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**XIX WORLD
CONGRESS,
ITALY
JUNE 22-26,
2007**

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**THE VENICE
OF PETER
HARRIS**

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**NEW
ORLEANS,
LOUISIANA
MAY 2005**

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IN THIS ISSUE:

- *From the Secretary General* 1
- *New Orleans, May 2005* 2
- *President's Letter* 3
- *H.E.L.P.* 4
- *Past Truth & Present Poetry, by Richard J. Bing* 5
- *Bridging the Gap, where clinical and basic sciences meet, by Karl T. Weber* 6
- *Report on Kofu Meeting* 8
- *In Memoriam Norman Alpert* 9
- *Report on ISHR-ES / SERVIER Research Fellowship 2002* 11
- *Rebuilding the Heart, by Piero Anversa* 13
- *The Bricks of Venice* 15
- *Meetings Calendar* 15

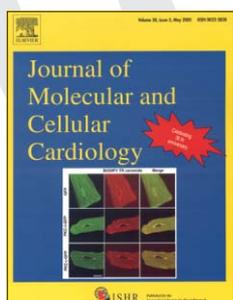
FROM THE SECRETARY GENERAL

As I write this letter, I am already approaching the end of the first year of my tenure as Secretary General, a post which I took over from Roberto Bolli (now our President-Elect) in August 2004. I have to admit that I took on this post with considerable trepidation, in the full knowledge that my predecessor, with his energy, dedication, vision and organization, would be an extremely hard act to follow. As it turned out, the last of these attributes actually worked to my advantage; because Roberto has kept such immaculate records, I have been able to find the answers to most questions that have arisen in the extensive files that he has shipped to me (I reckon he must have hired an entire freighter). Also, on the rare occasions that the files have failed me, Roberto has responded with instant advice by e-mail or phone. So, a big "thank you" to Roberto for making my job so much easier!



Moving on from one Roberto to another, Roberto Ferrari, our President, announced in the previous issue of *Heart News and Views* the prospect of the European, American and Japanese Sections holding their annual section meetings in 2007 in Italy, in conjunction with the **XIX World Congress** in Bologna. I am delighted to announce that the commitment of these Sections to this exciting new venture has now been confirmed, as has the decision of the Australasian Section not to hold a separate section meeting that year. I would like to take this opportunity to thank the leadership of each of those Sections for their bold and visionary approach in supporting the single most important event in our Society's international calendar, and of course Roberto (as the Congress organizer) for taking on this important

(continued on page 2)



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challenge with his usual enthusiasm and creativity. The logistical details remain to be finalized and will be communicated to the membership in due course. Nevertheless, the current plan is for each of the three pertinent Sections to hold a thematically distinct meeting at a different venerable Italian university on the days immediately preceding the World Congress, before gathering together at the *Palazzo della Cultura e dei Congressi* in Bologna for the Congress itself. The likely themes and host universities are as follows:

European Section: Injury and Cardio-protection, University of Padova.

American Section: Heart Failure and Cardiomyopathies, University of Bologna.

Japanese Section: Cardiovascular Regeneration, University of Ferrara.

In addition to the World Congress, and of course our excellent journal (*Journal of Molecular and Cellular Cardiology*) and newsletter (*Heart News and Views*), the International Section is also responsible for organizing a number of highly prestigious awards, to recognize outstanding scientific achievement in cardiovascular biology and medicine at all levels of the career ladder. The full details of these awards are available on the ISHR web site (www.ishrworld.org) but, to remind you, their frequency and remit are as follows:

Annual Awards

- **Outstanding Investigator Prize** (only in non-World Congress years): Recognizes an outstanding scientist who has made major and independent contributions to the advancement of cardiovascular science and who is likely to further develop his/her research in the future.
- **Keith Reimer Distinguished Lecture:** Recognizes scientific achievements in the field of ischemia, coronary hemodynamics, cardiac metabolism or contractile mechanisms.

- **Janice Pfeffer Distinguished Lecture:** Recognizes scientific achievements in the field of cardiovascular remodeling, hypertrophy or heart failure.
- **President's Lecture** (new—first award in 2006): Recognizes scientific achievements in the field of cardiovascular molecular biology, genetics, genomics or proteomics.

Triennial Awards (at the World Congress)

- **Peter Harris Distinguished Scientist Award:** Recognizes lifetime contributions to cardiovascular science.
- **Research Achievement Award:** Recognizes an outstanding scientist who has made major and independent contributions to the advancement of cardiovascular science and who is likely to further develop his/her research in the future.
- **Richard J. Bing Award for Young Investigators:** Recognizes outstanding endeavors by new investigators in research activities, and encourages continued biomedical research careers broadly related to cardiovascular biology.

I encourage you to participate in these awards by making nominations (either directly to me or through your International Council representative, as appropriate), to ensure that deserving candidates continue to be considered and recognized. I am particularly anxious that we have as many high-quality applications as possible for the Richard J. Bing Award for Young Investigators competition to be held at the XIX World Congress in 2007. To this end, I urge senior ISHR members to begin encouraging their young faculty members, fellows or even research students now, while there is still time to complete those key experiments!

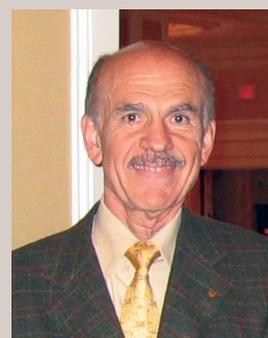
While on the topic of ISHR awards, I would like to end my letter by congratulating Dr Eric Olson (2005 Outstanding

Investigator Prize Recipient), Dr Edward Frohlich (2005 Janice Pfeffer Distinguished Lecturer) and Dr Masao Endoh (2005 Keith Reimer Distinguished Lecturer), who have received or soon will receive fully-deserved awards at the annual meetings of the American Section (New Orleans, May 2005) and the Japanese Section (Osaka, December 2005). The due recognition of such outstanding investigators from different parts of the globe reflects well on the international nature and aspirations of our Society.

Metin Avkiran, PhD, DSc.
Secretary General

NEW ORLEANS, LA MAY 2005

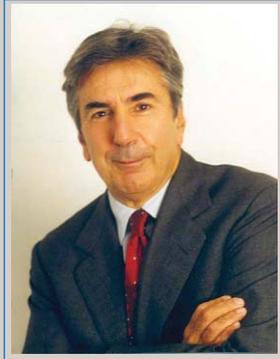
The Keynote Lecture *Nitric Oxide as a Unique Signaling Molecule in the Cardiovascular System* by Nobel Laureate **Louis J. Ignarro** was one of the highlights of the **XXVII American Section Meeting** in New Orleans (May 12-15, 2005).



Louis J. Ignarro

In the forthcoming issues of *Heart News and Views* we will publish a report on the meeting, as well as biographies of Edward Frohlich (2005 Janice Pfeffer Distinguished Lecturer) and Eric N. Olson (2005 Outstanding Investigator Prize Recipient), and a report from Asa B. Gustafsson (Winner of the Young Investigator Award Competition).

