There are situations in life, when a decline in health can be so catastrophic that the patient or his family are grasping at any straw, taking any therapeutic measures, no matter how perilous and new. Typical examples are organ failures affecting liver, heart, or kidneys. In many instances organ transplantation is the only treatment, and considerations involving the choice of donor, cadaveric or life become secondary. Live donors are now commonplace in kidney transplantation; lung transplantation also permits each of two donors to provide a lobe of lung to a patient with end stage lung disease (1). The situation, however, is not at all settled in transplantation of the liver, where the right hepatic lobe of a living donor is transplanted into a recipient, whose diseased liver has been removed. This has opened up a lively and sometimes bitter ethical dispute about the safety of the donor who sacrifices part of his liver to save the recipient’s life. Sometimes the donor belongs to the patient’s family, but it may be an acquaintance, who in the spirit of ultimate altruism risks his health to save the desperately ill. In such cases the ethical considerations become of overriding importance, particularly since at present several liver donors in the United States have died (1). Should the surgeon expose a perfectly healthy donor to these dangers? Efforts have been made to deal with this issue by forming committees to collect information about risk to the donor. Additional regulatory oversight has been suggested, which might delay or abort efforts to treat terminal liver disease by partial liver transplantation. Any delay for critically ill patients is fatal. In the basic sciences, committee supervision is the rule for evaluation of research programs. The investigator must detail every corner and cranny of his projects. In clinical research, the ethical value of a project becomes the main subject of this critique. Those who have been members of a research committee which oversees clinical projects know that the scientific aspects often are less scrutinized than ethical considerations.

History teaches us that most advances in medicine have been made by individual initiative rather than by committee decision and supervision. The early development of cardiac surgery, in particular cardiac transplantation and surgery of valvular and congenital heart disease, was entirely spontaneous: these pioneers did not depend on consensus by committees. Neither was the pioneering surgery of Gibbon or Lillehei (cardio-pulmonary bypass surgery) subjected to committee oversight, although Lillehei used a live donor. More oversight of cardiac transplantation may have been useful, considering the rather wild, ambitious pursuit of early cardiac transplantations. Committees can talk a new idea to death by excessive discussion of its pros and cons. To pour an original idea into the ironclad mold of rules and regulations can destroy the bloom of spontaneity. Self-discipline and common sense should be sufficient in many cases to apply the brakes.

What then are the borders and limits of individual initiative as compared to organized and supervised research? We believe that the birth and exploratory steps of a research project should be entirely the domain of individual investigators. They should be able to choose their co-workers, and to plan the future course. Initially committee actions should be restricted to matters of funding. Once the idea has taken root and involves issues of patients’ health, supervision by advisory groups is indicated.

Committees should not stifle the creative drive, the enthusiasm of pioneers; particularly they should not delay surgical correction. Respect for the patient and the investigator should guide the research progress at least in

(continued on page 2)
its initial phase. Self regulation should be the most important aspect of both clinical and experimental research.

**Reference**


Richard J. Bing, M.D.

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**PRESIDENT’S LETTER**

IN THE LAST EDITION of this report describing the internet operations of the ISHR I might have exaggerated a little in my description of the size of our operation. Our web site actually runs on two servers. The first is the University of South Alabama server at www.usouthal.edu/ishr. This server uses the unix operating system which is great for billboard-type web sites where you simply follow links from page to page. The University either has donated the web space to the ISHR or just forgot to send us a bill, I am not sure which. From the onset we wanted some “functionality” on our site. About four years ago my oldest son, Michael, an engineer with Panasonic, showed me how he could manipulate large databases from web sites. I asked him if he could write software to automate our membership directory. He said he could but that it would require a Windows-based server. Hence our need for a second server.

The Windows server is an innocuous looking PC nestled in a corner of my office. In 1996 there was a local computer company here in town called Racer. They assembled computers from cheap parts and sold them through a local outlet. One day they had an advert in the paper for a 325 mHz computer for $325 (a dollar a megahertz). That was near light-speed in those days so we bought three of them for the department. In 1998 one of them was put out to pasture when our secretary decided she needed something faster. I thought the retired racer would make a good server for the ISHR so I bought 256 mb of memory for it and a copy of Windows 2000 Server operating system. Total outlay for the ISHR: $300.

