MOLECULAR biology has taken over biological sciences. In some respects, its application to clinical medicine has been disappointing. Yet, molecular biology has recently led the way to therapeutic triumphs, resulting in the successful treatment of a series of hitherto lethal conditions. For us interested in problems of the heart and circulation, these successes are relevant, not only because all biological sciences are interconnected, but because heart disease may be secondary to some of these primary disorders.

In 1960, Nowell and Hungerford, two physicians at the University of Pennsylvania, discovered a chromosomal abnormality in the cells of patients with leukemia and suggested that it may play a role in the etiology of the leukemia. This abnormally small chromosome 22 was named the Philadelphia chromosome for the city in which it was discovered. The Philadelphia chromosome was the first specific mutation to be associated with cancer. Initially this malformed chromosome 22 was thought to represent a deletion of a large portion of the chromosome long arm; however, in the early 1970s with the development of chromosome banding techniques, Janet Rowley showed that the Philadelphia chromosome results from a reciprocal translocation between chromosomes 9 and 22, t(9;22). Her studies indicated that most of the long arm of chromosome 22 was translocated onto the long arm of chromosome 9 and a small distal portion of chromosome 9 was translocated to chromosome 22 forming the Philadelphia chromosome.

Molecular characterization of the chromosome translocation breakpoints and subsequent identification of the genes involved clarified the connection between the chromosome abnormality and leukemia. Most of the c-ABL proto-oncogene is translocated from chromosome 9 to a position within the middle portion of the BCP (breakpoint cluster region) gene on chromosome 22. The c-ABL gene is a cellular homologue of the v-ABL gene of Abelson murine leukemia virus; it specifies a protein with tyrosine kinase activity that plays a role in normal

(continued on page 2)
The normal c-ABL proto-oncogene becomes activated or oncogenic when some of its amino-terminal (N-terminal) amino acids are removed which has the effect of releasing the ABL kinase from its normal regulatory constraints. The BCR-ABL hybrid gene formed from the chromosome translocation removes the N-terminal ABL sequences and replaces them with BCR sequences resulting in a constitutively active ABL kinase and unwanted and uncontrolled cell growth.

The Philadelphia chromosome was first identified in patients with chronic myelogenous leukemia (CML). It is now known to occur in almost 100% of CML patients. It also has been identified in about 5% of children and 30-40% of adults with acute lymphocytic leukemia. Transcription of the hybrid BCR-ABL gene in CML produces an 8.5-kb fusion transcript that encodes a 210-kDa hybrid protein, the activated tyrosine-specific kinase. This BCR-ABL fusion oncogene is able to transform primary hematopoietic cells in culture and induce hematopoietic neoplasms in mice. In ALL the BCR-ABL rearrangement often produces a shorter fusion transcript and hybrid fusion protein (185 to 190 kDa).

Tyrosine kinases are important in the regulation of numerous key cellular and developmental processes as they serve as growth factor receptors and as transducers of intracellular communications. The chimeric tyrosine kinase proteins resulting from gene fusions such as the BCR-ABL fusion represent novel, tumor-specific products and as such are ideal targets for new molecular therapeutic strategies.

It is not surprising that progress in the field of molecular therapeutics depended on discoveries from basic research and on development of new technologies. First, chromosomal abnormalities were found by kario-typing. Later, tools of molecular genetics such as situ hybridization, gene amplification and DNA sequencing, identification of fusion transcripts, immunoblotting, measurement of kinase activity, and anti-proliferative assays were developed. Finally, it was the clinician and the pharmacologist who developed the therapeutic implications of these fundamental discoveries.

The clinical success depended on the successful inhibition of tyrosine kinase. This was first demonstrated in vitro by groups from the Ciba-Geigy (now Novartis) Company and by workers at the University of Oregon who tested several compounds of the 2-phenyl-aminopyrimidine class. One compound (imatinib mesylate) exhibited specific inhibition at the submicromolar level. This molecule, also known as Gleevec or ST1571, binds in the active site of the ABL tyrosine kinase and prevents the binding of ATP. The compound showed efficacy and safety in patients with CML, and many patients treated with this compound went into complete remission, a remarkable therapeutic triumph. In fact, initial trials with this drug were so successful that Gleevec received the fastest FDA approval of any drug in history (2 months).

Tyrosine kinases also play a role in the etiology of the idiopathic hypereosinophilic syndrome (HES). This disease has relevance to the cardiologist as it is frequently accompanied by heart disease. This syndrome also results from the presence of a tyrosine kinase which is susceptible to the specific inhibitor imatinib mesylate (Gleevec). The cardiac manifestations of HES result from eosinophilia infiltration of the myocardium (Loeffler syndrome), resulting in acute necrosis, followed by thrombosis, and finally by myocardial fibrosis. As in CML, patients with HES can go into complete remission when treated with the tyrosine kinase inhibitor. These results represent a triumph of the combination of fundamental and clinical studies.

There has been much discussion about the application of molecular biology and genetics to the bedside. Here we have a brilliant example that such an application is feasible. This should give us hope that a combination of molecular biology and clinical medicine can find therapeutic approaches to incurable diseases.

**Selected publications:**


I am grateful for the constructive help of Dr Faye Eggerding.

*Richard J Bing, M.D.*
PETER HARRIS was an influential international statesman in cardiology. He was at the forefront of the revolution in biomedical research that started more than 40 years ago and paved the way for radical new treatments that are now taken for granted in most branches of medicine.