PRESIDENT'S LETTER



Dear Reader,

WHEN Jim Downey passed to me the Presidency of the ISHR in Brisbane, he mentioned that I had to get my pen ready. I didn't immediately understand what he meant, and I thought that it was my command of English – not always so good – and that perhaps I misunderstood him. In fact, my understanding was correct, and it is unbelievable how time flies, and how punctually Dutch Tom is in reminding me to write a new article for Heart News and Views!

Well, here I am again, and I would like to pass onto you this time a very important message, and this is that I am beginning to feel even prouder to be the President of the ISHR, and particularly of the World Section. The main reason for this is that, perhaps, I feel that we are going to achieve something during this period - to hold a truly giant meeting with all ISHR Sections involved. This is the mission of the World Section, and this mission will be fulfilled in Bologna. I have already had two really excellent meetings with the leadership of the European Section, both with its President Gerd Heusch, and with its President-Elect and my great friend Fabio Di Lisa. I met with Fabio in Padova and Bologna, and with Gerd in Nice, and we had long discussions about how to arrange a day dedicated to the European Section in Padova, prior to the World Congress which will be held in Bologna. This is an excellent arrangement because Italy will host the European Section, we will learn a great deal from their Section Meeting, and they will also be able to bring a lot of delegates to the World Congress! At the same time, we also had a very fruitful meeting in Bologna with a delegation from the North American Section (Tish Murphy, Rick Moss and Bill Weglicki), our Secretary General Metin Avkiran, and the "Grandfather", or should I say "Godfather", of the ISHR, David Hearse.

In front of the Fountain of Neptune on the Piazza del Nettuno, Bologna, in April 2005. From left to right: Daniela Sala (Director of the Congress Agency), Bill Weglicki, Rick Moss, Metin Avkiran, Roberto Ferrari, David Hearse and Fabio Di Lisa. The photo was made by Tish Murphy.



We spent one day and two nights (therefore two dinners and one lunch!) in Bologna visiting all of the possible locations, the old university museum, and the main congress centre, and discussing how best to organise the one-day meeting in Bologna dedicated to the North American Section prior to the World Congress. Again, this will allow us to learn from them and have a big delegation from the US already in Bologna for the opening ceremony of the World Congress. I am particularly looking forward to meeting with the Japanese Section – I already have my ticket to Osaka - and I am offering them my own University of Ferrara as the possible location for their one-day Meeting. This is where Copernicus and Paracelsus studied. Ferrara is a lovely city only 25 minutes from Bologna by train; therefore it is an ideal location for their pre-meeting.

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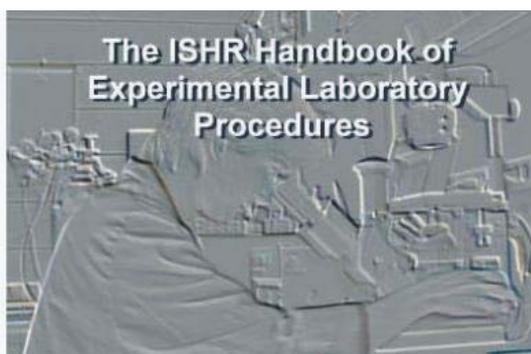
The other Sections should not feel left out, and we still have the University of Pavia, which would be more than welcome to host one or more ISHR Sections or Inter-Sections before the World Congress.

Together we will enjoy the World Congress in the oldest universities in the world! But ... this achievement is much more. We have agreed that the larger Sections will arrange at least two symposia during the World Congress in Bologna and I think that this will really reinforce the World spirit of our Society. Possibly, 2007 will be a turning point for the ISHR and its World Congresses. We are working on it, and I hope that we will be successful. As you know, nobody can do anything alone, and I am lucky enough to have a great group in each Section that is assisting me in achieving this end point. Many thanks to all of them, and *arrivederci a Bologna!!!*



Roberto Ferrari

THE ISHR SOLICITS ARTICLES FOR THE



HANDBOOK OF EXPERIMENTAL LABORATORY PROCEDURES

IN 2003 the ISHR started the Handbook of Experimental Laboratory Procedures (H.E.L.P.) on the ISHR International's web site www.ishrworld.org. The concept was to provide a very practical description of useful laboratory procedures which would benefit all investigators. The advantage of the cyberspace format is that these pages are living documents that can be updated whenever an advance in the technology occurs. Also, the authors are available to answer specific questions by email. Currently we have how-to articles on perfusing the isolated heart, isolating cardiomyocytes, measuring infarct size, patch clamping and several biochemical procedures. The pages are being heavily used if the amount of email that I receive related to my offering on the site is any indication.

The ISHR would like to expand this

service and I am asking anybody who would be willing to share their practical knowledge about how to execute a useful procedure to write an article for the site. Please direct all correspondence to me, the H.E.L.P. editor, at jdowney@usouthal.edu. You can inform me of your idea and I will work with you to H.E.L.P. you put your idea into the suitable format. All you must supply is the text in a word processor format and any useful figures. We will convert it to the HTML format and load it on the site. Also you can send me the address of any existing web site that provides useful information and we can add it as a link to the site.

The ISHR envisions H.E.L.P. as becoming a major resource for the research community over the years to come. The H.E.L.P. pages should greatly reduce the difficulty involved in getting a new method

up and running in the laboratory. Also, the web pages are citable and that can greatly reduce the size of a methods section. The H.E.L.P. pages are not meant to be scholarly review articles and not only is referencing not required it is actually discouraged. Rather, they are meant to be practical. Potential pitfalls should be discussed and links should be used liberally in the pages to direct the reader to the web sites of the relevant equipment and chemicals suppliers. That makes the pages very easy to write. The broader the variety of offerings on the ISHR's H.E.L.P. site the more successful it will be. I therefore encourage everyone to take a look at the site and think about what you could contribute to enhance this service.

Jim Downey. Ph.D.
Past President

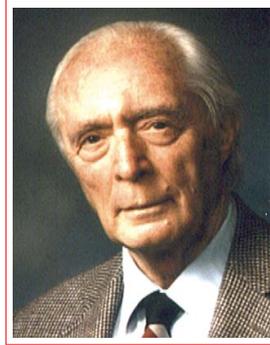
PAST TRUTH & PRESENT POETRY

As a medical student in Freiburg, Germany, in 1929, I attended lectures in zoology by Hans Spemann. I recall him as a quiet, thoughtful teacher. Despite his rather monotonous presentation, we students respected him because he had received a Nobel Prize. We did not know that he had pioneered nuclear transfer, a technique which many years later became important in the research on embryonic stem cells. Stem cells are not restricted to mammalian organisms, they also play an important role in the growth of plants, as a population of undifferentiated cells in the meristem forms leaves, flowers, and stems. Each time a new leaf or flower develops, new cells leave the meristem and are added to the growing plant. Apparently, evolution has preserved the ability of cells to renew and to rebuild for at least 1.6 billion years, the estimated date of divergence of lineage of plants from animals.

