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HEART NEWS AND VIEWS

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PAST TRUTH & PRESENT POETRY

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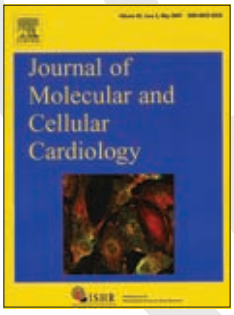


THE HEART OF THE MATTER

A CAREER IN CARDIO-VASCULAR RESEARCH

Ole D. Mjøs, MD PhD

I was born in Bergen, Norway, March 8,1939. I finished my medical curriculum at the University of Bergen in 1964 intending to be a clinician in internal medicine; however, first I wanted to try scientific research. In 1967, after my obligatory time as medical doctor in the military service, I became a cardiovascular research fellow at the Institute for Experimental Medical Research, Ullevål Hospital, University of Oslo. Prof. Fredrik Kiil, the leader of the Institute and my supervisor, was a well known renal physiologist who had contributed to the construction of an artificial kidney. He wanted to conduct cardiovascular and renal physiology in intact dogs, and was of the opinion that although there were many studies in isolated organs, *in vivo* studies of integrated cardiovascular function in health and disease were lacking. Over the years his Institute became the most important cardiovascular research institute in Norway. Hundreds of research fellows have received their Ph.D.s from the Institute, and have "infiltrated" universities, hospitals and research institutes in Norway and elsewhere as outstanding researchers/professors.

Professor Kiil had already begun studies of the hemodynamic effects of acutely elevated aortic blood pressure in the dog, and I was to study myocardial uptake/metabolism of glucose, lactate, pyruvate and free fatty acids (FFA) during acutely elevated blood pressure. First I had to learn how to correctly insert a catheter into the coronary sinus in anesthetized dogs, which was quite a challenge. I initially measured myocardial blood flow, oxygen consumption (MVO_2) and substrate

uptake; however, the results of these studies were difficult to interpret be–cause elevation of aortic pressure not only increased the work load of the heart, but also changed the arterial concen–trations of the substrates. These initial studies established what was to become a life-long interest of mine: the role of FFA in myocardial function and metab–olism in health and disease of the heart.

My interest in FFA was triggered by studies by Challoner and Steinberg (1966-1968) on the effects of high concentrations of FFA on myocardial oxygen consump–tion in the isolated, healthy rat heart. They demonstrated that elevated concen–trations of FFA caused a 30-40 % increase in MVO_2 and concluded that high FFA caused an "oxygen wastage" of the heart (although they did not measure the well known mechanical factors of the heart (rate, contractility, tension) which are the most important determinants of MVO_2). Therefore, my goal was to study the effect of elevated plasma FFA on MVO_2 in healthy, intact, anesthetized dogs with simultaneous recording of all hemodynamic parameters. I subsequently demonstrated that high plasma FFA caused a substantial rise in MVO_2 that could not be explained through changes in the hemodynamic determinants of MVO_2. In 1972, these studies formed the basis of my Ph.D. thesis: "Effects of free fatty acids on myocardial metabolism and performance". I recall being very proud that two articles reporting this work were published in the *Journal of Clinical Investigation.*

At the Institute in Oslo I had an especially good collaboration with John Kjekshus, who is an outstanding cardiac researcher, particularly in the area of infarct size and heart failure. In 1970 he was on a sabbatical year with Dr Eugene Braunwald in San Diego. The "hot message" from there was that early intervention in myocardial infarction, by favourably influencing the balance between cardiac oxygen supply and demand, could limit infarct size. In their classic paper from 1971, with the late Peter Maroko as first author, they showed that increased myocardial oxygen demand increased, and reduced oxygen de–mand reduced, the size of an ischemic injury following acute coronary artery occlusion in the dog. When Kjekshus came back to Oslo, we immediately embarked upon studies to investigate whether reduction of plasma FFA, through reduction of myocardial oxygen demand, would also reduce the ischemic area. We found that reduction of plasma FFA both in the normal state and during infusion of isoproterenol/noradrenaline reduced the ischemic area measured by ST elevation following acute coronary occlusion in the dog. These studies supported the concept of "metabolic intervention" in the heart, which, over the years, has been an important therapeutic challenge in the treatment of acute myocardial infarction and heart failure in humans. The idea that agents favouring myocardial glucose metabolism are "good" for the ischemic heart, while increased myocardial metab–olism of FFA is "bad" for the ischemic heart has been the leading theme of my research.

For years our 1977 paper in the Lancet was one of the most cited in the whole cardiovascular literature

After finishing my Ph.D., I received an NIH postdoctoral fellowship to the well-known Cardiovasular Research Institute (University of California, San Francisco). In 1972-1973 I worked with Dr Richard J. Havel, who was one of the most prominent researchers on lipoproteins in the world, and conducted studies on remnant particles produced during the metabolism of triglyceride-rich lipoproteins of blood plasma and intestinal lymph in the rat. This work provided me with a good basis for later studies on cholesterol and ischemic heart disease.