A science scholar at King’s College, London, UK, Harris trained in medicine at Kings College Hospital, qualifying in 1946. During house appointments at King’s and the Brompton Hospital, he obtained his MD in 1951, winning the university gold medal and a PhD in 1955. That was followed by a 2-year Nuffield Fellowship at the Bellevue Hospital and Columbia University, New York, USA. On his return to the UK, he was appointed lecturer, in 1957, and reader in medicine, in 1962, at Birmingham University.

His career, which was dedicated to exploring the cardiovascular system and the origins of heart disease, can be viewed as three chapters. During the 1950s and early 1960s, he was in the mainstream of research, and used established methods of haemodynamic measurements to explore cardiac output and pulmonary blood flow and the metabolism of the heart muscle. In the process, he compiled an immense body of knowledge that was the basis for the European section of an international work on cardiology: Calcium and the Heart. The study group was also the forerunner of the International Society for Heart Research, which, in 1986, created the prestigious Peter Harris Award for Achievement in Research.

The third element to Harris’s career involved his fascination with the evolution of the cardiovascular and related systems, and love of travel. In a series of essays in 1983, he traced the way that the origins of clinical heart failure might lie in ancient reflexes. And expeditions to the Andes and Himalayas raised questions in his mind about the long-term adaptation in llamas, yaks, other animals, and people to their environment. His study of the right ventricle of the heart and the blood flow to the lungs of yaks showed they had adapted genetically to high altitude by eliminating the vasoconstrictor response due to reduction of oxygen; and a study of crossbreeds, the dzo and stols, revealed that this characteristic was inherited as a simple autosomal dominant.

In 1988, Harris described a new disease in man at altitude occurring widely in Tibet, sub-acute infantile mountain sickness. It affected infants born at low altitude and brought to live in a place higher up. He believed the syndrome illustrated his view of the evolutionary processes involved in the development of the circulation to promote the survival of the species.

Away from the laboratory he was a talented musician and artist, and he showed a leaning toward satirical writing. His wife Francesca survives him.

In 1970, Harris organised a meeting of the European section of an international study group for research in cardiac metabolism, which resulted in the publication of one of the most influential works on cardiology: Calcium and the Heart. The study group was also the forerunner of the International Society for Heart Research, which, in 1986, created the prestigious Peter Harris Award for Achievement in Research.

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I AM WRITING to you from post-war America. We continue to see the aftermath of the terrorist attacks of 9-11 play itself out on the world stage. Our staunchly conservative government is asserting itself like no other in recent memory. As a result, historically strong alliances are being strained by President Bush’s new America-first policy. What kind of world order will emerge from all of this is anyone’s guess. The ISHR was contacted in April to see if we wanted to join the coalition of the willing but we politely declined. As it turned out, coalition forces had more than enough cardiac biochemists to accomplish their mission in Iraq without us.

The terrorist threat has already claimed one ISHR casualty. The Australasian section’s meeting originally scheduled for Bali had to be canceled in the aftermath of the terrorist bombing there. It has been rescheduled to meet in Melbourne August 7-9, 2003. Otherwise, this year’s meetings schedule seems to be proceeding on schedule. Fortunately, none of our meetings is scheduled for regions with a SARS travel advisory. I just returned from a meeting in Japan. Although SARS has not yet spread to Japan, all Asian travelers are nervous. When my Delta flight landed in Narita (Tokyo) it pulled in between two Chinese airliners. I tried to hold my breath until I cleared customs. The direct result of the Asian SARS scare was very empty aircraft both coming and going. It was great for those traveling in coach but one wonders how long the airline industry can keep flying with so many empty seats.

Leslie Lobaugh, the ISHR’s executive secretary, has been hard at work with the section secretaries to get an accurate census of our worldwide membership. At the time of this writing we have 2576 active members. The number is somewhat fluid because we receive new applications through the web site almost every day. The breakdown is Australasian: 91, Chinese: 373, European: 746, Indian: 44, Japanese: 406, Latin American: 69 and North American: 847. Leslie had gone through the international database and cleared out all of the inactive members. We are constantly updating our membership information to keep it as accurate as possible. However if you move, get a new email address or phone number we have no way to know unless you contact us and let us update your listing. Please take a minute and go to www.ishrworld.org and look at your contact information in the membership directory to see if it is current.

We use the ISHR database for email communications with the membership. This includes the latest PDF version of this publication, HEART NEWS AND VIEWS, along with meetings announcements and other important information. Every time I send out a mailing I get about 10 bounced emails (email addresses that are no longer valid). We have no choice but to erase those from the database. Please get your current email address to us so we can keep you abreast what is happening in the ISHR. Send us updates.

As the saying goes, there is strength in numbers, and that certainly holds true for the ISHR. At 2576 members we still remain the worlds largest organization devoted solely to heart research. Nevertheless there are thousands of potential members still not in our organization. The Basic Cardiovascular Sciences council of the American Heart Association has nearly twice that many members. Granted, that includes a large number of vascular biologists who might not see the ISHR as their primary affiliation, but there are still many cardiac researchers who are not members. Please ask your colleagues and students if they are members. If they are not, urge them to consider joining the society. By the way, most sections have a very attractive student rate. A membership form can be found at www.ishrworld.org.