Today the miraculous potential of stem cell research fills newspaper columns, occupies congressional committees and floods government agencies. They possess long term self-renewal (the ability to divide independently without senescence) and pluripotency (the ability to generate disparate cell types). They are relatively undifferentiated and highly clonogenic, and are capable of unlimited, undifferentiated proliferation *in vitro* and *in vivo*. They have high levels of telomerase activity. Telomeres are elements which seal the ends of chromosomes and consist of more than a hundred repeats of nucleotides, which are gradually lost as the cells divide and age, resulting in senescence of the cell. Telomerase is responsible for the synthesis and maintenance of telomere repeats.

Early in his career, Hans Spemann developed tuberculosis and to pass the time during recovery he familiarized himself with Developmental Biology (see Kiessling and Anderson). At the time it was understood that a single fertilized

28. HANS SPEMANN AND
STEM CELL RESEARCH



RICHARD J. BING

egg undergoing multiple cleavages gives rise to all individuals, and that only sperm and egg maintain the full complement of inheritance. While working in Würzburg, using a loop of hair from his newborn son to separate two cells of a blastomere of a salamander, he investigated whether one developed into the head and the other into the tail; however two complete salamanders developed. He then repeated the experiment by separating each blastomere of a four cell salamander and four salamanders developed. This went on until the eighth-cell stage, when development became unpredictable. Then he performed his classical experiment by transferring both zygotic nuclei into one half of an egg's cytoplasm. After they had cleaved several times, he manipulated one of the embryonic nuclei into the other side of the cytoplasm. A second embryo was formed. This constituted the first nuclear transfer in history. It proved that nuclear division does not decrease the genetic information in the embryonic nucleus.

For a while, amphibians remained a favored experimental model. Gurdon in 1962 transplanted nuclei from differentiated intestinal epithelial cells blastocysts of feeding tadpoles into enucleated recipient eggs. He showed that the nucleus can promote the formation of a differentiated intestinal cell and at the

same time contain the genetic information necessary for the formation of all other cell types. Later, nuclei were also transplanted into enucleated frog eggs from early and late frog embryos. Only transplanted nuclei from early embryos resulted in normal tadpoles.

What is the relevance of nuclear transfer for stem cell research? Nuclear transfer results in a blastocyte, a ball of trophoblast cells, sealed together with tight junctions that contain the inner cell mass of undifferentiated stem cells that develop into an embryo. Nuclear transfer, the transfer of the nucleus of a somatic cell into the protoplasm of an enucleated egg cell, can result *in vitro* in the formation of a blastocyst, which then becomes a source for embryonic stem cells. For those who believe that life begins at conception and that blastocysts are human beings, nuclear transfer is non-ethical, regardless of whether blastocysts are growing in a test tube or obtained from fetuses. Unfortunately, biologically blastocysts grown *in vitro* do not measure up to those developing in utero, because of smaller inner cell mass. Only time will tell, whether human embryonic stem cells obtained from *in vitro* grown blastocysts are viable and can differentiate into target tissue. Even if this procedure is successful, it must overcome religious and ethical objections!

Aside from embryonic stem cells, work on mesenchymal, neural and hematopoietic stem cells may be rewarding. The stakes are high, the reward is the successful treatment for disorders of the central nervous system or diabetes. Much has been said about the usefulness of useless science, that is science which first appears to be irrelevant to human welfare and health, but which later turns out to become the cornerstone of new approaches to the treatment of disease. Who would have thought that experiments on salamander embryos and feeding tadpoles would

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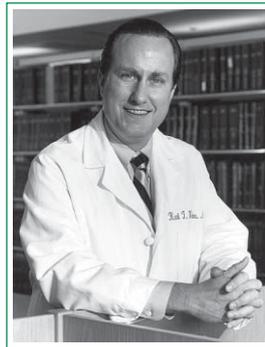
BRIDGING THE GAP. WHERE CLINICAL AND BASIC SCIENCES MEET

BY KARL. T. WEBER, M.D.

ROVANIEMI, Finland is situated along the Arctic Circle bordering on Lapland. Its winters stretch from October to May with the sun rarely ascending above the horizon for months at a time. Today was yet another dark day of winter, a Monday in late March. Rovaniemi was home to physician Nicole Saarinen, who was not mindful of the weather. Instead, she took comfort in caring for her patients.

In clinic today Nicole saw Mr. E, a 66-year-old retired carpenter, who 1 year ago had an uneventful anterior myocardial infarction (MI) without evidence of left ventricular (LV) dysfunction. Three months later, however, he reported breathlessness with minimal exertion and the appearance of lower extremity edema. Nicole found his heart's apical impulse to not be displaced, but there was a new holosystolic murmur that radiated from the apex to the axilla, which increased in intensity with isometric hand grip. Nicole diagnosed congestive heart failure (CHF) due to a previous MI and mitral regurgitation secondary to anterior papillary muscle dysfunction without left ventricular (LV) dilatation. An echocardiogram was obtained to monitor LV size and shape over time. She had prescribed: an angiotensin converting enzyme (ACE) inhibitor to attenuate the impact of effector hormones of the renin-angiotensin-aldosterone system on salt and water retention, vascular impedance and progressive chamber dilatation; and furosemide, a loop diuretic, to assist in eliminating expanded portions of his intra- and extravascular volumes, together with KCl supplementation to prevent hypokalemia. Today, Nicole was gratified to find Mr. E's symptoms and signs of CHF had resolved; however, she wondered should furosemide be continued? Clinical trials had demonstrated the efficacy of ACE inhibitors in the long-term management of heart failure and in preventing progressive LV dilatation. But did Mr. E

PLEASE DON'T TAKE MY SUNSHINE AWAY



still need furosemide? There was little doubt it had eliminated the salt and water retention that led to his CHF, but would it prove detrimental in the long run? In pondering these questions, Nicole could not help but be influenced by today's clinic patients.

First, Mrs. C, a 39-year-old Lapp whose diminutive stature and darker skin could not easily be discerned from behind the thick coat of reindeer fur folded on her lap. Mrs. C had complained of recent onset, disabling back pain. A crush fracture of her lumbar spine was found on x-ray. Serum 25(OH)D was reduced while circulating parathyroid hormone (PTH) and calcitriol (1,25(OH)₂D₃) were elevated. Nicole diagnosed secondary hyperparathyroidism (HPT) with PTH-mediated bone resorption accounting for a reduction in bone mineral density (BMD) and strength leading to vertebral fracture. The parathyroid glands' enhanced secretion of PTH had been provoked by hypovitaminosis D due to virtually no sunlight during winter months in Lapland. Nicole would turn to a "sunshine substitute," high-dose vitamin D, together with dietary Ca²⁺ supplements.

Next, Mrs. M, a 32-year-old veiled Arab immigrant from Pakistan who, as an adolescent, had moved with her family to Norway. Mrs. M was visiting a friend in Rovaniemi who brought her to clinic today because of left ankle pain. X-ray revealed a fractured fibula. Strange thought Nicole that this presumably healthy, menstruating woman would sustain a spontaneous fracture. Serum PTH was markedly elevated and likely due to hypovitaminosis D related to Mrs. M's dress code that since adolescence had reduced sunlight exposure and predisposed to bone softening, or osteomalacia. Nicole prescribed high-dose vitamin D, a calcium supplement, and other appropriate therapy.