During the early seventies the initial steps to establish a brand new University and Medical School in Tromsø, which would become the northern-most university in the world, had taken place. I applied for and was granted a top-position in the Department of Physiology. Prior to starting in Tromsø, I completed a fellow–ship in Michael Oliver's research group in Edinburgh. There we continued studies on how to favourably alter the balance between metabolism of glucose and FFA in myocardial ischemia. The year in Edinburgh was very good both scien–tifically and socially, and I began several long-lasting collaborations, notably with Rudolph Riemersma and Norman E. Miller. In addition, something important and unexpected came out of my stay in Edinburgh: Norman Miller had just completed his studies on the cardio–protective effect of elevated plasma HDL-cholesterol. Immediately after coming to Tromsø, I contacted researchers involved in the Tromsø-Heart-Study, Dag Thelle and Olav Helge Førde, and invited them and Norman Miller to collaborate. The result was the article by Miller, Thelle, Førde and Mjøs: "The Tromsø Heart-Study. High-density lipoprotein and coronary heart-disease: a prospective case control study" (*Lancet*, May 7, 1977, pp 965-8). This study demonstrated for the first time that low levels of plasma-HDL predisposed the heart to suffer acute myocardial infarction. For years this paper was one of the most cited in the whole cardiovascular literature, and has since become a "citation classic" in *Current Contents*. For me this was a rewarding "side-step" from my own studies in myocardial metabolism.

WE are pleased to present the third article in our autobiographical series entitled, "The Heart of the Matter: A Career in Cardiovascular Research". Dr Ole Mjøs, Professor and Chairman of the Department of Medical Physiology at Tromsø University and Chairman of the Norwegian Nobel Committee, has provided a remarkable account of his career path, highlighting his contributions to cardiovascular medicine, to establishing the University of Tromsø, and to human rights and world peace. We are grateful to Dr Mjøs for sharing the amazing story of his successful career in and beyond cardiovascular research.

The Norwegian Crown Princess, Mette Marit, is presenting the Award for Outstanding Cardiac Research for 2002 from the Norwegian Heart Foundation to our Department of Medical Physiology (Photo: Scanpix, Norway).

I started as Professor and Chairman of the Department of Medical Physiology at the University of Tromsø in 1974-1975. My major challenge was to establish a research group in experimental cardiology, including the areas of myocar–dial function, myocardial metabolism, myocardial infarction and heart failure, with a special focus on how to protect the ischemic myocardium. We began using dogs, and set up all the methods that I was familiar with from the Institute in Oslo. Later, research using isolated myocytes and isolated rat and mouse hearts became increasingly important. We currently have between 15-20 members in the group, and our department has produced 38 Ph.D. candidates and more than 350 international publications from 1976 to the present, demonstrating that our group is one of the most productive research groups at the University of Tromsø. I would particularly pay tribute to Terje Larsen PhD and Kirsti Ytrehus MD, PhD for their excellent contributions and collabo–rations over the past 25-30 years.

From 1980-1981 I spent a sabbatical year with the late Jim R. Neely (Hershey, Pennsylvania, USA), conducting research on the role of FFA in hypothermia. Jim, who died a few years after my sabbatical year with him (much too early - he always said that he had bad genes!) is probably the most brilliant cardiac researcher I have ever met, and I am extremely thankful for the year in his laboratory. From 1997-1998, research fellow Anne Jonassen and I spent a sabbatical year in Derek Yellons laboratory, the Hatter Institute, University College London. In collaboration with Michael Sack, first in London and later in Cape Town, she studied possible mechanisms for the cardioprotective effect of insulin in the isolated, perfused rat heart and found that the cardioprotective effect of insulin could in part be explained through an anti-apoptotic effect. I am very thankful to Derek Yellon for his support during this time. In later years, members of our department have also had good research collaborations with Lionel Opie and Amanda Lochner in South-Africa.

From 1989-1996 I served as President of the University of Tromsø and became very interested in human rights and peace issues. During this time, the Nobel Peace Prize Laureates Desmond Tutu and Rigoberta Menchu received honorary doctorates from the University of Tromsø. In 2002, I contributed to the establishment of a Centre of Peace Studies at the University of Tromsø, the only university peace centre in Norway. In 2003, I became Chairman of the Norwegian Nobel Committee. During my time here we have awarded the Nobel Peace Prize to: Shirin Ebadi (human rights), Wangari Maathai (sustainable environment), Mohamed El Baradei (against nuclear weapons) and Muhammad Yunus (microcredit against poverty). It is a great privilege to serve as Chairman of the Committee for the most prestigious prize in the world!

I have been fortunate to do cardiovascular research throughout my life, to contribute to establishing the University of Tromsø, to contribute to establishing a well-regarded cardiac research group, and to work on human rights and peace in the world. Thereby I have had the privilege to build bridges between health and peace in the world. I thank all the members of the Department of Medical Physiology and all other collaborators for their excellent cooperation. I also thank my wife for her life-long support - without her I would not have been where I am today!

It is a great privilege to serve as Chairman of the Committee for the most prestigious prize in the world

We all have our dreams for a good life, for successful research and for peace in the world. The famous Norwegian author Olav H. Hauge has written the beautiful poem "It's the Dream", that I would like to conclude with.

"It's the dream we carry in secret
that something wonderful will happen
that must happen
that time will open
that doors will open
that mountains will open
that springs will gush
that the dream will open
that one morning we will glide into
some harbour we didn't know was there".