James M. Downey
Atherosclerosis and its complications represent the most common cause of death in Western societies. Over the past few years we have witnessed a paradigm shift in our understanding of the underlying principles of atherosclerosis. This new view supports the concept that inflammation is the central orchestrator of atherosclerotic lesion formation, progression, and eventual rupture. Chronic inflammation results in endothelial dysfunction, and facilitates the interactions between modified lipoproteins, monocyte-derived macrophages, T cells and normal cellular elements of the arterial wall inciting early and late atherosclerotic processes. This paradigm has fueled exponential interest in evaluating inflammatory markers of atherosclerosis, of which high sensitivity C-reactive protein (CRP) has emerged as one of the most important. As such, the inflammatory marker CRP is one of the most powerful independent predictors of myocardial infarction, stroke, and vascular death in a variety of settings, with prognostic value extending across various ethnic groups, and in men and women in different age groups. More recently, elegant work by Ridker and colleagues has demonstrated that CRP may be a better predictor of future cardiovascular events than LDL-cholesterol, and that baseline CRP evaluation adds prognostic value to conventional Framingham risk assessment. The link between CRP and atherosclerosis was initially suggested to be that of a “surrogate biomarker” vs a mediator of atherosclerosis. This view has been recently revisited; with observations suggesting that CRP has a direct effect to promote atherosclerotic processes and endothelial cell inflammation. In this report our data are summarized, which suggests that CRP functions as a powerful proatherogenic factor, in addition to a risk marker of atherosclerotic and metabolic events.

Effects of CRP on Endothelial Cell Activation and Angiogenesis
A growing body of evidence implicates CRP as a direct mediator of endothelial dysfunction. First, CRP at concentrations known to predict vascular events, directly upregulates endothelial cell adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin. These adhesion molecules play a key role in the facilitating leukocyte-endothelial interaction, an early step in atherogenesis. Once the leukocytes adhere to the dysfunctional endothelium, CRP promotes the release of MCP-1, a key chemoattractant chemokine, which facilitates leukocyte transmigration through the endothelium. Third, CRP directly promotes the release of potent endothelium-derived contracting factors, such as endothelin-1 (ET-1) from endothelial cells. ET-1 is not only one of the most potent vasoconstrictors currently known, but also appears to be a mediator of CRP-induced upregulation of adhesion molecules and MCP-1. More important are observations demonstrating the ability of CRP to directly quench the production of nitric oxide (NO) from the endothelium. NO is the key endothelium-derived relaxing factor, which plays a pivotal role in the maintenance of vascular tone and reactivity. In addition to being the main determinant of basal vascular smooth muscle tone, NO acts to negate the actions of potent endothelium-derived contracting factors such as angiotensin-II (Ang-II) and ET-1 and serves to inhibit platelet and leukocyte activation and maintain the vascular smooth muscle in a non–proliferative state. Human recombinant CRP, when incubated with human endothelial cells at concentrations demonstrated to predict vascular events, potently inhibits both basal and stimulated NO release, in part via destabilizing endothelial nitric oxide synthase (eNOS) transcript. In addition, CRP inhibits the eNOS protein expression, and the downstream effector of NO, cyclic GMP. By virtue of inhibiting eNOS expression and NO release, CRP blocks NO-dependent processes, such as angiogenesis. When studied in vitro, using both scratch–wound assays, and endothelial cell migration studies, CRP consistently inhibits angiogenic responses, in a NO-dependent fashion. Angiogenesis is a key compensatory mechanism in chronic ischemia, and the ability of CRP to inhibit angiogenesis has important clinical implications for patients with coronary artery disease. Endothelial cell apoptosis is an important contributor in lesion formation, propagation and eventual rupture. Through inhibiting NO production, CRP facilitates endothelial cell apoptosis, uncovering yet another proatherogenic and proinflammatory phenotype. Recent evi-
Evidence also implicates CRP as a direct promotor of CD14-induced endothelial cell activation. In addition to the aforementioned effects of CRP on endothelial cell adhesion molecules, and vasoreactive hormone release, CRP functions to upregulate the transcription factor NFκB (unpublished observations) NFκB has been implicated as a key mediator of atherosclerosis. The majority of proinflammatory genes expressed in endothelial cells during the initial phase of lesion formation and in response to inflammatory mediators are dependent on NFκB activation. Recent evidence suggests that CRP directly increases the degradation of IκB-α and subsequently activates the NFκB pathway in endothelial cells (unpublished observations). The proatherogenic effects of CRP on endothelial activation are exaggerated in the hyperglycemic milieu, suggesting an important mechanistic link between hyperglycemia, endothelial dysfunction and cardiovascular disease. Lastly, patients with elevated levels of CRP have been shown to elicit impaired endothelium-dependent vasodilatation, suggesting that CRP may be a useful clinical tool for endothelial vaso-motion.

**Effects of CRP on Macrophage LDL-Uptake**

Uptake of LDL by macrophages is an important process contributing to plaque progression. Recent evidence suggests that CRP directly promotes native LDL-uptake into macrophages, a process that is ET-1 dependent, and inhibited during co-incubation with the ET_A/B receptor blocker, bosentan. CRP also increased basal ROS production, and potentiated the effects of Ang-II on ROS formation. These effects were also inhibited by losartan, indicating that increased CRP-mediated ROS formation in VSM cells was related, in part to increased AT_R expression. Lastly, in an in vivo model of carotid balloon angioplasty, CRP exposure facilitated AT_R expression, with resultant increases in neointimal formation, VSM migration and proliferation, and promoted collagen and elastin production, key matrix proteins in the vessel wall. These effects were attenuated by angiotensin receptor blockade with losartan. Therefore, CRP exerts direct proatherosclerotic effects at the level of the VSM (in addition to the endothelium) in part, via increased AT_R expression and signaling. No effect of CRP was found on AT_R, which may be vaso-protective in certain settings. Likewise, we did not observe an effect of CRP on Ang-II release.