Then, Mr. K, a 76-year-old widower and nursing home resident with a history of hypertension and occasional ankle edema for which he received a beta blocker and furosemide. He was brought to clinic complaining of hip pain and x-ray revealed a nontraumatic hip fracture. Serum levels of albumin-corrected Ca²⁺ and 25(OH)D were each reduced while plasma PTH was elevated. Yet another case of secondary HPT due to hypovitaminosis D? But there was more. Aside from his confinement to the nursing home and lack of exposure to sunlight, Mr. K's age and immobilization were also contributory. And what role did the beta blocker and loop diuretic play regarding the health of his bony skeleton?

Questions

How would these 3 cases impact on Nicole's management of Mr E? Would she continue to prescribe furosemide?

Answer

In 1928, the Nobel prize for chemistry was awarded to Adolf Windaus for his studies "on the constitution of the sterols and their connection with vitamins," specifically vitamin D.

Upon exposure to sunlight and ultra-

PLEASE DON'T TAKE MY SUNSHINE AWAY

violet B radiation, vitamin D, a steroid hormone, is synthesized in the epidermis. Aging decreases the skin's ability to produce vitamin D, particularly amongst the elderly. Vitamin D enters the circulation, where it is bound to a vitamin D-binding protein, and transported to the liver to be converted to 25(OH)D, an index of vitamin D stores. 25(OH)D is a precursor to 1,25(OH)₂D₃, or calcitriol, the biologically active, circulating metabolite of vitamin D formed in the kidneys. A nuclear receptor for calcitriol, or VDR, a member of the steroid superfamily of receptors and phosphorylation of the 1,25(OH)₂D₃-VDR complex, leads to its interaction with retinoic acid X receptor and subsequently with vitamin D-responsive elements in the nuclei of target cells. In osteoblasts, this complex increases the mRNA expression of bone morphogenic proteins (e.g., osteocalcin and osteopontin). In diseased soft tissues, the upregulated expression of these proteins contributes to dystrophic calcification, such as calcific aortic sclerosis. In the intestine this complex promotes Ca²⁺ absorption and in the kidney Ca²⁺ reabsorption.

Hypovitaminosis D results from limited

sunlight exposure and the inadequate endogenous production of vitamin D. The subsequent reduction in intestinal Ca²⁺ absorption and resultant hypocalcemia stimulate PTH secretion—a form of secondary HPT. PTH enhances bone Ca²⁺ resorption while decreasing renal Ca²⁺ clearance. In the case of Mrs. C, dark winter months and her cold climate-based clothing led to hypovitaminosis D with secondary HPT. Lapps are the smallest people of Europe averaging 5ft in height. Mrs. M also had hypovitaminosis D and secondary HPT, where PTH induces renal phosphate wasting to result in osteomalacia. The Oslo Health Study found marked elevations in plasma PTH in veiled Pakistani women living in Norway, compared to Norwegian controls, and which are accompanied by vitamin D deficiency. The same is true for veiled Arab women living in Denmark. Hypovitaminosis D is a common risk factor for secondary HPT in elderly nursing home residents and an important predictor of HPT is their daily furosemide dosage. Beta adrenergic receptor antagonism, with or without a thiazide diuretic, has been suggested to protect BMD and reduce the risk of fracture, however, this remains controversial. Mr K's furosemide would likely overcome any favorable response to beta blockade.

Elevations in plasma aldosterone, such as appear in CHF, promote an increased excretion of Ca²⁺ and Mg²⁺ in both urine and feces, leading to secondary HPT with subsequent loss of BMD and bone strength. Co-treatment with spironolactone, an aldosterone receptor antagonist, attenuates these losses at both sites to preserve bone strength. Furosemide accentuates the urinary loss of these cations seen with aldosteronism and contributes to reduced BMD. The combination of hydrochlorothiazide and spironolactone normalizes urinary Ca²⁺ and Mg²⁺ losses seen with aldosteronism to preserve BMD. Finally, usual daily doses of furosemide promote the urinary excretion of thiamine. Vitamin B₁ deficiency can depress myocardial contractility.

Nicole was correct in pondering the wisdom of continued furosemide treatment in Mr. E, a now compensated, euvolemic patient. Spironolactone alone, or together with a thiazide diuretic, might prove just as effective and safer on skeletal health. In addition, she elected to prescribe Mr. E with supplemental vitamin D, calcium, magnesium and thiamine.

Karl T. Weber, M.D. ■

HANS SPEMANN AND STEM CELL RESEARCH

(continued from page 5)

develop into new approaches to the treatment of a large variety of human ailments! Hans Spemann deserves the credit for having initiated a new aspect of fundamental biology which hopefully will develop into the successful treatment of disease.

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Richard J. Bing, M.D. ■

REPORT ON THE XXI ANNUAL MEETING OF THE JAPANESE SECTION

(NOVEMBER 24-25, 2004; KOFU CITY, JAPAN)

THIS was only my second visit to an ISHR meeting in Japan. The last was the World Meeting in Kobe 1992. That was fun, but very formal; twelve years later and my experience was entirely different. Clearly the Kofu meeting was much smaller and intrinsically more informal. However, I would be surprised if the setting was entirely responsible for the change of experience.

I had a great time discussing work with numerous scientists, and I learned a lot, but I don't wish to dwell on this (excellent though it was) because one can explore this in the pages of the JMCC supplement. I do wish to comment on the general experience, however.

Firstly, I was deeply impressed by the fact that the entire proceedings were carried out using the English language. Considering that, aside from myself, Mark Vos and Juan Tamargo, there were few non-Japanese delegates at the meeting, it would have been perfectly understandable for the native language to have

prevailed. My understanding is that more than merely an expression of the Japanese legendary hospitality, this was an extension of the acceptance that English is the lingua franca of science and its use mandatory in any forward thinking local scientific community. More than its use, it was the quality of its use that so impressed me. All the presentations were easy to follow and only rarely did the post-talk discussions require any language intervention, so to speak.

This extended itself to the social milieu. The level of interaction with the delegates included not only challenging discussions about work, but also a great deal of knowing humour, self-deprecation and warmth. I must confess my previous visit

to Japan had been a bit of a strain after a few days, forever anxious to avoid forgetting to bow, etc. This time – none of that.

I'm not sure what is behind all this, but I suspect the hand of Keitaro Hashimoto may be responsible for a great deal. Keitaro organised the meeting with the help of colleagues and his wife and daughter. One can only be impressed by Keitaro's courage and vision.

The conference dinner was a masterpiece. On certain occasions in the past, ISHR meeting dinners around the world have been, how can I put this, slightly odd. Typical oddness has included

(continued on page 10)



Mount Fuji, as seen during a trip with Mrs Hashimoto, who took the trouble to show me the sights.



NORMAN ALPERT who died on November 28, 2004 at the age of 82 will be remembered by all who knew him as generous, kind hearted, a visionary of his time, and one who enjoyed life to its fullest.