I have a pretty good understanding of Windows 98 but Windows 2000 is quite different. When I set up the server I knew nothing about security and decided that the 5 cm-thick book that came with the software couldn’t be that important to read. I just selected the defaults and made a few educated guesses as it asked me questions during the install process. The thing worked amazingly well for about a month. Then one day I got a “disk full” error. That seemed strange since we were only using about a quarter of the capacity of the hard drive. The ISHR had been hacked! I found a 2 gigabyte folder on the disk called madk@tz. The file could not be accessed nor could it be erased. A search of the internet revealed that madk@tz was an underground pirate software and porno exchange which had been parked on the ISHR’s computer to take advantage of our high-speed connection. At that point I had to call in another computer expert. This time it was the son of a colleague, Sailen Barik, in biochemistry. Titus Barik was then a computer major at Georgia Institute of Technology and happened to be very conversant with Windows 2000 Server. He rebuilt the system filling all of the security holes that I had left wide open.

The old racer has been running smoothly ever since. Actually even though 325 mHz may seem like computing at geologic speed by today’s standards, it is still one of the fastest-responding computers that I connect to on the internet. That is probably because it is not super busy. It does more that just serve the ISHR, however. Also, on the site is the Department of Physiology’s home page at physiology.usouthal.edu and right next door are two antique motorcycle sites that mysteriously ended up on the site physiology.usouthal.edu/restor/ and physiology.usouthal.edu/mbvmc/.
The Latin American Section held its X Meeting in La Plata, Argentina. The aim of the organizing committee was to offer to basic and clinical cardiologists a meeting of the highest possible scientific quality in an attempt to re-establish the former enthusiasm of the people who initiated the Section. We also wanted to encourage discussion between clinical and basic researchers to bridge the gap often observed between the bench and the bedside.

The meeting was held at the Golden Room of the Town Hall, a very traditional building situated at the geographic center of the city, just in front of the Cathedral. There were more than 200 attendees and the format was two days of plenary sessions. International guests were Dr Donald Bers (USA), Dr Roger Hajjar (USA), Dr Paolo Tucci (Brazil), Dr Otoni Moreira Gomes (Brazil) and Dr Luis Folle (Uruguay). All the international guests received the title of distinguished guests of the town in the formal opening ceremony. There were also poster sessions, with 52 presentations. The prize “Dr Juan Carlos Fasciolo” to the best poster on basic research was given to the poster “Regressão and prevention of myocardial hypertrophy and fibrosis by Na+/H+ exchange inhibition” by Dr N.G. Pérez et al from the Centro de Investigaciones Cardiovasculares, University of La Plata. The second prize was for the poster “Na+/Ca2+ exchanger regulates resting tone in human umbilical arteries” by Dr J. Raingo et al from the Department of Biological Sciences, Faculty of Sciences, University of La Plata.

A highlight of the meeting was a debate on “Clinical Trials”. This debate was moderated by Dr Carlos Bertolasi, and the participants were a basic scientist (Dr Horacio Cingolani), a specialist in ethics (Dr Alberto Mainetti), a specialist in hemodynamics (Dr Liliana Grinfeld), and a clinical cardiologist (Dr Arturo Cagide).

A social aspect was the attendance to a performance in the new Argentino Theatre of La Plata, and a final barbecue (“asado”) at the end of which Dr Eduardo Escudero delighted the attendees with a piano performance and a wonderful repertoire of most famous tangos.

The foreign visitors took advantage of the sunny although very cold weather, and walked the streets of La Plata, visiting the Cathedral and the central building of the University, the Museum of Natural Sciences, as well as some commercial streets, hunting for souvenirs.

We believe that the meeting met at least part of its goals, and hope that our Section can keep evolving and growing.

Alicia Mattiazzi, M.D.
La Plata, Argentina
The Slovak contingent of the ISHR hosted a Satellite meeting in the High Tatras immediately preceding the European Section meeting in Szeged, Hungary. The meeting was held in Stara Lesna which is located in the beautiful High Tatras Mountains in the north-eastern part of the Slovak Republic. The conference (June 29 – July 2, 2002) was in a perfect time of the year to capture the natural beauty of the surroundings.

