is possibly an adverse effect of elevated TNF-α in patient with dilated cardiomyopathy” and “Effect of telmisartan on cardiovascular complications associated with STZ-induced Type I diabetic rats”, respectively.

The Nirmal K Ganguly Award, which is given for clinical research in the area of cardiovascular diseases, was shared by Dr Pretty Mathew and Dr Anuja Shah for their presentations entitled “Comparison of closed loop control versus manual administration of propofol using bispectral index in cardiac surgery” and “Comparison of primary aspiration of thrombus using aspiration catheter with conventional stenting in patients with ST elevation myocardial infarction”, respectively. Dr R Kler and Mr Sumith R Panicker won awards for the best posters.

The scientific meetings were followed by a joyful cultural programme and bountiful dinners. These events brought the members together to celebrate the success of the meeting and to enjoy typical Indian cuisine and Indian wines.
I was very honored to receive the Young Investigator Award of the North American Section at the 2007 XIX World Congress in Bologna, Italy, for my work on the function of microRNAs (miRNAs) during heart disease. miRNAs are small, non-coding RNAs that negatively regulate gene expression in a sequence-specific manner by inhibiting mRNA translation or promoting mRNA degradation. My work led to the discovery of a network of miRNAs embedded in myosin heavy chain genes, the dominant regulators of cardiac contractility, that controls cardiac and skeletal muscle gene expression, stress-responsiveness and contractility.

Although originally from the Netherlands, in January 2005 I started my postdoctoral training in the lab of Eric Olson at the University of Texas, Southwestern Medical Center. Since it is becoming increasingly clear that miRNAs are very powerful regulators of human disease, I am very excited to be in the unique position to be able to extend our findings to a next level as part of miRagen Therapeutics, a new biotech company initiated by Eric Olson and others that focuses on the therapeutic use of miRNAs in cardiovascular disease.

**MiRNA Function in Cardiac Disease**

The heart responds to diverse forms of stress by hypertrophic growth and reprogramming of cardiac gene expression, which culminate in a loss of pump function, arrhythmias, and sudden death. MiRNAs are ~22-nucleotides in length and inhibit translation by interacting with the 3’ untranslated regions of specific mRNA targets. To date, the functions of only a handful of miRNAs have been determined, but their powerful effects on cellular phenotypes, impact on such a substantial fraction of the genome, and evolutionary conservation across divergent species point to miRNAs as key regulators of physiological and pathological processes.

Previously, we identified a signature pattern of miRNAs that are dysregulated during pathological cardiac hypertrophy and heart failure in humans and mouse models of heart disease. Gain- and loss-of-function studies in mice have revealed profound and unexpected functions for these miRNAs in the heart, including the control of myocyte growth and identity, contractility, energy metabolism, and stress responsiveness, providing glimpses of new regulatory mechanisms for heart disease (Figure 1) (Ref. 1).

A hallmark of heart disease is the down-regulation of alpha-myosin heavy chain (MHC), a fast-contracting myosin, and up-regulation of beta-MHC, a slow myosin, resulting in a diminution of cardiac function (Ref. 2). Previously, we showed that a cardiac-specific miRNA (miR-208) encoded by an intron of the alpha-MHC gene is required for cardiomyocyte hypertrophy, fibrosis and expression of beta-MHC in response to stress and hypothyroidism. miR-208 also represses the expression of fast skeletal muscle genes in the heart. Thus, the alpha-MHC gene, in addition to encoding the major cardiac contractile protein, regulates cardiomyocyte growth, identity and gene expression in response to stress and hormonal signaling through miR-208 (Figure 2). These actions of miR-208 are mediated, at least in part, by THRAP1, a thyroid hormone receptor coregulator that is targeted for repression by miR-208 (Ref. 3).

**The MyomiR Network**

More recently, we have discovered two miR-208-related miRNAs encoded by other MHC genes. This network of miRNAs embedded in MHC genes, which we
Figure 2. Requirement of miR-208 for cardiomyocyte hypertrophy and fibrosis

A schematic diagram of a heart following thoracic aortic banding (TAB) is shown on the left.
Sections of hearts of wild type and miR-208 null mice are shown following sham operation or TAB for 21 days.
High magnification views of the ventricular wall are shown at the bottom.
Trichrome staining identifies fibrosis in blue.
Note that hypertrophy and fibrosis are diminished in mutant mice compared to wild type following TAB.

designated as the MyomiR network, represents an ancient mechanism for the control of cardiac and skeletal muscle gene expression and contractility. Our recent data indicate that it is actually the miRNAs hidden in the myosins that through an intimate form of cross-talk regulate the expression of myosin genes they are embedded in and thereby very potently determine muscle function and remodeling in response to stress. This discovery offers powerful opportunities for the therapeutic manipulation of miRNAs in the settings of cardiac and skeletal muscle disease.

Conclusions and Future Directions
Our understanding of the biology of miRNAs is still in its infancy. With perhaps a thousand miRNAs encoded by the human genome, only a few of which have been studied in any detail, much remains to be learned about the regulation and functions of miRNAs. An important challenge for the future will be to identify the downstream targets that mediate the actions of miRNAs in development and disease. The potent roles of miRNAs in the heart’s stress response and in the control of cardiac function and dys–function suggests opportunities for therapeutically exploiting the biology of miRNAs in the settings of congenital and acquired heart disease, especially for pathological cardiac remodeling.

References

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