**Effects of CRP on Bone Marrow Derived Endothelial Progenitor Cells**

Postnatal neovascularization is a process that is vital to the compensatory physiologic response in chronic ischemia. Myocardial ischemia provides a potent stimulus to angiogenesis and the subsequent development of collateral vasculature that maintains and/or revitalizes cardiac tissue. The mobilization and differentiation of bone-marrow derived endothelial progenitor cells (EPCs) has recently been shown to be important in this process of neovascularization. In fact, recent evidence suggests that EPCs contribute to over 25% of endothelial cells in newly formed blood vessels. More recently, the number and migratory activity of circulating EPCs has also been shown to inversely correlate with risk factors for coronary artery disease. In this vein, recent work suggests that EPCs incubated with human recombinant CRP, at concentrations known to predict...
adverse vascular outcomes, exhibited decreased survival and increased apoptosis. This reduction in EPC cell number was dose dependent, and at a CRP concentration of 20µg/mL, there was an approximate 80% reduction in cell number at seven days. Additionally, EPCs incubated with human recombinant CRP exhibited decreased expression of EC specific markers Tie-2 and EC-specific Lectin indicating an upregulation of EC specific markers Tie-2. This reduction in EPC cell number was dose dependent, and at a CRP concentration of 20µg/mL, there was an approximate 80% reduction in cell number at seven days. Additionally, EPCs incubated with human recombinant CRP exhibited decreased expression of EC specific markers Tie-2 and EC-specific Lectin indicating an upregulation of EC specific markers Tie-2.

Conclusions
A growing body of evidence implicates CRP as a powerful risk marker for diverse cardiovascular and metabolic diseases. Initially, this association was suggested to be a surrogate one, wherein CRP functioned to highlight increased levels of vascular inflammation, and in this fashion identify patients at heightened risk of atherothrombosis. This dogma has been recently revisited, with observations from our group and others suggesting that CRP functions as a direct partaker in lesion formation, and directly uncovers a proatherosclerotic and proinflammatory phenotype. Thus, CRP may not just be a marker of atherosclerosis and coronary events, but also a mediator of this disease because it contributes to the substrate underlying lesion formation, plaque rupture, and coronary thrombosis. The CRP-atherosclerosis story is nothing short of a self-fulfilling prophecy.

References

Subodh Verma, M.D., Ph.D.
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Human C-reactive protein (CRP) elicits direct proatherogenic and proinflammatory effects. CRP, at concentrations known to predict diverse vascular events, directly quenches endothelial cell nitric oxide (NO) production via destabilizing eNOS transcript. Via decreasing NO release, CRP inhibits angiogenesis, and stimulates endothelial cell apoptosis. In a synchronous fashion, CRP inhibits the release of the potent endothelium-derived contracting factor, endothelin-1 (ET-1), which in part, is responsible for CRP-induced upregulation of adhesion molecules ICAM-1 and VCAM-1. CRP potently upregulates MCP-1 release, a key chemoattractant chemokine responsible for leukocyte transmigration. Recent studies suggest that CRP also promotes NFκB upregulation in endothelial cells. At the level of the VSM, CRP promotes AT-1 receptor upregulation, and stimulates VSM migration, proliferation, and neointimal formation while concomitantly increasing reactive oxygen species production. CRP also inhibits endothelial progenitor cell survival and apoptosis and stimulates PAI-1 production (not shown in this diagram). In this fashion, CRP functions as an active participant in lesion formation, and hence is mechanistically linked to atherosclerosis.
FOR MANY OF US, setting MCQ is a way of life. Try this one:

What are the major advantages for members of the ISHR?

A. It is the only international society focussing on cardiovascular research
B. It is the society behind the well-respected Journal of Molecular and Cellular Cardiology
C. It publishes HEART NEWS AND VIEWS, now in full colour
D. It holds triennial scientific conferences, with the next being in Brisbane
E. All of the above.

What is the prize for the correct answer? Simple – free access to the web-site for the Brisbane meeting at www.heart2004.com!

THE LOCAL ORGANISING COMMITTEE has been working to bring you symposia which will demonstrate the advances in cardiovascular research since Winnipeg.

One major problem has been to cut down the 130 or so symposia suggestions to the 40 timeslots that we have allocated.

This has now been done and, by the time you read this, all the symposia chairpeople will have confirmed their involvement and we will be finalising the speakers.

The breadth of the topics is astounding and evidence that cardiovascular research remains one of the key research areas in biomedical sciences.

Further, this research is international – so the ISHR is the appropriate place to present new studies.

We hope to have the initial program on the web-site in August or September to show you what you can expect to hear in Brisbane.

THE ISHR has always emphasised young researchers and, once again, there will be financial assistance for young investigators to allow them to present their work in Brisbane. The details are already on the web-site even though the deadline is February 29th, 2004, the same date for all abstracts.

I will be applying to other funding bodies to increase the funds available for young investigators – so please send in your excellent applications to reinforce my contention that this congress will attract the best young researchers from around the world.
THERE HAS ALSO BEEN a lot of progress on planning the world congress of Clinical Pharmacology and Therapeutics which will run from the Sunday to Friday preceding our meeting at the same venue. More details can be found at www.cpt2004.com.

One highlight of CPT2004 will be a symposium on the Friday morning on the Pharmacology of Cardiac Protection, to be chaired by Jim Downey and myself. Another highlight will be a Thursday afternoon symposium on Drugs & Arrhythmias: Causes & Cures to be chaired by Terry Campbell.

Keep checking the CPT web-site for more details! There will be day registrations available to CPT2004 for ISHR members to allow us to participate.

OUR CONGRESS will be integrated with the annual scientific meeting of the Cardiac Society of Australia and New Zealand. Registration for either meeting will allow complete access to all sessions of both societies.