Born in Stamford Connecticut, Norman attended both Wesleyan and Columbia Universities. He received his PhD degree in Biophysics from Columbia University in 1951. Subsequently he moved to Chicago and joined the Department of Physiology at the University of Illinois where he ascended in rank from Assistant to Full Professor by 1965. In 1966 he moved to the University of Vermont, where he was Chair of the Department of Physiology and Biophysics for 29 years (1966-1995). As Chair, he was instrumental in building this department from scratch and making it into a Mecca of muscle and cardiovascular physiology. At the University of Vermont he played a key role not only in the growth and direction of the College of Medicine, but also of the University itself. Frequently, one would see Deans and the University President leaving his office after seeking his advice. While Chair, he was also elected President of the Association of Chairmen of Departments of Physiology (1975-1976).

Norman's contributions to cardiac physiology are significant and of historic importance. Notably his research on the crossbridge cycling mechanism of cardiac muscle has played an important role in our understanding of how cardiac muscle contraction is regulated. By working closely with Professor Louis Mulieri, he developed an elegant thermopile system to investigate the relationship between energy utilization and contractility of cardiac muscle. This ingenious system utilized sensors coated with antimony and bismuth to accurately measure energy utilization as heat production when a cardiac muscle was electrically stimulated. This device proved an important tool in differentiating and quantifying the rates of energy utilization during crossbridge cycling (actomyosin ATPase activity) and Ca^{2+} cycling by the sarcoplasmic reticulum

IN MEMORIAM



NORMAN ALPERT
1922-2004

(Ca^{2+} ATPase activity). These pioneering studies using isolated cardiac muscle strips were important in establishing our present understanding of the physiology of crossbridge and Ca^{2+} cycling kinetics in normal and failing hearts.

Norman's research interests took a molecular turn in the late 1980s. He became fascinated with aspects of gene structure and regulation in cardiac muscle. Around this time (1985), I joined his department as an Assistant Professor with little or no knowledge of cardiac physiology. He patiently explained to me how heat measurements could be used to determine ATP utilization by the crossbridges and Ca^{2+} cycling. It was his idea that Ca^{2+} cycling was altered in cardiac hypertrophy and he encouraged me to study the regulation of calcium cycling proteins, which led to some important discoveries. In recent years he developed a keen interest in understanding the role of myosin isoforms in cardiac muscle performance and pursued this in collaboration with Professor David Warshaw at the level of a single myosin molecule using the laser trap assay. It was not surprising that many of his observations at the tissue level were confirmed at the molecular level 30 years later.

His serious attitude to the advancement of science can be felt by his life long dedication to the study of the heart. It is only ironic that his research focus was to be the cause of his death. Norman had continuous NIH funding as a Principal Investigator to the very end.

Norman has played an important role in the growth and success of several organizations, most notably the International Society for Heart Research (ISHR). He served as a council member and as president of ISHR (1993-1994) and organized one of the most successful ISHR meetings (1992) at the University of Vermont. He has brought significant visibility to the ISHR through his life long dedication to this organization. He was a champion for basic cardiovascular research as the central focus of this organization and contributed to its success. He also served as the Editor of the Journal of Molecular and Cellular Cardiology (1992-1998) and as an Associate Editor of the American Journal of Physiology - Heart and Circulation (1981-1987).

Norman has had great influence not only on scientific organizations but also on many scientists both nationally and internationally. He was a great mentor and contributed to the success of many outstanding cardiac physiologists. I am honored to count myself among the long list of people who have benefited from his interaction and support. His knowledge and worldly wisdom have positively influenced many of his colleagues and their careers. Norman was widely sought after both as an advisor and as a leader in many professional circles and scientific organizations.

Despite all his achievements, Norman was very modest and never took much credit for his achievements. He had an unassailable personal character and integrity. Perhaps this had its roots in his earlier undergraduate education in Philosophy and his upbringing. Norman always emphasized the importance of applying research in a social context and

always considered the effects of research on society. These characteristics distinguished Norman from other scientists who stay constrained within their disciplines.

Norman had a rich life both inside and outside the academic circle and enjoyed sports very much. He was an avid tennis player and would challenge anyone to a game of tennis at 6:00 AM. He would often joke that he usually wins the game in the early morning because his opponent was still asleep. Norman was truly a good sport and he would always toast his win by buying a beer for the loser. His other

passion was sailing and for several years he was the Class A and Division 1 sailing champion on Lake Champlain. He never gave up sailing till the last moment and never missed taking his friends on his boat.

A sweet, humble and courteous man, Norman dedicated his life to seeking answers to many unanswered questions in science and in life. He was a father figure to me and to many fellow scientists. He truly will be missed by all who knew and worked with him. Our thoughts and best wishes are very much with his wife Laurel and their two sons, Adam and

Briar, and daughter Jamie. A fitting farewell is to quote one of Norman's most frequent statements, which is that: "We have a lot to learn, we have a lot to do and let's get to work".

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REPORT ON THE XXI ANNUAL MEETING OF THE JAPANESE SECTION

(continued from page 8)

psychedelic and longwinded speeches (often aided by time too long spent in the boudoire of the grape) and excessive fealty to the invited speakers, committee officials, etc. Here we had none of this.

Keitaro Hashimoto started out by telling us what a tough time he had raising the sponsorship money for the meeting. He had no need to do this (especially since, unlike some of his previous equivalents around the world, he actually succeeded). He then put his daughter on the spot by insisting she address the gathering. It was all very amusing and unexpected. But the real touch of class was when Keitaro made the invited foreign speakers (Mark, Juan and me) stand in front of the gathering and give an impromptu speech. It was clear that we required to be sincere, funny and above all succinct. It was a nice challenge that was met with great warmth from the audience, not least because it was cruelly set in the clear knowledge of our host that we had enjoyed a prolonged period of hospitality, much of it liquid.

Finally, Kofu is some way from the International Hub at Tokyo, and the



Dr Curtis enjoys a moment's peace between scientific sessions.

prospect of the journey by train had been playing on my anxious mind for some weeks before the trip. Perhaps my perspective has been warped by too long travelling on UK public transport, where native know-how is essential. To my delight, the train journey around Tokyo and out into the provinces and back went like a dream, with English language assistance always available (automatically displayed, and from staff).

In short, the meeting was excellent, our hosts wonderful and the whole exercise a scientific and PR success. The outcome is that, if I am asked by anyone about the possibility of a visit to Japan, my response would be simple: "you must go".

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PRESERVATION OF ENDOTHELIAL FUNCTION PREVENTS PLATELET ACTIVATION IN DIABETES MELLITUS

I was very fortunate to have been selected for the ISHR-ES / Servier Research Fellowship 2002. After graduating from Medical School at the University of Frankfurt, Germany in 2000, I started my first postdoctoral position in the Vascular Biology Working Group led by Dr Johann Bauersachs at the University of Würzburg, Germany. Encouraged by him, I proposed a research project on endothelium-platelet interactions. This study was completed in the laboratory of Prof. Keith Channon at the University of Oxford, UK, and was supported by the grant funds I received together with my Research Fellowship. The focus of my current and future work is concerned with endothelium-platelet interactions in cardiovascular diseases, predominantly the role of endothelium-derived nitric oxide as an endogenous platelet inhibitor and the influence of endothelial dysfunction on platelet activation in those diseases.