Ole D. Mjøs, MD, PhD
Tromsø, Norway

PRESIDENT 'S LETTER

Dear Reader,

Well, here we are again. The e-mail from Tom reminding me to prepare the final President's Letter for Heart News and Views has arrived with the usual Dutch punctuality. Three years have already passed. Tom is one of the few people who can manage to make me stick to a deadline. Time passes so quickly and I think that in this era of globalisation, we are all working too hard and under too much pressure, and I am not sure that it should be this way. As a result, it is only now that I have realised that in my three years as President, I have actually done nothing for the ISHR, apart from concentrating on the World Congress. However, this is not such a bad thing, as the Congress itself is a major step forward for the ISHR and it is the first time that the President has also been the World Congress organiser. Please do not worry, the ISHR is in good shape, as I have been lucky enough to have a fantastic team running it with me. Leslie, Metin and Tish have been wonderful in dealing with the administrative issues as well as the awards, competitions, elections, *etc*. Many thanks to all of them.

The Congress, believe me, has taken a lot of my time. This is of course my fault as it was me that had the crazy idea to convince the Sections to join the World Congress rather than hold their own individual Annual Meetings. I am still sure that it was a good idea, as it will enable the entire ISHR to fully participate in the World Congress. The idea to fuse the Section meetings came about because, I am afraid, I noticed that the International Section had lost a little of its spirit and enthusiasm. I grew up with the ISHR from my PhD days in London where I was perfusing rabbit hearts with Tom, under the supervision of Winifred Nayler. At that time, participation in the International ISHR Congress was a dream, something to fight for. The atmosphere was great, very familial. Maybe I am too nostalgic and romantic. There were no faxes, e-mails and mobile phones in those days, but lots of talk about the calcium paradox and the existence of post-ischemic reperfusion damage! However, there was a genuine spirit of participation in a fraternity of people with common interests. We were all proud to be at the closing dinner and to listen to Peter Harris's speech with his English humour.

Nowadays, let's be honest, the sense of belonging is less and the competition that the ISHR faces is tremendous. The opportunities to present ones work are endless. Just an example, the basic science abstracts submitted to the ESC Annual Congress amount to 2000. In Bologna we received 700! I believe that to survive, the ISHR needs to recover the early spirit and hold congresses which would be impossible not to attend it. Are we there? No, not yet, but I hope that Bologna 2007 will start the process. With the help of the Australasian, European, Japanese and North American Sections, as well as the others, and with a little help from Italy and a lot of friends, I hope that we are at least moving in the right direction.

Organising Bologna 2007 has been harder than I expected. Italy is going through a very difficult financial situation with regard to congress sponsorship. Even the government (normally dormant) decided to change all of the rules for congress sponsorship and organisation in 2007. We received the usual number of complaints, cancellations and unhappy comments. Yet, our enthusiasm has kept us going, and helped us put together the congress. I truly hope that you enjoy it, and that you can feel the spirit of what I have been working to achieve. If this is the case, then I will have accomplished something during my Presidency.

I am sure that Roberto Bolli will continue the process of rejuvenating the ISHR, and with his Italian/American influence and the Japanese input from the next Congress organiser Prof. Hori , I am sure that the ISHR will be in safe hands, and I wish him good luck.

Roberto Ferrari

PAST TRUTH & PRESENT POETRY

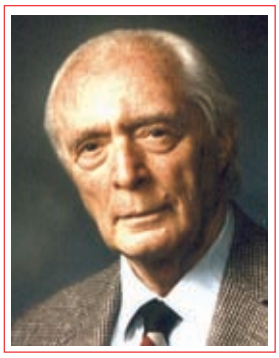
THERE comes a time when we must abandon our mad pursuit for scientific truth and epiphany of discovery to sail into the tranquil waters of retirement. It is a difficult transition for some, who are deeply involved in this pursuit, and have difficulties changing course. They try to continue their pet projects at all cost. The rest of us may choose a completely different course, finding satisfaction in writing, composing or painting. I have chosen the stories of two men, who during retirement continued their scientific career, but with a new and different objective. They are examples that the creative drive can persist to the end, and that new goals can renew and invigorate.

Edward M. Purcell (1912-1997), in 1945 simultaneously with Felix Bloch, dis–covered nuclear magnetic resonance (NMR). Their discovery changed diagnostic medicine, introducing imaging techniques (*e.g.* MRI). Edward Mills Purcell was born in Taylorville, Illinois; the co-discoverer of NMR, Felix Bloch was born in Zurich, Switzerland. The two Nobel Prize winners always maintained a cordial relationship; an hour after the Nobel announcement in 1952, Purcell received a telegram from Bloch: "I think it's swell for Ed Purcell, to share the shock with Felix Bloch."

In 1977, Purcell published a remarkable paper, "Life at Low Reynolds Number" in the *American Journal of Physics*. This paper was written later in his career, when he had terminated his work on magnetic resonance and on astrophysics. These studies use physics and mathematics for the definition of biological phenomena. Purcell also derived models to describe his results both experimentally and quantitatively. His subject was a study of the mechanism, by means of which a microorganism (E. Coli) swims in fluids with low Reynolds number — a far cry from his previous work on nuclear spin. He asked the question, "What are the physical limitations on the cell's ability to sense and respond to changes in environment?" For this naïve writer, the study is remarkable, because of Purcell's skills in translating biological phenomena into mathematical equations, expressing physical phenomena. His methods, rather than the results, are intriguing. As Purcell wrote, "finding out this strange thing about them got me thinking about this elementary physics stuff. Evidently the animal has a rotary joint and has a motor inside that's able to drive a flagellum in one direction or the other, a most remarkable piece of machinery." The freshness and enthusiasm with which Purcell reports his findings show the enjoyment he experienced from this change in direction, taken at the end of his career.