As the motto for the meeting suggests, this will allow the emphasis of the interrelationships between cardiovascular science and practice.

ANOTHER IMPORTANT REASON to come to Brisbane is to see the unique flora and fauna of Australia. The State of Queensland is a major tourist destination in Australia as we have the Great Barrier Reef, tropical rainforests, fantastic beaches, the great Outback and much more. Why not take time to see this part of the world? Check out the links to discover Brisbane or Queensland on either the CPT or ISHR meeting web-sites.

Further, Brisbane is only a short flight away from the wonders of New Zealand – examples are the volcanic areas of Rotorua and ski-ing in the Alps of the South Island as August is winter in the southern hemisphere. Then there are the tropical paradises of Fiji, New Caledonia, Samoa and many others. Is there a better way of spending your vacations in 2004?

THE SATELLITES are also progressing and we will be posting details of the scientific programs within the next few months. Details on the locations are already available on the web-site – the next thing is for you to make the decision on which one or more satellites you want to participate in!

See you in Brisbane in August next year!

Lindsay Brown, Ph.D.
REPORT ON THE FIRST ISHR-ES/SERVIER RESEARCH FELLOWSHIP

After completing my medical studies I started work in basic medical research in 1995 with Arnfinn Ilebekk and Knut Arvid Kirkebøen at the Institute for Experimental Medical Research at Ullevål University Hospital in Oslo. We studied the protective role of endogenous adenosine in an isolated piglet heart model of global zero-flow and low-flow ischemia (acute hibernation). This led to a PhD in 1999. In a short period of postdoctoral research in my previous laboratory in Oslo, we started to work with the intriguing phenomenon of myocardial preconditioning (PC) in anaesthetized pigs. At this time a group at the Karolinska Institute in Stockholm/Sweden, lead by Bertil Fredholm and Guro Valen was starting to look into the specific role of adenosine receptor subtypes in PC of genetically engineered mice. After some contact we decided to try and work together on this project. We wrote a grant proposal and were very honoured to be awarded the first ISHR-ES/SERVIER Research Fellowship in 2001. This made it possible for me to have a one-year postdoc position at the Karolinska Institute from August 2001 to August 2002. The results of this collaboration are presented below, as well as some background information about adenosine and PC.

The History of Adenosine, Preconditioning and Adenosine in Preconditioning

Studies of adenosine in the cardiovascular system began in 1929 with the discovery by Drury & Szent-Györgyi that extracts from various tissues containing adenosine produced bradycardia, hypotension and coronary vasodilatation. That adenosine also exerted direct cardioprotective effects on the myocyte itself was discovered in 1985 by Ely and coworkers. They showed enhanced recovery of function and higher postischemic ATP levels in hearts treated with adenosine, and proposed that adenosine served as an intracellular substrate to enhance salvage resynthesis of ATP during reperfusion. Protection induced by ischemic preconditioning has a bimodal distribution: an early phase (early PC) and a delayed phase (delayed PC). Additionally, myocardial PC can be evoked by systemic stimuli such as anisomycin, or by preconditioning of other organs. These phenomena represent adaptive and protective responses to ischemia, but differences in time courses of protection as well as target organ may indicate different underlying mechanisms.

Several endogenously produced substances have been implicated as triggers of this response. Since 1993 it has been known that transient exposure to exogenous adenosine or agonists can mimic early PC against infarction. Endogenous adenosine initiates and mediates early PC against infarction in most species. The role of adenosine in delayed PC has been investigated, and it is probably involved in protection against infarction, as transient exposure to adenosine or adenosine agonists induces delayed PC against infarction. Adenosine may also be involved in protection by remote PC.

Despite massive experimental evidence for the beneficial effects of adenosine during ischemia and reperfusion, it is not used in the treatment of patients with acute coronary ischemia. The reason is that administration of exogenous adenosine can cause systemic side effects, such as hypotension, bradyarrhythmias and induction of “coronary steal” if a critical coronary stenosis is present. When given intravenously to humans, adenosine causes vasodilatation with increased sympathetic activity, additionally it may cause discomfort with facial flushing, headache, chest pain and dyspnoea. Moreover, rapid degradation in the blood makes continuous intravenous - or possibly intracoronary infusion necessary to obtain a sustained effect on the myocardium. Hence, the role of the five known adenosine receptor subtypes (A1, A2a, A2b, A3, A4) and the effect of corresponding selective agonists in cardioprotection is of crucial importance.

Study of the Role of Adenosine Receptor Subtypes in PC at the Karolinska Institute

The main aim of our project was to clarify the role of adenosine A1-receptors and A3-receptors in PC. The Karolinska Institute provided very good...
opportunities to investigate this in mice, and has a very good international reputation as an excellent research institution. One group there lead by Guro Valen has established mouse heart perfusion since 1998. Furthermore, another group lead by Bertil Fredholm has produced a mouse deficient of the adenosine A1 receptor, and had available mice lacking the A3 receptor produced elsewhere. The mouse genome has been characterized, and the genetically engineered mouse may be a powerful tool to unravel the mysteries of gene function, thus potentially providing new insight into cardiovascular physiology and pathophysiology (and other organ/cell systems, of course!). However, the mouse is small and studies of physiology are particularly demanding in that species, requiring more sophisticated equipment and handling than larger species.