The scientific theme for the conference was “The Failing Heart: From molecular mechanisms to clinical application”, and the aim was to bring basic bench scientists together with clinical cardiologists to exchange information and ideas on the latest advances in the mechanisms, treatment and management of heart failure. The meeting, which attracted 120 participants, was organized by the Institute for Heart Research of the Slovak Academy of Sciences in Bratislava, with Dr Ján Styk as President, Dr Attila Ziegelhöffer as Coordinator, but with the bulk of the workload (and sweat) falling on the shoulders of the Secretary, Dr Tanya Ravingerová. Tanya did an excellent job in organizing the conference. The meeting benefited from its international nature. The Czech Republic, Japan, USA, France, Canada, UK, The Netherlands, Hungary, Belgium, Australia, Germany, Poland, Turkey, Israel, India and Denmark were all represented on the lecture podium in addition to the host Slovak Republic.

It is not possible to list all of the international speakers but a few of the notables included Jim Downey, ISHR President, Lindsay Brown, Chairman of the XVII ISHR World Congress that will be held in Brisbane in 2004, and Naranjan Dhall, Executive Director and CEO of the International Academy of Cardiovascular Science (IACS). The topics ranged from “Molecular Abnormalities in Ischemic Heart Disease”, and the “Pathophysiology of Heart Failure in Different Experimental Models” to “Genetic Aspects of Heart Failure” and “Metabolism, Hypertrophy and Hypertension”. Overall, the 66 lectures were well attended and audience participation unusually good throughout this 3.5 day meeting. A delightfully light and amusing special session was organized on the topic of “Serendipity and Frustration in Cardiovascular Research”. The objective of this unique session was to have selected lecturers present their thoughts (and in many cases, personal experiences) of how a lucky, unplanned opportunity actually led to an important finding that ultimately changed the direction of cardiovascular science. I must admit, Drs Seymour, Ruigrok, Downey and Borgers had an extremely challenging task but the laughter and applause that greeted each talk was clear proof that they had successfully achieved their goals.

There were several organizational highlights within the meeting as well. On the first day, Dr Ján Slezák, Vice President of the Slovak Academy of Sciences honoured Drs Makoto Nagano, Naranjan Dhall and Norman Alpert for their roles in creating the new IACS. The IACS was the sponsor of two symposia that preceded the meeting. Dr Lindsay Brown roused the audience with a stirring presentation on the upcoming ISHR World Congress in Australia in 2004. He sold the audience on a great scientific program, beaches, a fun city, beaches, feeding crocodiles, (did I mention beaches) and a very cheap Australian dollar! Looks like it’ll be an outstanding event. At the final Banquet, Dr Ján Slezák received the Norman Alpert Award from the IACS. Awards were also presented to Margaret Chandler (USA), Anna Kicinska (Poland) and Kristina Nagyova (Slovak Republic) for the most outstanding poster presentations.

Socially, this meeting was a tremendous success. The fact that we were a captive audience accommodated in the isolated High Tatras helped to keep the group together and stimulated interactions. However, the trip way up into the High Tatras to allow us to wander pathways beside rushing streams and flowing waterfalls surrounded by a lush green forest was a clear highlight. In the all too hectic pace of a scientist’s life, an opportunity to casually stroll and reflect within the solitude of lush forest is to be treasured indeed.

From start to finish, scientifically and socially, this was a meeting not to be missed! If you did miss it, well, you’ll just have to catch the next ISHR meeting in your part of the world. This Society was built on the value of its meetings and it continues to be a strength in 2002.
THE FIRST NAMED LECTURE OF THE ISHR:  
THE KEITH REIMER DISTINGUISHED LECTURE

WITH THE RECENT ADDITION of the Research Achievement Award (the “Nobel Prize” of the ISHR) and the Outstanding Investigator Prize to the preexisting Bing and Harris Awards, the ISHR now has a rich portfolio of awards to recognize prominent scientists. However, named lectures are conspicuously absent from our repertoire of honors, which is in contrast to almost every major biomedical Society. Named lectures are important not only to commemorate investigators who have made seminal contributions to research and whose name is attached to the lecture, but also to enrich the program of scientific meetings by featuring outstanding speakers. Accordingly, in July 2001 I proposed that the ISHR establish a named lecture that will be a highlight of ISHR World Congresses and Section meetings. I was pleased that Council accepted my proposal. The overwhelming majority of Council members agreed to name this lecture the “Keith Reimer Distinguished Lecture” in honor of Keith’s contributions to scientific knowledge and to the ISHR. As you know, Keith was a leader in the study of myocardial ischemia, and for 25 years has moved this field forward in many important ways, including the discovery of preconditioning. In addition, Keith had a long history of contributions to the North American Section of the ISHR, for which he served first as Secretary and then as President. It is the intent of this lecture to honor his memory and to recognize all that he has done for science and for our Society.