34. THE REFRESHING CHANGE

A NEW SCENT FOR OLD NOSES



RICHARD J. BING

The other man, who changed the direction of his scientific goals late in life, is Max Delbrück (1906-1981). I have previously described his passage from physics to biology [*HN&V* 2001; **9**(3): 1-2]. Max was born in Berlin and received his Nobel Prize together with Salvador Luria and Alfred Hershey. Most of his scientific work concerned phage research, which became the landmark in the history of molecular biology, since it furnished evidence that bacterial inheritance is also mediated by genes. Having been personally ac–quainted with him, I learned to admire his interest in music and literature, part of his romantic personality. In 1976, Delbrück got interested in Phycomyces. As he wrote: "I have studied an organelle of the fungus Phycomyces, the sporangiophore, in the belief that in the field of transducer physiology, as in genetics, essential progress will require the use of a suitable microorganism. (…) This organelle is exquisitely sensitive to light, to gravity, to stretch, and to a stimulus which is believed to be olfactory." This was a new venture, which gave him a new vigor and enjoyment. He and his coworkers summarized their work in the *Bac–teriological Reviews* in 1969. "We believe what we can learn from Phycomyces is relevant to the next phase of our quest for a mechanistic understanding of life." Delbrück was intrigued that Phycomyces accomplishes this through mechanisms other than electrical signals.

How wonderful, this late burst of energy, this enjoyment of the search of life's miracles, whether in science or art. How great it is to get away from the common–place humdrum of contemporary politics and intrigues, and from the daily petty annoyances. How great it is to search once more for the secrets of life!

Thanks to Dr Ruigrok for his years of friendship. He too will find inspiration in his music and science.

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(continued on page 7)

BRIDGING THE GAP. WHERE CLINICAL AND BASIC SCIENCES MEET

BY KARL T. WEBER, M.D.

A DILEMMA ON ORCHID ISLAND

AT the wheel of his Volvo sat Seymour Lavin. Sy and his new bride, Joyce, were headed south on US 1 to their home in Orchid Island, Florida. Sy glanced from the roadway over at Joyce. He marveled at her beauty. Her short, sleeveless white sundress created a ravishing image he savored for some minutes.

Traveling eastward on Route 510, the Lavins drove past orchards of ripened citrus fruit. Joyce carefully crossed her tanned, slender legs as she shifted effortlessly to face Sy. "Sweetie, look at these luscious grapefruits. I've been told they're so healthy for you."

"Yeah," stammered Sy, and added, "my internist told me grapefruit juice (GFJ) would lower my cholesterol and improve my ratio of low- to high-density lipo–proteins."

"We should drink more freshly squeezed GFJ," added Joyce.

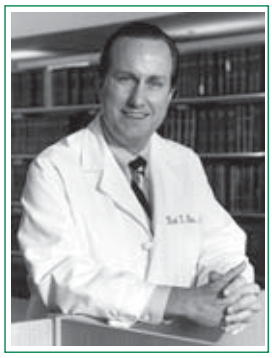
Sy maneuvered the Volvo onto Route A1A. Soon, the Lavins reached their plush beachfront estate. Sitting in their screened-in porch, admiring the sights and sounds of the surf, Joyce began to massage her right thigh and shin. "Maybe it's shinsplints from last night's walk," she commented, wincing with pain. "I should see Dr Ogden tomorrow morning."

Sy agreed. "Let's forego our evening walk and let you rest." That night, Sy was too tired for any fun and games.

The next morning, with beams of sunlight bathing the kitchen, Joyce entered and stood facing Sy in a pro–vocative pose as he worked the electric juicer that forcefully crushed grapefruit halves. "Honey, I've followed your advice and prepared a pitcher of freshly squeezed GFJ. And sorry about last night. It may have been my antihistamine that made me so sleepy."

Joyce took herself over to Dr Ogden's in her red BMW, her blonde ponytail trailing behind her like a flapper's scarf in an open-aired Deusie.

Philippe Ogden, a chiropractor, was



impressive, with tanned sinewy forearms and a well-developed chest that ended in a slim waistline. What a hunk, thought Joyce. She related her recent symptoms and marveled at the feel of Philippe's powerful hands as they massaged her right and left legs, and then each of her thighs. Philippe inched closer, their bodies almost touching, as he pressed down firmly on Joyce's flexed knee which he brought to her chest.

"You're so good," she purred. "I feel better already."

"Mrs Lavin," Philippe cautioned. "You can't avoid the Florida heat. You'll sweat a lot. I recommend you regularly take a licorice-based herbal tea; it reduces salt and water loss. You can buy it over at Shrugg's."

On the way home, Joyce stopped at Shrugg's. As she browsed the paperback display of best sellers, pharmacist Hiram Salker came rushing up.

"Fine morning, eh, Mrs Lavin?" as he wiped away beads of sweat that had formed on his bald head. His eyes longingly explored Joyce's well-pro–portioned physique.

"Good morning, Hiram. It sure is a fine day," responded Joyce as she thought about Philippe's massage.

"Will there be anything special today?"

"Yes, Dr Ogden suggested I pick up a licorice-based herbal tea."