The Role of the Adenosine A1 Receptor in Remote, Delayed Preconditioning

The first experimental series I entered into concerned a putative role of the adenosine A1 receptor in remote, delayed preconditioning. The model was established by a previous PhD student, Shinichi Tokuno, who found that mice with severe atherosclerosis due to apolipoproteinE/1LDL receptor deficiency had spontaneous ischemic events in their hearts and brains. When hearts of these animals were isolated and subjected to global ischemia, heart function was improved and infarct size reduced compared with hearts of non-infarcted mice. This finding could be mimicked by inducing brain ischemia through bilateral occlusion of the internal carotid arteries 24-36 hours earlier in wild type mice, but not in mice deficient in the inducible nitric oxide synthase gene (Tokuno et al. 2002). I wanted to study a possible role of the adenosine A1 receptor in this model through using mice without the A1 receptor. To characterize adenosine release, microdialysis probes were placed in the brain and the femoral artery before carotid artery ligation, and microdialysates collected for measurement of adenosine and its metabolites. Adenosine and its metabolites increased locally in the brain as well as in the circulation after carotid artery ligation. Therefore, other mice were subjected to the same preconditioning protocol, and their hearts isolated to study function and infarct size after induced global ischemia. We found that A1 receptor knockout mice as opposed to their wild types could not be protected by remote, delayed preconditioning. We studied whether this may be due to influence on mitogen activated protein kinase (MAPK) phosphorylation during ischemia and reperfusion through serial sampling of hearts during perfusion, ischemia, and reperfusion, protein extraction, and immunoblotting with phosphospecific antibodies against ERK1/2, JNK, and p38 MAPK. However, although both ERK1/2 and p38 were phosphorylated during reperfusion after global ischemia, there was no clear-cut modification by remote, delayed preconditioning, and no marked difference between wild-type and knock out. Thus, we concluded that although remote, delayed preconditioning signals through adenosine using the adenosine A1 receptor, signalling to MAPK may not be important for myocardial protection at the stage of organ effects (manuscript submitted).

The Role of the Adenosine A3 Receptor for Classic Preconditioning

Due to slow breeding of the A1 receptor knock outs, I could not pursue studies in those mice as I would have wished. Instead I switched to the adenosine A3 receptor knockouts, where the primary target was to study whether these mice could be preconditioned by classic preconditioning of the isolated heart before induced global ischemia. Wild types achieved infarct reduction and functional improvement after classic preconditioning, but this effect was lost in mice deficient of the A3 receptor which tended towards being protected against ischemic injury. We are currently supplementing these data with gene array studies, where I collected hearts of preconditioned or control perfused wild type and knockout mice serially during preconditioning, ischemia, and reperfusion for analysis with the Affymetrix chip. PhD student Jiangning Yang is currently analysing the data to identify families of genes which may be up- or downregulated, which may provide new insights into the possible signal transduction pathways of the adenosine A3 receptor in ischemic preconditioning (manuscript in progress).

Other Projects

During my stay in Stockholm I was also involved in a study attempting to clarify if and how adenosine signals to nuclear factor kappa B with the aid of a luciferase reporter mouse. That was a study of highly surprising findings, which is still ongoing. It may become something rather exciting, or may end in the Journal of Irreproducible Results.

Conclusion

Studies of genetically engineered mice support an important role of adenosine receptor subtypes for preconditioning triggering, and may provide us with new insights into the mechanisms and signal transduction of this effect. I learned many new aspects of integrative mouse physiology and signal transduction analysis during my stay at the Karolinska Institute, and thank SERVIER for the opportunity.

References

2. Ely SW, Mentzer RM, Lasley RD et al.
IN DECEMBER 2002 the International Section created a named lecture that will be an important part of ISHR World Congresses and the North American Section meetings. The lecture is named after the late Janice Pfeffer in honor Janice’s contributions to scientific knowledge. At the time of her untimely death Janice was a leader in the study of myocardial remodeling and heart failure. It is the intent of this lecture to honor her memory and to recognize all that she has done for her field.

The Janice Pfeffer distinguished lecture will be held at each World Congress of the ISHR. In the non-Congress years, the endowers have asked that the lecture be held at the annual meeting of the North American Section to which Janice belonged. The speaker, however, will be selected from the entire membership of the Society. This lecture is intended to be a high profile event and should be scheduled as a keynote plenary lecture. The International Council will select the speaker. **The topic of the lecture will be in the field of remodeling, heart failure and/or hypertrophy but the content should be chosen to be of broad interest to the cardiovascular 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 the *Journal of Molecular and Cellular Cardiology*, and featured in HEART NEWS AND VIEWS, and on the ISHR website.

The International Council believes 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.

This award is funded by generous contributions from: F. Hoffman-LaRoche Ltd, AstraZeneca LP, Bristol Myers Squibb Co, Genzyme Biosurgery, Novartis Pharmaceuticals Corporation, Scios Research Group, and the Michael and Keri Whalen Foundation.

The 2003 Janice Pfeffer Distinguished Lecture will be delivered by Dr Piero Anversa (Valhalla, NY) during the XXV Annual Meeting of the North American Section (June 28 - July 1, 2003; Mystic, Connecticut).
We continue publishing brief biosketches of the 82 Founding Fellows of the ISHR.

For a complete list of the Founding Fellows, see HEART NEWS AND VIEWS 2001;9(1):8


Saul Winegrad

ISHR member since 1973.
Current position: Professor of Physiology, School of Medicine, University of Pennsylvania.
Training: B.S. Chemistry, M.D. University of Pennsylvania; Intern, Peter Bent Brigham Hospital; NIH; University College London.
Honors: Guggenheim Fellowship, Fogarty Fellowship twice, Award of Merit, AHA
Major research interests: Intracellular and transmembrane movements of Ca in activation and regulation of contraction of striated muscle; regulation of cardiac contractility by post-translational changes in myofibrillar proteins; regulation of cardiac contractility and filament integrity by myosin-binding protein C; chemical signaling between heart and coronary vessels in matching contractility to blood flow.
Most admired scientist: Andrew Huxley.
Relaxation: traveling, photography, music.