The Keith Reimer Distinguished Lecture will be held at each World Congress of the ISHR. In the non-Congress years, the lecture will be held at the meeting of the Section to which the selected speaker belongs. For example, if the selected speaker belongs to the Japanese Section, the Lecture will be held at the Japanese meeting; if he/she belongs to the Australasian Section, it will be held at the Australasian meeting, etc. This lecture is intended to be a high profile event which will be usually scheduled in lieu of a keynote plenary lecture. The speaker will be selected by Council and should be a leading scientist who has made major contributions to our understanding of cardiovascular biology. The topic of the lecture should be of broad interest to the scientific community. The speaker will be reimbursed for travel expenses, and will receive a plaque and a $1,000 honorarium. He/she will be announced in JMCC, HEART NEWS AND VIEWS, and on the ISHR website.

The Keith Reimer Distinguished Lecture will be a befitting tribute to the memory of Keith, an outstanding scientist and a staunch supporter of the ISHR. In addition, it will enhance the content of our scientific meetings by providing a high-quality presentation. I believe this initiative is another example of the continuing growth of the ISHR as a professional Society, and brings us on a par with other major societies. As always, your comments/suggestions are welcome. Please write to rbolli@louisville.edu.

Roberto Bolli, M.D.
Secretary General and Treasurer, ISHR

Report on the XXII European Section Meeting (July 3-6, 2002; Szeged, Hungary)

The city of Szeged, situated about 200 km south-east of Budapest may not be widely known outside Hungary. For Hungarians, however, Szeged is famed for its University, its fine Secessionist architecture, local produce (principally paprika and salami) and its summer sunshine record. Home to Albert Szent-Györgyi who first extracted ascorbic acid from local sun-ripened paprika, Szeged’s early July climate did not, for the most part, disappoint those who came seeking the sun. Those of us who sought scientific stimulation as well as the sun were doubly rewarded. The meeting in Szeged represented something of a renaissance of the European Section of the ISHR which had held no local meeting since 1999. The good atten–
dance at this meeting in Szeged, with some 450 registered participants, was a clear reflection upon the high calibre of the scientific programme and the enthusiasm of ISHR members, from Europe and further afield, to support the Section.

The scientific programme consisted of six plenary lectures, 21 thematic symposia incorporating presentations by keynote speakers and short original communications, a young investigator competition, and some 200 poster presentations. Thus, participants were treated to a very full and rewarding, if tight-fitting, programme. In reviewing such a large programme I can present only a glimpse of the variety and depth of the coverage of current cardiovascular research that was represented. The first of the plenary lectures was given by Professor Sir George Radda, of Oxford University and Chief Executive Officer of the UK Medical Research Council. Sir George outlined his vision of biomedical science in the post-genomic era, using the study of cardiac intermediary metabolism as a paradigm. The plenary lecture was followed by three parallel symposia on mitochondria, energy metabolism in heart failure and the coronary circulation. Keynote speakers in these symposia included Keith Garlid (USA), Andrew Halestrap (UK), Fabio DiLisa (Italy), William Stanley (USA), René Lerch (Switzerland), Heinz Rupp (Germany), Fabio Recchia (USA), Jürgen Schrader (Germany), Ulrich Decking (Germany), David Stepp (USA) and Alain Nitenberg (France). The second of the plenary lectures was given by Rudi Busse (Germany) on endothelial modulation of vascular tone. Wednesday afternoon brought another three parallel symposia. A symposium on cell death in heart failure included contributions from Jutta Levy (Israel), winner of the Israeli sectional Young Investigator competition 2002, provided a summary of elegant investigations providing new insights into the Frank-Starling relationship. Parallel symposia on atrial fibrillation and nitric oxide actions on failing myocardium. The role and regulation of myocardial potassium currents was addressed in another symposium in which speakers included Ursula Ravens (Germany), Antonio Zaza (Italy) and David Lathrop (USA). A third symposium on Wednesday afternoon focussed on current concepts in cardioprotection and was given in honour of Professor László Szekeres’ 80th birthday. László Szekeres was for many years head of the Department of Pharmacology at the Albert Szent-Györgyi Medical University in Szeged and it was appropriate that he should have been honoured thus at an ISHR meeting in his adopted city. In introducing the symposium, Jim Parratt (UK) reminded us of Laszlo Szekeres’ numerous contributions to cardiovascular pharmacology, spanning more than 50 years, and his contribution to the activities of the ISHR in the most recent 30 years. Speakers who contributed to this Festschrift were Derek Yellon (UK), Attila Ziegelhöffer (Slovak Republic), Edward Carmeliet (Belgium), Richard Gryglewski (Poland) and Jean-Claude Stoclet (France).