"What will you be using it for?" asked Hiram

"Mr Lavin and I are quite health conscious. We exercise regularly," she said with a flirtatious twinkle in her eye, knowing full well the effect it would have on this little man. "Working out is not only good for cardiovascular fitness, it's also good for controlling our cholesterol. Dr Ogden suggested we take this tea to conserve salt and water when working out."

"That's a fine idea, Mrs Lavin." To reinforce his concern, Hiram added, "We also have pure licorice candies from the Netherlands." He also noted, "your husband should drink GFJ regularly to lower his cholesterol. You don't want Mr Lavin to have a heart attack during one of your workouts."

"We began a GFJ regimen just today," noted Joyce. "Thank you."

"My pleasure," Hiram said, his eyes traveling up Joyce's legs. "Call on me anytime. I would even make a house call for you, Mrs Lavin," he said, his eyes pausing at her chest.

"Hiram, you're too kind. Something you just said reminded me of something. Oh, yes. Men with a bald spot at the back of their head are so sexy. Those whose baldness is expressed at their scalp line are so cerebral." She paused for effect. "And men who are bald all over think they're sexy." Joyce turned and made her exit.

Later in the week, Sy and Joyce each developed leg cramps after their workouts.

Sy also complained, "Since I stopped taking my antihistamine, my stuffy nose and teary eyes have become a nuisance. I'm going to need a pill that doesn't make me sleepy."

Over at Shrugg's, Sy proclaimed, "Hiram, my internist should have called in a prescription."

"Yes he did. This antihistamine

doesn't enter the brain, so no drowsiness. It's taken morning and afternoon."

A week passed. That Sunday evening, the Lavins expected guests. They included Gopal and Geeta Shankar, a cardiologist and his wife who lived next door. Guests were standing poolside engaged in conversation with Joyce as Sy approached with an iced pitcher of screwdrivers. Without warning, he went down in a heap, not 10 feet from his guests. Gopal sprang into action. Finding no pulse, he began CPR while Geeta immediately called fire rescue. Minutes later, paramedics arrived, maintained CPR, established intravenous access, and applied ECG leads. Gopal found *torsades de pointes*, a form of ventricular tachy–cardia with QRS complexes appearing at a rate of 200 bpm and of changing amplitude that twisted around the isoelectric line. He immediately applied electrical shock to the chest; sinus rhythm was restored. There was no ECG evidence of acute myocardial infarction, but the QT interval was markedly prolonged and there were prominent U waves. Gopal gave intra–venous magnesium sulfate. Sy's blood pressure recovered and spontaneous ventilation returned. "Joyce," asked Gopal, "is your husband taking any medications?"

"Only an antihistamine," she re–sponded tearfully.

"We'll take him to the hospital for observation. You can ride with us in the ambulance. Sy's chaotic heart rhythm and abnormal ECG are puzzlesome," said Gopal as the ambulance drove off.

What is your diagnosis?

Answer

In the CCU Gopal reviewed the data. Sy, a 66-year-old male, would likely have coronary artery disease and be at risk of sudden cardiac death. But *torsades* with prolonged QT interval? *Torsades* was associated with acquired prolongation of ventricular repolarization that accom–panies the use of quinidine or procain–amide, and electrolyte disturbances. The prominent U wave suggested hypo–kalemia. Indeed, serum K^+ was reduced and corrected. But why K^+ loss? Sy was not on a diuretic. He must be receiving something that promotes urinary K^+ excretion.

Gopal asked Joyce, "Does Sy exercise regularly? Has he had leg cramps of late?"

"Yes, both Sy and I have leg cramps. We thought it was related to our workouts. Come to think of it, these cramps appeared since we began taking that licorice-based herbal tea and licorice candy from Holland."

Licorice. This was an important clue to K^+ loss, thought Gopal. But the marked prolongation of the QT interval? There had to be something more than hypo–kalemia. "Has Sy been dieting?"

"No. We are careful with our diet, but no store-bought supplements or fads you read about. To reduce our cholesterol we take GFJ," responded Joyce.

"And tell me the name of the anti–histamine Sy is taking."

"It's called terfenadine."

Terfenadine (T) is implicated in QT prolongation and ventricular arrhythmias, including *torsades*, and sudden cardiac death. These rare complications are seen in association with increased T levels when given with certain antibiotics, such as ketoconazole or itraconazole, that inhibit cytochrome P450. These drug inter–actions, however, were not at play in Sy's case. Could GFJ be implicated? Gopal's literature search indicated there was an emerging body of evidence that linked GFJ with enhanced bioavailability of T and QT prolongation. Additionally, GFJ has the potential, like licorice, to enhance urinary K^+ excretion.

The next morning on rounds, Gopal went back to the CCU. Sy had fully recovered and there was no recurrence of *torsades* or other ventricular arrhythmias.

A second-generation selective H1 receptor antagonist, T is a potent antagonist of the delayed rectifier K^+ current in cardiomyocytes. As a prodrug, T is biotransformed by cytochrome CYP3A4 in the liver. Inhibition of this step allows for the accumulation of unmetabolized T. GFJ and its flavonoids inhibit CYP3A4. Flavonoids also inhibit renal 11β-hydroxysteroid dehydrogenase, the guardian enzyme that preserves the specificity of the promiscuous steroid receptor for mineralocorticoids. It too is inhibited by glycyrrhizic acid, the active principle of licorice. In combination, GFJ and licorice, derived in Sy's case from herbal tea and imported candies high in licorice, would permit more plentiful glucocorticoids to act as mineralo–corticoids and predispose to hypokalemia and ventricular arrhythmias.