Peter H. Sugden

Current appointment: Professor of Cellular Biochemistry (personal chair), NHLI Division, Faculty of Medicine, Imperial College London, UK.
Research interests: Intracellular signaling especially regulation of intracellular events by protein phosphorylation and dephosphorylation. This developed from an initial interest in metabolic regulation. Mitogen-activated protein kinase cascades and their roles in cardiac physiology and pathology, especially in the hypertrophy of the cardiac myocyte and its responses to cytotoxic stresses. Regulation of transcription and translation by protein phosphorylation. Endothelin and Gq protein-coupled receptor signaling. Small G proteins (Ras and Rho families).
Non-professional achievements: In the long distance running arena, England International (marathon, personal best 2 h 18 min). Winner, London-Brighton 54 mile race (1987) and many other ultramarathon races; p.b. for 50 miles, 5 h 1 min (1985).
Interests: Alcohol (especially beer and the wines of Bordeaux), travel (especially in Europe), Reading Football Club (soccer), cricket (Warwickshire CCC), eating out in France and Spain, The (London) Times crossword puzzle, commercial aviation, boring people with my running experiences.
Most admired scientist: Sir Howard (later Lord) Florey, who was awarded the Nobel Prize in 1945 (with Fleming and Chain) for the discovery and development of penicillin.

Richard J. Bing

First President of the ISHR and, along with Dr Lionel Opie, founding editor of the J Mol Cell Cardiol.
Current Post: Professor of Medicine, Univ. of Southern California, and Director of Experimental Cardiol., Huntington Medical Research Institute, Em. Visiting Associate, California Inst. of Technology.
Qualifications: Univ. of Bern; Carlsberg and Rockefeller Institutes, Johns Hopkins Univ., Honorary degrees from Johns Hopkins Univ., Univ. of Bologna, German Acad. of Med.
Research emphasis: Cardiac metabolism, coronary microcirculation, congenital heart disease, myocardial infarction, heart transplantation, coronary blood flow, etc.
Publications: Two books, 450 research papers.
Most admired scientist: Homer W. Smith.
Relaxation: Music.
**Ketty Schwartz**

ISHR member since 1977. Secretary General ISHR-European Section 1992-98.  
**Current positions:** Vice-President of the Board of Governors of the National Inst. for Health and Medical Research (Inserm); President of the Scientific Council of the French Muscular Dystrophy Association (AFM); Member of the Scientific Council of the French Network of Génopoles.  
**Training:** Universities of Paris V and XI; Pasteur Institute.  
**Research interests:** The molecular mechanisms that regulate the function of cardiac and skeletal muscles in both the normal and pathological states.  
**Major research contributions:** Demonstration that the myocardium can modify its molecular phenotype depending upon its work conditions (isomyosins, isoactins and calcium-ATPase of the sarcoplasmic reticulum). Development of genetic cardiology through the study of cardiomyopathies and muscular dystrophies, with the discovery of cardiac myosin binding protein C and lamin as disease-causing genes. Developement of cell therapy of the failing heart and participation to the first phase 1 and 2 human trials using myoblasts.  
**Publications:** Over 350 refereed articles Science Citation Index most cited paper: Three myosin heavy-chain isozymes appear sequentially in rat muscle development. Nature 1981;292:805-9 (524 citations)  
**Positions in scientific organizations and honors:** 35 national or international committees; Head of the French Research Directorate, '01-02; Knight of the Legion of Honor; Officer of the National Order of Merit; Silver Medal of the National Center of Scientific Research.  
**Most admired scientist:** Marie Curie

**Richard L. Moss**

ISHR-NA Section: Member of Council since 2000; Chair, Local Organizing Committee, 24th Annual Meeting, 2002; President Elect 2003-2006.  
**Current position:** Chair of Physiology, Director of Cardiovascular Research Center, University of Wisconsin-Madison.  
**Training:** PhD Physiology & Biophysics, University of Vermont; post-doctorate, Boston Biomedical Research Institute.  
**Research interests:** Regulation of contraction and contraction kinetics in striated muscle, mechanisms of myosin function, contractile dysfunction in heart failure.  
**Summary of research:** Myocardial contraction is influenced by the properties of myosin and regulated by Ca²⁺, accessory proteins, and myosin binding to thin filaments. To assess protein function in working skinned myocytes, we acutely extract endogenous regulatory proteins and replace them with alternate forms, e.g., extraction of MyBP-C accelerates contraction kinetics, while extraction of TnC reduces the cooperativity of force development. We use gene knockouts/ins together with acute biochemical replacements of proteins to distinguish mechanisms of cardiac phenotypes in these animals, i.e., changes in the specific protein or secondary compensatory mechanisms.  
**Avocations:** Reading, fishing, applied oenology.

**Norman R. Alpert**

**Training:** Columbia University (Physiology and Biophysics).  
**Current position:** Professor, Department of Molecular Physiology and Biophysics, University of Vermont College of Medicine.  
**Positions in scientific organizations:** President, Cardiac Muscle Society (1981-82); President, American Physiological Society Cardiovascular Section (1988-89); Vice President and Member of Board of Directors of the International Academy of Cardiovascular Sciences (1996-present).  
**Research:** Our studies are currently directed at uncovering the molecular basis of heart failure in NYHA Class III and IV failing human hearts (mitral regurgitation and dilated cardiomyopathy). We demonstrated a depression in myofibrillar ATPase activity, an increase in the cross-bridge force-time integral, a marked depression in calcium cycling and a blunting of the force-frequency relationship. In FHC failure we showed that L908V and R403Q propelled actin filaments faster than controls (in vitro motility assay) and that this could be accounted for by a decrease in attachment time (single molecule laser trap measurements).  
**Favorites:** Playwright, Bernard Shaw; Author, Richard Feynman; Composers, George Gershwin, Harold Arlen; Lyricists, Lorenz Hart, Ira Gershwin, E.Y Harburg; Musicians, Yo Yo Ma (classical), Miles Davis (jazz); Personal Activities, sailboat racing, tennis, swimming.