On Thursday morning, the third plenary lecture was given by Eduardo Marbán (USA). Dr Marbán described recent experimental work in his own laboratory on genetic manipulation of ion channels as a basis for somatic gene therapy of cardiac arrhythmia. Winners of recent ISHR awards were joined by Jennifer Van Eyk (Canada) and Jürgen Schrader (Germany) in a symposium on recent advances in cardiovascular research. The winner of the 2001 ISHR-ES/SERVIER Research Fellowship, Hilchen Sommerschild (Sweden) described work on the mediation of remote cardiac preconditioning following transient cerebral ischaemia. Carmit Levy (Israel), winner of the Israeli subsection’s Young Investigator competition 2002, provided a summary of elegant investigations providing new insights into the Frank-Starling relationship. Parallel symposia on atrial fibrillation and nitric oxide actions on myocardial function included key note talks by Marcel Borgers (The Netherlands), Stephane Hatem (France), Anton Tuinenburg (The Netherlands), David van Wagoner (USA), Rainer Schulz (Germany), Steven Sollott (USA) and Ajay Shah (UK).

On Thursday afternoon, one of three symposia was designated as the meeting’s Young Investigator competition. Five finalists presented a diverse and stimulating range of studies and were subjected to what can only be described as a demanding interrogation by the selection panel and members of the audience. Other symposia on Thursday afternoon were dedicated to nuclear receptors and genetic and genomic studies of cardiomyopathy, Ludwig Neyse (UK), Martin Wehling (Germany), Ludwig Bohlmann (Germany), Claude Delcayre (France), Jens Mogensen (UK), Anne Helbling-Leclerc (France) and Hugh Watkins (UK) contributed the key note addresses to these symposia.

Following the afternoon symposia on Thursday, the meeting delegates removed, en fête, to an evening of relaxation at Ópusztaszer. The National Historical Park at Ópusztaszer is a fine venue for presentation of the folk crafts and equine skills of the ancient Magyars, set in the vast wilderness of the Great Plain. It is therefore ironic that, in a week characterised by soaring temperatures and searing sun, the temperature fell by 17 °C in the 60 min interval between leaving the congress center and arriving at Ópusztaszer, data reliably provided by Cherry Wainwright’s cell phone handset. That it should rain as well as turn cold for an open-air event can only be regarded as the worst of British bad luck. Such are the vicissitudes of the weather in the British Isles that it was truly astonishing to learn how few of my countrymen actually carry an umbrella when you need to borrow one. More astonishing still was the realisation that some Americans actually possess an umbrella. But the rain was short-lived.
and did not dampen the enthusiasm for fine food, good companionship and a little after-dinner folk dancing to maintain the peripheral circulation.

Friday morning saw a return to bright summer sunshine and the temperature around 30°C for a full day of symposia and posters. Wolfgang Schaper (Germany) delivered the fourth plenary lecture on mechanisms of arteriogenesis. Three symposia on Friday morning provided comprehensive coverage of current work in myocardial ischaemic injury, gene and cell therapy, and excitation-contraction coupling. Keynote speakers included Metin Avkiran (UK), Adrian Saurin (UK), Andreas Busch (Germany), Thomas Eschenhagen (Germany), Jonathan Leor (Israel), Lior Gepstein (Israel), David Eissner (UK), Gerd Hassenfuss (Germany), Ernst Niggli (Switzerland), Karin Sipido (Belgium) and Andrew Trafford (UK).

Friday afternoon began with the fifth plenary lecture by Jim Downey (USA) who reviewed current evidence for the role of mitochondrial K<sub>ATP</sub> channels in the mechanism of ischaemic preconditioning. Dr Downey’s address served as a timely introduction to one of the afternoon symposia, which was very fully programmed, on new aspects of preconditioning research which included keynote lectures by Michael Cohen (USA), Brian O’Rourke (USA) and Michael Marber (UK). Other symposia on Friday afternoon focused on extracellular matrix-cytoskeleton interactions, and neurohormonal mechanisms in cardiac disease, with contributions from Hans Eppenberger (Switzerland), Elisabeth Ehler (Switzerland), Zhenlin Li (France), Marcus Schaub (Switzerland), Vincent Christoffels (The Netherlands), Jane-Lise Samuel (France), Sandor Juhász-Nagy (Hungary), Thomas Rau (Germany), Sian Harding (UK) and Thomas Eschenhagen (Germany).