NO Bioavailability and Platelets

Nitric oxide (NO), generated by NO synthase (NOS), inhibits platelet activation as demonstrated by *in vitro* experiments such as inhibition of platelet aggregation by endothelial cells or NO donors. Chronic inhibition of NO formation in animal models is associated with impaired fibrinolysis, and enhanced thrombin and tissue factor generation. Previous reports described increased platelet activation in disease states with impaired NO bioavailability such as acute coronary syndromes, heart failure, diabetes and hypercholesterolaemia. However, the direct relationship between NO bioavailability and platelet activation in humans remained unclear.

A newly developed biochemical marker, which can also be easily obtained from a blood sample, focuses on the downstream signaling of NO. NO activates the soluble guanylyl cyclase (sGC), leading to the formation of cGMP, which activates cGMP-dependent protein kinases (GK). Type I cGK has been shown to mediate the vasodilator action of NO in mouse aorta. A promising new tool for the analysis of the cGMP-dependent pathways is the phosphorylation state of the cGK I substrate vasodilator-stimulated phosphoprotein (VASP), which has been shown to be a marker of the activity of the

NO/cGMP pathway in a number of studies of endothelial function and dysfunction in animal models and human vessels. VASP-phosphorylation provides a sensitive monitor of defective NO/cGMP-signaling, and reduced NO bioavailability in several pathophysiological states correlates with reduced VASP-phosphorylation.

We demonstrated that acute reduction of NO bioavailability *in vivo* rapidly increases platelet activation, which is immediately reversed by the NO donor glycerol-tri-nitrate (GTN), demonstrating a direct and rapid relationship between NO bioavailability and human platelet function *in vivo*. Our observations suggest that platelet activation in healthy individuals *in vivo* is suppressed by tonic NO production resulting in immediate platelet activation when NO production is inhibited. When VASP-phosphorylation was normalized after GTN, markers of platelet activation such as surface P-selectin and CD40-ligand returned to baseline conditions.

These findings suggest that NO may modulate platelet activation in vascular disease states. In patients with advanced atherosclerosis and endothelial dysfunction, impaired endothelium-dependent release of NO leads to reduced platelet



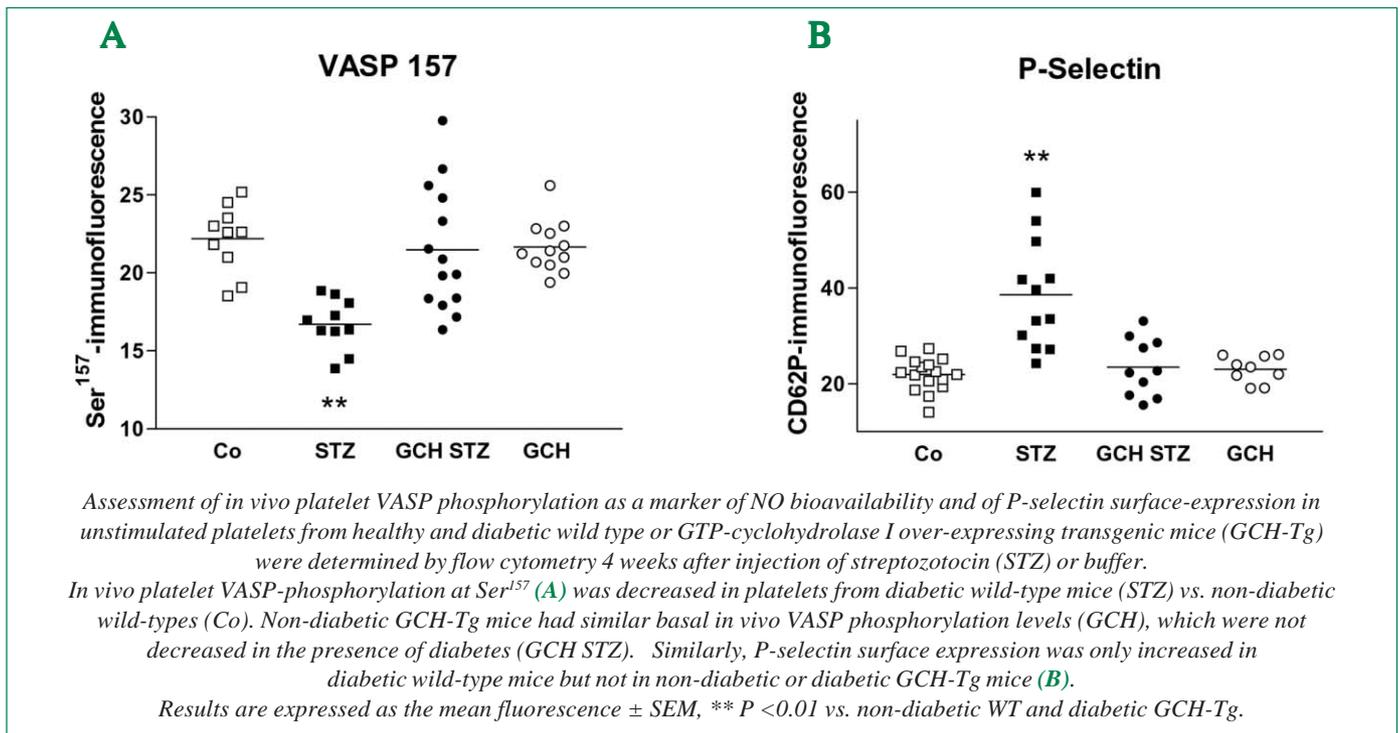
Andreas Schäfer, M.D.

cGMP formation. It remained uncertain whether endothelial-derived NO has a more important role in tonic suppression of platelet activation *in vivo*. In addition, the possibility that selective rescue of endothelial dysfunction in vascular disease states is sufficient to normalize platelet activation remained unexplored.

Of several vascular disease states, patients with diabetes mellitus have particularly marked deficits in NO-mediated endothelial function and an increased risk of thrombosis and accelerated atherogenesis. Increased platelet reactivity has been suggested as a potential mechanism contributing to the accelerated atherosclerosis seen in diabetic patients through such detrimental effects as capillary microembolisation, local progression of vascular lesions and triggering of acute arterial thrombosis.

Diabetes, Nitric Oxide and Platelet Activation

In diabetic mice, vascular endothelial dysfunction is associated with uncoupling of eNOS within the endothelium due to oxidation of its essential co-factor tetrahydrobiopterin (BH4), resulting in a specific loss of endothelial NO bioavailability. Targeted over-expression of the rate-limiting enzyme for BH4 biosynthesis (GTP-cyclohydrolase I, GCH) in endothelial cells in a transgenic mouse strain (GCH-Tg) reduces eNOS uncoupling and restores NO-mediated endothelial function in diabetic mice, thus providing an *in vivo* model of selective rescue of



endothelial NO bioactivity in diabetes.