2003 outstanding investigator prize of the ISHR

Dr Issei Komuro of the Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, Chiba, Japan, has been selected as the winner of the 2003 Outstanding Investigator Prize of the International Society for Heart Research.  

The award will be presented during the XX Meeting of the Japanese Section that will be held in Tokyo, Japan, on November 22-24, 2003.  

The Outstanding Investigator Prize recognizes cardiovascular scientists who have made major contributions to our understanding of cardiovascular disease and are internationally regarded as leaders in their field.
ISHR MEETINGS CALENDAR

- **August 7-9, 2003. XXVII Meeting of the Australasian Section: “New Science at the Heart of New Therapies”**. Melbourne, Australia. **Enquiries:** Dr S. Pepe, The Baker Heart Research Institute, Melbourne, Australia. Tel. +61 3 8332 1310; Fax +61 3 8332 1314; E-mail spepe@baker.edu.au; Website www.baker.edu.au/ishr

- **August 16-18, 2003. XII Meeting of the Latin American Section.** Buenos Aires, Argentina. **Enquiries:** Dr A. Mattiazzi, Centro de Investigaciones Cardiovasculares, Facultad de Medicina, 60 y 120, 1900 La Plata, Argentina. Tel./Fax +54 221 483 4833; E-mail ramattia@atlas.med.unlp.edu.ar or aral@sinectis.com.ar

- **August 30 - September 3, 2003. XXV Congress of the European Society of Cardiology.** Vienna, Austria. **Enquiries:** E-mail webmaster@escardio.org; Website www.escardio.org

- **November 9-12, 2003. Scientific Sessions of the American Heart Association.** Orlando, FL. **Enquiries:** American Heart Association, Meetings and Councils, 7272 Greenville Avenue, Dallas, TX 75231. Tel. +1 214 706 1543; Fax +1 214 373 3406; E-mail scientificconferences@amhrt.org; Website www.americanheart.org

- **November 22-24, 2003. XX Meeting of the Japanese Section.** Tokyo, Japan. **Enquiries:** Dr S. Mochizuki, The Jikei University School of Medicine, Division of Cardiology, Department of Internal Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan. E-mail m_seibu@jikei.ac.jp

- **August 7-11, 2004. XVIII World Congress of the International Society for Heart Research.** Brisbane, Australia. **Enquiries:** ISHR 2004 Congress, PO Box 164, Fortitude Valley QLD 4006, Australia. Tel. +61 7 3854 1611; Fax +61 7 3854 1507; E-mail heart2004@ozac.com.au; Website www.heart2004.com

## XII Meeting of the Latin American Section
**Buenos Aires, Argentina**
**August 16-18, 2003**

### Schedule

**Symposium:** Ischemic heart disease - Emerging concepts  
**President:** Dr Raul Domenech Lira (Chile)  
**Moderator:** Dr Ricardo J. Gelpi (Argentina)

**Conference:** Cardiac hypertrophy and failure: Molecular causes vs consequences  
**President:** Dr Hernan Gomez Llambi (Argentina)  
**Speaker:** Dr Richard Walsh (USA)

**Symposium:** Frontiers in cardiac basic research - Genetic approaches to the comprehension of cardiovascular disease  
**President:** Dr Luis Folle (Uruguay)  
**Moderator:** Dr Alberto Crotogini (Argentina)

**Conference:** Blockade of Na+/H+ exchanger as a therapeutic strategy  
**President:** Dr Liliana Grinfeld (Argentina)  
**Speaker:** Dr Horacio Cingolani (Argentina)

**Mini Course:** Molecular biology - Basic concepts and their application in cardiac pathologies  
I. Introduction to molecular biology  
II. Molecular Biology in the cardiology practice - Present and future  
**Director:** Dr Gladys Chiappe de Cingolani (Argentina)

http://latin.ishrworld.org
HEART NEWS AND VIEWS

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a private French pharmaceutical company committed
to therapeutic advances in cardiovascular medicine as well as other key therapeutic areas. We have successfully
developed products in the field of cardiovascular diseases
(ischemic heart disease, hypertension, and heart failure),
as well as in other major therapeutic fields. A number of
landmark studies like PROGRESS, EUROPA, PREAMI, PEP,
and HYVET are being conducted with our support.

The dynamism of our research is ensured by consistent allocation of as much as over 25% of the annual turnover
of the Group to search for new molecules and develop
their therapeutic applications.

Servier supports a number of important projects in the field
of cardiology, such as the Education and Training
Programs of the European Society of Cardiology.

Servier is also the founding father of The European Cardiologist Journal by Fax and Dialogues in
Cardiovascular Medicine, a quarterly publication with a worldwide
circulation edited by

Roberto FERRARI and David J. HEARSE.

Dialogues discusses in a comprehensive way issues from
the cutting edge of basic research and clinical cardiology.

The forthcoming issue, devoted to
INFLAMMATION & CORONARY ARTERY DISEASE
will feature articles by:

P. Libby, C. Kluft, A. Maseri
and J. Danesh

For further information on
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