Abridged from Weber KT. A dilemma on Orchid Island. *Cardiovasc Res* 1999; **43:** 2-6.

Karl T. Weber, M.D. ■

(Continued from page 5)

The Refreshing Change

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Richard J. Bing, M.D. ■

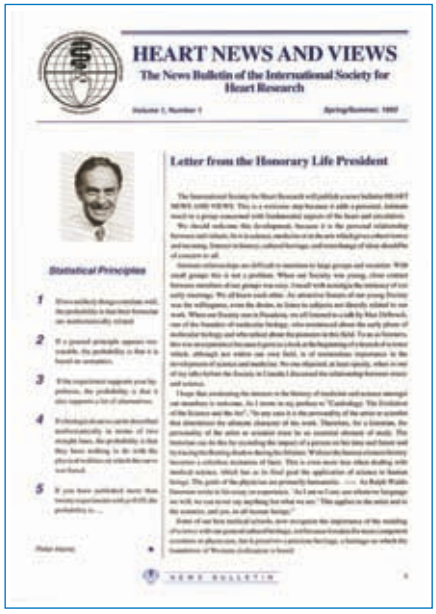
From the Editorial Office

IT was during a flight between Tokyo and Beijing, in May 1992, that Naranjan Dhalla asked me to establish a News Bulletin for the ISHR. We had just attended the XIV World Congress of the ISHR in Kobe, where Naranjan was elected President, and some of us were now travelling to China to participate in a post-Congress satellite meeting. After my initial hesitation and a long phone call (when I was back at home) with David Hearse, who was Secretary General at that time, I accepted Naranjan's invitation. In the spring of 1993 the first issue of *Heart News and Views (HN&V),* which was sponsored by Bayer AG, was printed.

Most of the work on Heart News and Views has been done in this cottage in Friesland, the most northern province of The Netherlands. Here, the foxglove is one of the few things that remind me of my former professional life.

The First Issue

In his President's Message, Naranjan Dhalla wrote: 'The publication of *HN&V* is intended to improve communication among geographically separated ISHR Sections as well as scattered member–ship. It is hoped *HN&V* will contain matters of interest from all Sections, a calendar of cardiovascular events, reports from international and regional meetings, special achievements of members, and pages from the history of cardiovascular sciences'.



HEART NEWS AND VIEWS

The News Bulletin of the International Society for Heart Research

Letter from the Honorary Life President

Statistical Principles

Among the other contributors to the first issue were Richard J. Bing (our Honorary Life President), Peter Harris (whose speech at the dinner during the European Section meeting in 1975 in Brussels had prompted me to become a member of the International Study Group for Research in Cardiac Metabolism, as the ISHR was called at that time), and Thomas Brand (the winner of the Richard J. Bing Award for Young Investigators at the World Congress in Kobe). An important member of the Editorial Board was Barbara Ward, who would keep an eye on my use of the English language. We became acquainted with each other at the Cardiothoracic Institute (and the Devonshire Arms pub!) in London, where I spent a sabbatical in 1977.

1993-2002: The 'Black and Blue' Period

The contents of the first issue, and the viewpoints that were displayed therein, have been the basis for subsequent issues of *HN&V*.

From the beginning, in addition to announcements and reports of ISHR meetings, the publication of contributions from promising young investigators has been a primary objective of *HN&V*. Thomas Brand's report was followed by reports from the winners of the Richard Bing Award in 1995, 1998, 2001 and 2004. Moreover, numerous reports from winners of Young Investigator Awards conferred at various Section meetings have been published in the newsletter.

Despite this emphasis on young researchers, the senior researcher has not been neglected in *HN&V*. Biographies of the 1992, 1995, 1998, 2001, 2004 and 2007 winners of the Peter Harris Dis–tinguished Scientist Award, conferred on senior scientists to recognize a lifetime of scientific achievement, have also been published in *HN&V*.

Between 1994 and 1998 *The Speis–enstein Files*, a series of scenes from academic life, was published in *HN&V*. These articles were written by "P.H. from the Longboat Key Health Sciences Institute in Florida". Peter Harris has been a constant source of inspiration to me and in the course of time we became good friends. During our first visit to Longboat Key, my wife and I visited the Health Sciences Institute, which was just a small table with a computer and a fax machine in the apartment on the Gulf of Mexico where Peter and his wife Fran were living. A compilation of the thirteen instalments of the *Speisenstein Files* can be found on the ISHR website.

During the XVII European Section meeting in Bologna (1996), I attended a concert of chamber music composed by Richard Bing. The next morning I asked Dr Bing whether he would be willing to write something for *HN&V*. He started his first article as follows: 'History when presented as a mere recital of facts makes for difficult reading, but when connected to per–sonalities, acquires flesh and blood. The term "past truth" refers to factual events accompanying a scientific discovery while "present poetry" stresses their human, romantic aspects'. Dr Bing has since contributed an article in the series *Past Truth & Present Poetry* to every issue of *HN&V*. Twenty eight of his more than thirty articles have been published as a book: *Past Truth & Present Poetry – Medical discoveries and the people behind them* (ISBN 1 903378 44 3). More recently, *Dialogues in Cardiovascular Medicine* has started to re-publish selected articles under the title *Matters@Heart*. Throughout the years, Richard has been the ideal contributor and I will miss our correspondence by e-mail, which frequently started with a paragraph on music.