The hospitality of the meeting organisers reached its apotheosis in the conference banquet held in the ornate dining hall of the Hotel Tisza. To feed several hundred people (with anything more than loaves and fishes) requires some degree of formality on the part of the restaurant staff but no such formality was required of, or displayed by, the guests at this feast. The atmosphere was one of great relaxation and of celebration. We witnessed here the award of prizes to the Young Investigator competition winner, Tibor Ziegelhöffer (Germany) for his work in Wolfgang Schaper’s laboratory in Bad Nauheim (Germany) on the role of volume-regulated chloride channels in the mechanism of arteriogenesis, and runners up, Luigi Venetucci (UK) and Christophe Heymes (UK). The European section also honoured Peter Carmeliet (Belgium) with its research achievement award. For many of us, including a group of seasoned volupturners from Essen, the enjoyment of this banquet continued into the small hours of Saturday morning.

The prospect of a fourth day of scientific exploration may have daunted many but the scientific sessions remained lively on Saturday morning. The final plenary lecture was given by Roberto Ferrari (Italy) on myocardial remodeling, and preceded three well-attended symposia. These symposia covered myocardial oxidative stress, congenital and acquired arrhythmic disorders, and the heart in diabetes. Invited speakers at these symposia included Claudio Ceconi (Italy), Anna Cargnoni (Italy), Rick Schulz (Canada), Peter Ferdinandy (Hungary), Tamás Fazekas (Hungary), Paul Volders (The Netherlands), Carlo Napolitano (Italy), Marc Vos (The Netherlands), Jutta Schaper (Germany), Tanya Ravingerova (Slovak Republic) and Valeria Kecskeméti (Hungary). The last of these symposia was dedicated to the memory of Maria-Sophia Koltai, whose sudden and untimely death was announced during the preceding year and whose experimental and clinical work in the field of diabetic cardiomyopathy is well known.

Throughout the meeting, “free communications” were given either as short oral communications during the symposia or as poster presentations on Wednesday and Friday. The selections of original communications for oral communication during the symposia were made by individual symposia organisers. The format worked very well and gave many young workers the opportunity to speak alongside more established scientific names. This is a practical and laudable way of covering the range of current research effort in a...
particular area. The place of the poster presentation is now well-defined in scientific meetings of this type and both the number and quality of posters presented was high with almost no “no-shows”. I’m not sure that anyone would yet claim to know the secret to successfully incorporating poster sessions within a large meeting format but the Szeged meeting organisers have come close. Four things seem to be obligatory: (i) place the posters close to the other activities of the meeting, (ii) group the posters appropriately under relevant section headings, (iii) schedule dedicated poster sessions and get them moderated by chairmen who can lead discussion, and (iv) provide food. In my experience all these essential elements were present and worked together to make for lively and informative interaction.

Szeged 2002 was a memorable, highly successful and enjoyable meeting that combined all the best elements of the best ISHR meetings: scientific stimulation, discussion, physical satiety, friendly interaction. Ágnes Végh, the Chair of the meeting, and her hard-working local organising committee have already received the thanks and praise of many others more eloquent than I. I can only add that for those of us who travel to more meetings than we should, a meeting such as Szeged 2002 is a rare and enjoyable event, made unique by personal effort and attention to detail. 

Nagy köszönöm, Ágnes!

Gary F. Baxter, Ph.D.
London, UK

In Memoriam

Keith Arnold Reimer

Keith Arnold Reimer, M.D., Ph.D., a Professor of Pathology at Duke University Medical School and a superb experimental cardiologist and cardiac pathologist, died on March 15, 2002. He was 56 years old. The cause of death was metastatic adenocarcinoma of the kidney.

Keith was born in Beatrice, a small town in Nebraska, on April 10, 1945. He graduated from high school in a class of 7 students. Typical of Keith is the fact that by the time he had graduated, he had taken every course offered by this small school except Home Economics. After graduating from high school, he attended Bethel College in North Newton, Kansas from which he graduated in 1967. While at Bethel, he met and married Susan Stuckey. He entered Northwestern University Medical School in Chicago, Illinois in 1967 and graduated in 1972 from the medical scientist training program with both an M.D. and a Ph.D. degree.