We determined how the selective prevention of endothelial dysfunction by maintaining endothelial NO bioavailability in GCH-Tg mice would influence platelet activation in diabetes. We demonstrated an important role for endothelium-derived NO in regulating platelet activation *in vivo*: First, basal NO release tonically inhibited platelet activation in healthy animals; withdrawal of NO led to rapid platelet activation. Second, increased platelet activation in diabetes, in association with chronically reduced NO bioavailability, was rescued by endothelium-specific preservation of eNOS function. Our results in the GCH-Tg mice now clearly suggest a pivotal role for endothelium-derived NO in tonic inhibition of platelet activation under physiological conditions *in vivo*, and for loss of endothelium-derived NO in the pathogenesis of platelet activation in vascular disease states. The conservation of platelet VASP-phosphorylation in the GCH-Tg diabetes group is consistent with

previous observations of preserved vascular NO bioavailability and endothelial function in this transgenic mouse model. Accordingly, we found increased surface-expression of P-selectin and CD40-ligand on unstimulated platelets in whole blood from diabetic WT mice. P-selectin can participate in platelet adhesion to the endothelium and is certainly responsible for platelet-leukocyte adhesion, which in turn was significantly increased in our study in diabetic animals. When VASP-phosphorylation was preserved in diabetic GCH-Tg mice, expression of P-selectin and CD40-ligand was similar to healthy WT mice. This conforms with an earlier study reporting inhibition of P-selectin and CD40-ligand surface-expression by cAMP-/cGMP-dependent protein kinases, whose activation can be monitored by VASP-phosphorylation.

The impact of activated platelets on morbidity and mortality in diabetes is extremely relevant, because enhanced platelet activation is an initial step in atherosclerosis and responsible for lesion progression and excessive cardiovascular complications associated with diabetes. The results from the GCH-Tg mice suggest that therapies to specifically target

endothelial dysfunction in patients with diabetes or other vascular disease states should result in salutary effects on platelet activation, mediated through restoration of endothelium-derived NO.

Conclusion

We demonstrated that acute and chronic changes in systemic NO bioavailability modulate platelet activation under *in vivo* conditions. Reduced NO bioavailability in many cardiovascular diseases (*e.g.* diabetes) might directly contribute to platelet activation in these patients, and thereby influence disease progression.

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Andreas Schäfer was the winner of the ISHR-ES / SERVIER Research Fellowship 2002.

REBUILDING THE HEART: REALITY OR FANTASY

BY PIERO ANVERSA, M.D.

THE LAST FOUR YEARS have changed dramatically our understanding of the biology of the heart. The discovery that adult hematopoietic stem cells (HSCs) retain a remarkable degree of developmental plasticity and differentiate across tissue boundaries has generated tremendous enthusiasm in the scientific and clinical community. Experimental results demonstrating the ability of HSCs to reconstitute infarcted myocardium in mice [1] were rapidly implemented in patients [2] and several double-blind clinical trials are ongoing in Europe, Asia and in the United States. This extraordinary example of translational research has been violently challenged by negative studies [3, 4], which have become popular and have found easy hospitality in high impact factor journals. The difficult question is why the scientific community is so strongly divided and why nothing constructive has been done to resolve the controversy. The suggestion that laboratories with different results become engaged in a collaborative effort to clarify the dispute has been offered repeatedly by one side of the fence but the other has no interest in pursuing this avenue. Confusion and debate prevail, not the desire for clarity and understanding. An interesting aspect of the disagreement is that the groups involved are the same that have been arguing for nearly two decades whether the heart is a postmitotic organ or a self-renewing organ capable of significant myocardial regeneration [5]. These opposite views are not limited to biological issues but condition the direction of cardiovascular research and the development of novel strategies for the treatment of the failing heart. The possibility of extrinsic and intrinsic cardiac repair [1, 5] is confronted by alternative modalities such as skeletal myoblasts and embryonic stem cells [6].

The notion that the heart has no capacity for regeneration was established in the 1920s because, with the techniques available at that time, mitotic figures in myocytes were difficult to recognize. This conviction gained further support in the 1970s from autoradiographic studies of thymidine incorporation in hearts of animals during postnatal growth and after conditions of overload [7]. DNA synthesis in myocyte nuclei was not detected or was found to be negligible. The dogma was then introduced that the heart survives and exerts its function until death of the organism with the same number of cells that are present at birth. Because a certain fraction of the population reaches 100 years of age or more, an inevitable consequence of this paradigm is that cardiac myocytes are immortal, functionally and structurally. Although the bases for this view are illogical, the attempts made to propose a paradigm shift were dismissed initially and, more recently, opposed strongly [8]. Proliferating myocytes, expression of nuclear proteins implicated in the cell cycle, karyokinesis and cytokinesis have been undermined and claimed to be inconclusive, difficult to interpret or a collection of artifacts [3, 4, 8]. Similarly, the identification of resident cardiac stem cells (CSCs) which are self-renewing, clonogenic and multipotent [9, 10] had little impact on the detractors of myocardial regeneration.

This is the climate that regenerative cardiology faces today. The ingrained belief that the heart is a static organ with no turnover of myocytes and vascular cells was dramatically shaken by the documentation that HSCs adopt the myocyte lineage [1, 11, 12]. HSCs and CSCs may become new, critical therapeutic tools for acute and chronic heart failure. Experimentally, the injection of HSCs or

DURING the ISHR World Congress in Brisbane, the International Council approved my proposal that all of its members be asked to submit at least one article, during their six-year tenure, to Heart News and Views. The content of the article will be at the discretion of the Council member but should be of broad interest to the Society. I am pleased to introduce the first of this series of articles, by Piero Anversa, a distinguished scientist and the recipient of the 2004 Research Achievement Award of the American Heart Association.

This new series of articles will add diversity and bring fresh ideas to our newsletter while enabling all Council members to contribute actively to the Society. I also hope the articles will stimulate constructive debate on important scientific and philosophical issues.