2003: Start of the Full Colour Period

In 1999 Jim Downey, the then President Elect and father of the ISHR website, took the initiative to create a web version of *HN&V*. He taught me how to keep the balance between compression and reso–lution. A few years later Roberto Bolli, who was Secretary General, asked me: 'How far are we from a full colour version?' My answer that it was only a matter of money appeared to be wrong, because almost immediately I was confronted with big problems related to colour man–agement (rgb *vs* cmyk, solid *vs* process Pantone colours, *etc*). Thanks to two visits to the Medical Publishing Division of Servier in Paris, the first full colour issue (which by then had grown from 8 to 16 pages), with a completely new layout, appeared at the beginning of 2003. These crucial visits to Paris were kindly arranged by Dr Laurence Alliot from Servier, who has been our generous sponsor since 1999.

Between 2001 and 2006 a number of new awards were established by the ISHR: the Research Achievement Award, the Keith Reimer Distinguished Lecture, the Outstanding Investigator Prize, the Janice Pfeffer Distinguished Lecture, and the President's Lecture. Biographies of the winners of these awards and also of the annual ISHR-ES/Servier Research Fel–lowship were published accordingly in *HN&V*.

In 2003 Karl T. Weber accepted my invitation (after having pursued him for several years) to start a series that would integrate the basic and clinical sciences: *Bridging the Gap – Where clinical and basic sciences meet.* This issue contains the tenth instalment of his highly readable and interesting medical mysteries.

The last issue of 2005 is perhaps my favourite one, wherein Lionel Opie described the history of the European Section: 'How Even Europeans Can't Get Their Numbers Right'. During our intensive exchange of e-mails in the period that Lionel was performing his research, it was fascinating to see how he gradually disclosed the facts about the origin and the first years of our Society.


HEART NEWS AND VIEWS

THE NEWS BULLETIN OF THE INTERNATIONAL SOCIETY FOR HEART RESEARCH

HISTORY OF THE EUROPEAN SECTION OF THE ISHR

I would like to thank the past and current Presidents and Secretaries General of the Society for their invaluable initiatives, suggestions, advice, criticism and con–tributions. I also thank the Secretaries of

One of the last times I met Peter Harris was at the Glyndebourne Opera House in May 2002, where we attended a performance of Mozart's Don Giovanni.

the seven ISHR Sections, who have had the difficult tasks of dealing with the parcels (which I sometimes sent them at irregular intervals) and distributing the issues among their members.

In 2004 Dr Leslie Anderson Lobaugh, the Executive Secretary of the ISHR, became Deputy Editor of *HN&V*. Al–though we have met only twice (in Mystic, CT, during the American Section meeting in 2003, and in Brisbane during the World Congress in 2004), we know each other quite well because of the countless e-mails we have exchanged during the past three years. One of Leslie's first initiatives was the creation of a new series: *The Heart of the Matter – A career in cardiovascular research.* This issue contains the third article in this series, which became an immediate success, considering the symposium with the same title during the upcoming World Congress.

With a third grandchild on the way, an increasing number of musical activities, and an enormous amount of wood behind our cottage waiting to be chopped, it is time to say goodbye to you all and to lay the editorship of *HN&V* in Leslie's very capable hands.

Tom J.C. Ruigrok, PhD FESC FAHA ■

SILENCING MYOCARDIAL GENE EXPRESSION BY ADENOVIRAL DELIVERY OF SHRNA

It was a great honour for me to receive the ISHR-ES/SERVIER Research Fellowship in 2005 and I am delighted to describe the work that I have carried out during the Fellowship in this issue of HN&V. I completed my PhD in the Department of Experimental and Clinical Pharmacology and Toxicology, University Medical Center Hamburg Eppendorf in Prof. Thomas Wieland's group, before moving to the Cardiovascular Division at King's College London to do my postdoctoral training under the supervision of Prof. Metin Avkiran in 2003, where I have worked since then. The project was carried out in close cooperation with Prof. Thomas Wieland's laboratory in Mannheim.

Friederike Cuello, Ph.D.