At the end of his sophomore year in medical school, he entered the graduate school of Northwestern University and began work on his Ph.D. in the laboratory of R.B. Jennings. His thesis was entitled “Metabolic and Structural Alterations in Renal Cortex Following Ischemic Injury” and was one of the first studies on the mechanism of tubular cell death using an approach integrating metabolism and cell fine structure. These studies were well received in renal circles, but he was unable to continue them because he decided to take residency training in pathology.

After two years of residency training at Passavant Memorial Hospital in Chicago (now Northwestern Memorial Hospital), he returned to the Jennings laboratory as a post-doctoral fellow and began work on cardiac ischemia, which was the main focus of investigation in this laboratory. His initial effort was dedicated to cardioprotection provided by blockage of β-adrenergic receptors.

When Jennings moved to Duke, Keith joined him as an Assistant Professor of Pathology and they began a long collaboration that resulted in the development of a series of well-known concepts, such as the “wavefront phenomenon of cell death in acute ischemia” (published as Reimer, Lowe, and Jennings: The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 56:786-94, 1977 which has been cited over 1000 times), “the relationship between high-energy phosphate depletion, lactate accumulation, and myocyte death”, the development of an “animal model for protecting ischemic myocardium” (AMPIM), and finally the concept of “preconditioning with ischemia” (published as Murry, Jennings, and Reimer: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74: 1124-36, 1986 which has been cited over 1700 times). His scientific reputation rested on this solid foundation. These studies plus his skills as a teacher and pathologist led to his appointment as a Professor of Pathology at Duke in 1988.

The discovery of the protective effect of ischemic preconditioning has spurred an ever-expanding number of experimental studies, in a wide variety of tissues, with experimental confirmation of this remarkably protective phenomenon in a wide variety of settings including in common clinical situations. Ischemic preconditioning is one of the most reproducible phenomena in experimental biology. Since the original report of the phenomenon in 1986 in

NEWS BULLETIN
The first scientific steps I undertook at the Institute for Heart Research of the Slovak Academy of Sciences in Bratislava, Slovakia, where I worked the last two years of my medical studies as a student research fellow. After graduating as MD from the Medical Faculty of Comenius University in Bratislava in 1997, I decided to study for my PhD degree. At this time I attended a lecture by Professor Wolfgang Schaper and I was enormously impressed by his talk about the growth of collateral arteries. A few months later, in October 1998, I joined his laboratory at the Max-Planck Institute for Physiological and Clinical Research in Bad Nauheim, Germany.

History of the Collateral Circulation

In the 17th century the English physician Richard Lower pointed out that human coronary arteries anastomose with each other, and that fluid injected into one spreads also into the other. Since then, such interconnecting arterioles have been found in most organs and tissues of humans and of all mammals studied [1,2]. These pre-existent vessels can develop into large collateral arteries that may prevent or limit the damaging consequences of vascular occlusive diseases. Thirty years ago Professor Wolfgang Schaper started to investigate the underlying mechanisms of this process. To dif-

Swelling Cell - Doing Well?

Volume-Regulated Chloride Channels and Arteriogenesis

The cardiovascular community and the Duke community will miss him very much.

Robert B. Jennings, M.D.
Charles Steenbergen, M.D.
differentiate collateral artery growth from angiogenesis, i.e. capillary growth by sprouting and intussusception, it was termed arteriogenesis.

**“Back to the Future”**

In the previous studies in late 70’s endothelial cell swelling have been found to be one of the earliest morphological events visible after an occlusion of a major artery. Maintenance and regulation of cell volume are crucial for the homeostasis of living organisms. In response to swelling, endothelial cells activate the cation and anion channels allowing an efflux of osmolytes returning cell volume toward its original value. Activation of volume-regulated, outwardly rectifying Cl- channels (VRACs) seems to play a key role in this process. Therefore we investigated whether the inhibition of VRACs would be mirrored by the inhibition of arteriogenesis.

Recently, we have developed a mouse model of hindlimb ischemia, that allows us to separate spatially angiogenesis and arteriogenesis. This model involves unilateral femoral artery occlusion in a well defined site. Using this model we found that the growth and remodeling of preexisting inter-arterial collateral connections into mature collateral arteries is the most important process for the restoration of blood flow after femoral artery occlusion in mice [3]. In some previous publications angiogenesis was suggested to provide the basis for improved collateral-dependent flow in this animal model [4]. However, capillaries are not suitable as conductance vessels, as they lack the stability of arterial vessels. In order to be very effective in perfusion recovery following the femoral artery occlusion, capillaries would have to remodel into arterial vessels bridging the occlusion site. This does not appear to happen to any significant degree in the mouse, as the location and pattern of grown and preexisting collaterals is similar [3]. Moreover, the capillary density significantly increased after femoral occlusion only in the distal ischemic bed whereas no changes in capillary density were observed in the proximal hindlimb [3].