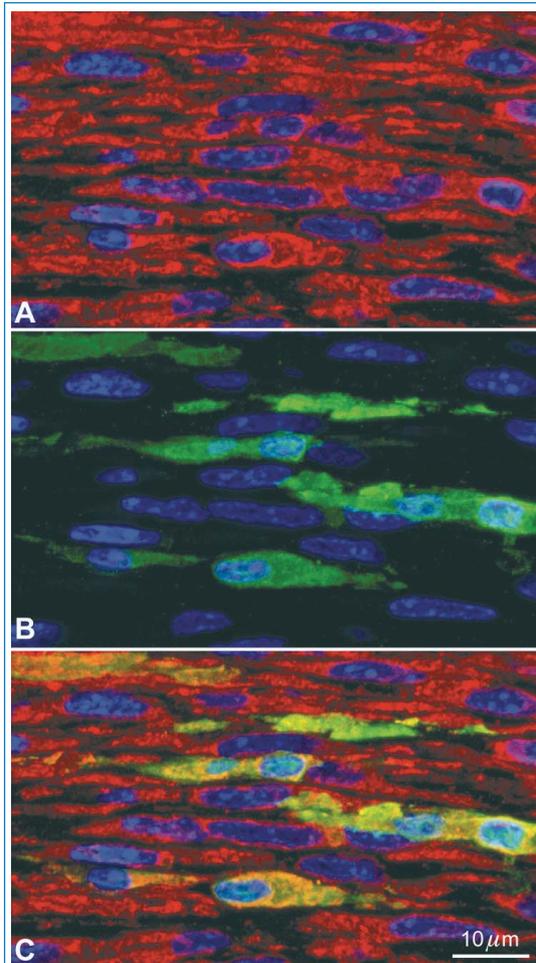
*Roberto Bolli, M.D.
President-Elect*

CSCs in proximity of an acute infarct results in a few days in a significant reconstitution of the dead myocardium (Figure). Cardiac repair is characterized by the formation of myocytes and coronary vessels that permeate the new tissue. It is remarkable and instructive that the detractors of myocyte replication place great emphasis on the methodology and postulate that the use of light microscopy is superior to confocal microscopy [3, 13, 14]. On this basis, they justify the inferior level of resolution of their micrographs and make clear their opposition to new technology. They affirmed the validity of old-fashioned, out of date protocols as long as they fit their unshakable view of the heart. Along those lines, astronomers may decide to observe celestial events with a binocular, abandoning the telescope.

The recognition that the heart belongs to the group of self-renewing organs changes drastically our understanding of the fundamental mechanisms regulating myocyte, vessel and organ homeostasis.

According to the new paradigm, the continuous turnover of myocytes results in a heterogeneous cell population that consists of young, adult, old and senescent parenchymal cells. And the proportion of these cell categories may change with age and pathologic states. The repopulating cells may originate from the bone marrow or reside in specific anatomical areas of the heart, where they can be activated to replace foci of damage. Defects in the stimulation, migration, growth and differentiation of progenitor cells may occur at several levels, limiting the formation of myocytes and coronary vessels. Myocardial regeneration necessitates the creation of parenchymal cells, resistance arterioles and capillary structures. Attenuation in stem cell function may result in the accumulation of senescent, poorly contracting myocytes and rarefaction of the coronary vasculature, which together constitute a critical determinant of end-stage failure.

Fundamental areas of stem cell research have to be addressed in the near future. The impact of age, gender, and type and duration of the cardiac disease on stem cell proliferation and lineage commitment is unknown. Aging and chronic heart failure may affect the pool of functionally competent progenitor cells, decreasing their ability to regenerate scarred myocardium. An important question involves whether distinct classes of stem cells condition the efficacy of myocardial regeneration. Heart failure manifests itself in different ways and the possibility to distinguish progenitor cells that assume a preferential progeny is of paramount relevance for human disease. According to the need, a new tool may become available for the predominant formation of myocytes and/or coronary vessels. The effects that HSCs and CSCs have had on “mending the broken heart” point in the right direction for a more biologically interesting view of the



Myocardial regeneration 10 days after infarction. The injection of bone marrow cells acutely after coronary artery occlusion results in the formation of cardiomyocytes in the region of damage. Bone marrow cells, enriched for c-kit, were obtained from transgenic mice overexpressing EGFP in 25% of the cells. Newly generated myocytes are positive for α -sarcomeric actin (A, red), EGFP (B, green) and α -sarcomeric actin and EGFP (C, yellow-green).

myocardium with unprecedented clinical implications.

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ISHR MEETINGS CALENDAR

- **August 5-8, 2005.** **XXIX Australasian Section Meeting, in conjunction with the Annual Scientific Meeting of the Cardiac Society of Australia & New Zealand.** Perth, Australia. **Inquiries:** Dr S. Pepe or Dr L. Delbridge. *E-mail* salvatore.pepe@baker.edu.au or imd@unimelb.edu.au
- **September 3-7, 2005.** **XXVII Congress of the European Society of Cardiology.** Stockholm, Sweden. **Inquiries:** *Website* www.escardio.org
- **November 13-16, 2005.** **Scientific Sessions of the American Heart Association.** Dallas, Texas **Inquiries:** *Website* www.americanheart.org
- **December 15-17, 2005.** **XXII Japanese Section Meeting - To Clarify our Current Standpoint and our Goal in the Heart Research Field.** Osaka, Japan. **Inquiries:** Dr M. Hori, Osaka University, Graduate School of Medicine, Dept of Internal Medicine and Therapeutics, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan. *Tel.* +81 6 6879 3631; *Fax* +81 6 6879 3639; *E-mail* mhori@medone.med.osaka-u.ac.jp; *Website* www2.convention.co.jp/22ishr-japan/
- **June 14-17, 2006.** **XXVI European Section Meeting.** Manchester, UK. **Inquiries:** *Scientific Secretariat:* Mrs R. Poulton, The University of Manchester, Room 1.302, Stopford Building, Oxford Road, Manchester M13 9PL. *Tel.* +44 161 2751628; *E-mail* roslyn.m.poulton@manchester.ac.uk *Meeting Secretariat:* The University of Manchester, ConferCare, Barnes Wallis Building, Sackville Street, Manchester M60 1QD. *Tel.* +44 161 3065068; *E-mail* mcc.reg@umist.ac.uk; *Website* www.meeting.co.uk/confercare/ishr2006
- **June 14-16, 2006.** **XXVIII American Section Meeting.** Toronto, Canada. **Inquiries:** Dr P. Liu, Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto, Rm 78A, 150 College Street, FitzGerald Building, Toronto, Ontario M5S 3E2. *Tel.* +1 416 946 8543; *Fax* +1 416 946 7545; *E-mail* hsrcentre.excellence@utoronto.ca; *Website* www.ishr2006.com
- **June 22-26, 2007.** **XIX World Congress of the ISHR.** Bologna, Italy. **Inquiries:** Dr R. Ferrari, Department of Cardiology, University Hospital of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. *E-mail* info@ishr-italy2007.org; *Website* www.ishr-italy2007.org

THE BRICKS OF VENICE

A STUDY OF VENETIAN BRICKWORK FROM THE 11TH CENTURY ONWARDS, IN WORDS AND WATERCOLOURS BY PETER HARRIS

AFTER his retirement in 1988, Peter Harris lived and worked in Venice for seven years, with enough leisure to study the architecture of Venice in depth and to read extensively about the city. *The Bricks of Venice* is a memorial to his great love of the city and is destined to become a classic epilogue to Ruskin's *The Stones of Venice*.

The text would have made a valuable book on its own, but we are fortunate that Peter was also a very competent water-colourist, and he illustrates our path with sixty-six delightful watercolours that fill out the story perfectly and turn this almost into a walking guide.

In February 2005 the sixty-six original watercolours were exhibited in the Arts Club at 40 Dover Street in London. You can read one of the chapters from the book and view two of the watercolours at: www.theoldschoolpress.com.



*Scuola della Misericordia (1532).
View from the Fondamenta Santa Caterina.*

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2005

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Volume 10 - Number 2

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