Taking advantage of this model we studied the effects of mibebradil, an effective blocker of VRACs, on the process of collateral artery growth. We found a significantly impaired perfusion recovery in the hindlimbs of mibebradil-treated mice seven days after the surgery as measured by laser Doppler imaging. Pedal hemoglobin oxygen saturation measurements mirrored the laser Doppler findings and underlined the physiological significance of the measured perfusion differences. To confirm that the deterioration in perfusion recovery in VRAC-blocker treated mice was due to an inhibition of arteriogenesis and not angiogenesis we performed a morphometric analysis of the inner diameters of the growing collateral arteries from the adductor region (upper leg) of the mouse hindlimbs. Our measurements showed a decrease in arteriogenic response in the mibebradil-treated group in comparison with control animals. In order to demonstrate endothelial cell swelling observed in our previous studies we dissected two superficial collateral arteries prominent in the adductor region from the ligated as well as the non-ligated side and analyzed them by light and electron microscopy. A typical ultrastructural pattern of a quiescent artery was observed in sections from the non-ligated side whereas a perinuclear vacuolization of endothelial cells from the midzone-sections of activated collateral arteries was observed as early as 4 hours after femoral artery occlusion. The perivascular edema was prominent as long as 24 hours after the ligation.

**From VRACs Activation to Collateral Artery Growth**

Ischemia was considered to be the most important trigger of compensatory vascular growth accompanying obstructive arterial diseases. This seems to be true only for angiogenesis. Arteriogenesis usually occurs in non-ischemic tissue and does not appear to depend on local ischemia. Therefore, physical factors, mainly fluid shear stress, have been hypothesized to be the arteriogenesis driving force. After occlusion of a major artery the pressure in the dependent periphery drops and blood flow through preexisting collateral vessels, if present in this region, will increase. Consequently, the shear forces acting on the vessel wall of these interconnecting arteries increase significantly providing an initial signal for their growth and remodeling. The signal is sensed by the vascular endothelium, which besides its other functions act as a mechanotransducer converting the mechanical stimuli into biochemical signals. The precise mechanisms of the endothelial shear stress signaling remains unclear. Nevertheless, some previous studies were able to show that volume-regulated endothelial Cl channels are involved in the initiation of this signaling process [5,6]. Thus, it is very likely that these anion channels are also involved in the signaling cascade of arteriogenesis. This hypothesis is also supported by the finding that blockers of VRACs, including mibebradil, were able to inhibit endothelial cell proliferation in cell culture [7].

Our morphological analysis showed that endothelial cell swelling is one of the first visible events in the activated collateral artery within the first 24 hours after ligation of the femoral artery. Activation of VRACs seems to play a key role in the process of maintenance and regulation of cell volume. As a result
of VRAC activation, the driving force for Ca\textsuperscript{2+} entry in to the cell increases representing a possible mechanism for the antiproliferative effect of chloride channel blockers. Additionally, the blockade of VRACs may induce an increase in the intracellular pH. This alkalization in turn may inhibit the proliferation of cells in the G0/G1 stage [8].

Taken together, our results suggest that endothelial chloride channels are involved in the initiation of collateral artery growth. Since endothelial chloride channels have been shown to be activated by shear stress, they may represent an important link between shear stress and arteriogenesis.

The ISHR – Young Investigator Award

The end of April brought some very exciting news to me. The International Jury selected my abstract among the six finalists for the Young Investigator Competition as a part of the 22nd European Section Meeting of the International Society for Heart Research in Szeged, Hungary. The meeting itself was scientifically excellent and held in an ISHR-typical warm and very friendly atmosphere. However, the real personal highlight for me was the honor itself to be selected as the winner of this prestigious award. I would like to take the opportunity to express my sincere gratitude to Professor Wolfgang Schaper - my scientific mentor and advisor. Furthermore I would like to thank all my collaborators and my family for their support.

References


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HEART NEWS AND VIEWS

HEART NEWS AND VIEWS is the official News Bulletin of the International Society for Heart Research and is published every fourth month.

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