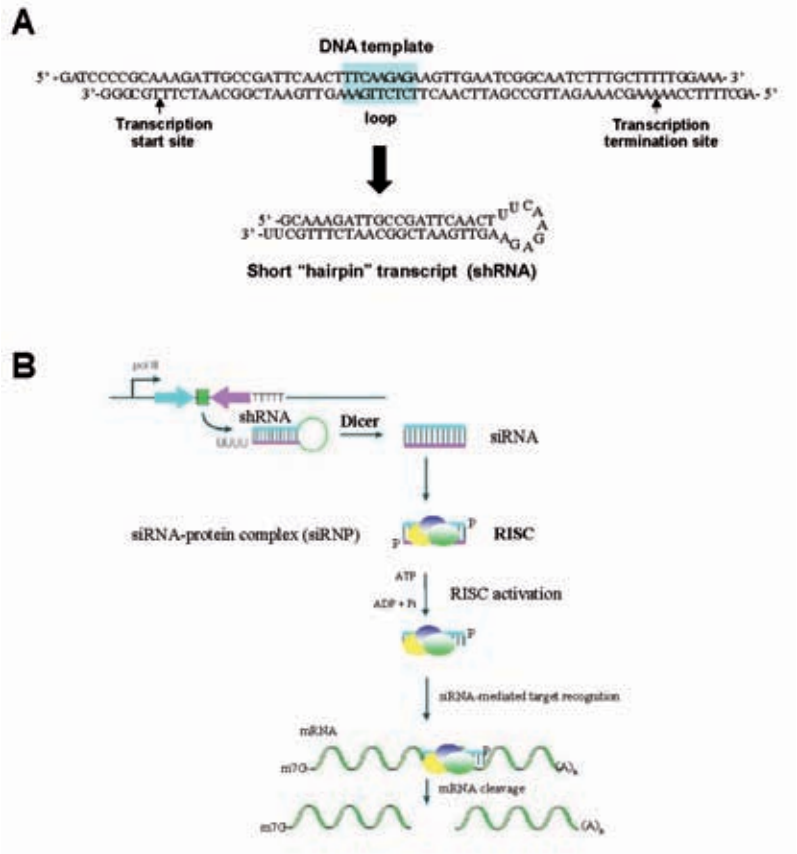


Figure 1. A: *Nucleotide sequences of (1) A PKD-silencing DNA template that was delivered into myocytes using the novel adenoviral vector AdVshRNAPKD1, and (2) the resultant transcript, within which the shRNA sense and antisense strands associate in cis to form a shRNA.*
B: *The molecular mechanism by which specific gene silencing is achieved. Within cells, shRNA transcripts are cleaved by Dicer, a RNase III family enzyme, to produce siRNA duplexes. These are then incorporated into a multi-protein nuclease complex, known as RNA-induced silencing complex (RISC). Subsequently, the siRNA duplex unwinds, in an ATP-dependent manner, and the single stranded antisense strand guides RISC to its homologous target mRNA for endonucleolytic cleavage. The target mRNA is cleaved at the centre of the duplex region between the guide siRNA and the target mRNA, resulting in suppression of gene expression.*

RNA Interference

In cardiovascular biology, considerable progress has been made in determining gene function through the genetic manipulation of cultured cells and intact animals (mainly transgenic mice). In the context of cardiac myocyte biology, primary cultures of neonatal and adult ventricular myocytes have been trans–fected with wild-type and/or consti–tutively active constructs, using plasmid-based or adenoviral vectors, in *gain-of-function* studies. In some instances, it has been possible to carry out *loss-of-function* investigations, by transfection with dominant negative constructs or using antisense approaches. However, the low transfection efficiency of con–ventional transfection techniques in myocyte preparations (up to a maximum of 40% in neonatal and 0% in adult cells) and the unconfirmed mechanism of action of many dominant negative mutants have markedly hindered progress. It is also prohibitively expensive and time-con–suming to develop *in vivo* transgenic models for every gene under inves–tigation, without prior *in vitro* indication of gene function. Recently, the method of RNA interference (RNAi) has come into prominence as a new method for sup–pressing the expression of targeted genes in mammalian cells.[1] This method has also attracted attention as a new approach to disease therapy.[2] The application of RNAi technology to determine gene function in

myocardium, however, is once again hampered by the low transfection efficiency achieved in myocytes with conventional methods. Nevertheless, newer adenoviral methods have now been developed that allow the efficient delivery of small-interfering RNA (siRNA) moieties, which produce RNAi-mediated gene silencing, into mammalian cells.[3] The focus of the project was to develop and characterize a method for adenoviral delivery of short "hairpin" RNA (shRNA), allowing targeted silencing of specific genes in identifiable myocardial cells. The method was validated by targeting the expression of a gene of current interest in our laboratory, namely the serine/threonine kinase protein kinase D (PKD), in cultured neonatal and adult rat ventricular myocytes.

Construction of a Novel Adenoviral Shuttle Vector, pADTracksi

As the first step in this work, we modified the adenoviral shuttle vector pADTrack[4] for the delivery of shRNA into cardiac myocytes. The novel adenoviral shuttle vector created, which we named pADTracksi, contains a multiple cloning site downstream of the RNA polymerase III H1-RNA gene promoter, for insertion of gene silencing templates, and additionally enhanced green fluorescent protein (EGFP) under the control of a separate CMV promoter. This allows the ready determination of transduction efficiency and thus adjustment of virus dose (*i.e.* the multiplicity of infection, or MOI) to achieve the desired efficiency; furthermore, it facilitates functional studies (*e.g.* contractility, pH regulation, Ca^{2+} handling, electrophysiology) in targeted cardiac myocytes that are selected on the basis of EGFP fluorescence.

shRNA Template Design

Using the Invitrogen Block-It®shRNA design tool, three different templates for shRNA were designed, such that their ultimate 21 nucleotide siRNA products targeted different parts of the PKD1 mRNA transcript. The obtained nucleotide sequences were subjected to a BLAST search to detect homology with other sequences, and were confirmed to have no significant homology with other mRNA transcripts. Each oligonucleotide is designed to have restriction sites at either end for insertion into pADTracksi, a transcription start, a termination site and a loop structure. **Figure 1** illustrates our experimental approach in silencing PKD expression in myocytes, using adenoviral delivery of an shRNA template. Transcription from the template, under the control of the polymerase III H1-RNA promoter, produces a PKD-specific shRNA, also as illustrated in **Figure 1A**. **Figure 1B** illustrates the mechanism by which specific gene silencing is achieved through siRNA generation in infected cells (see figure legend for details).

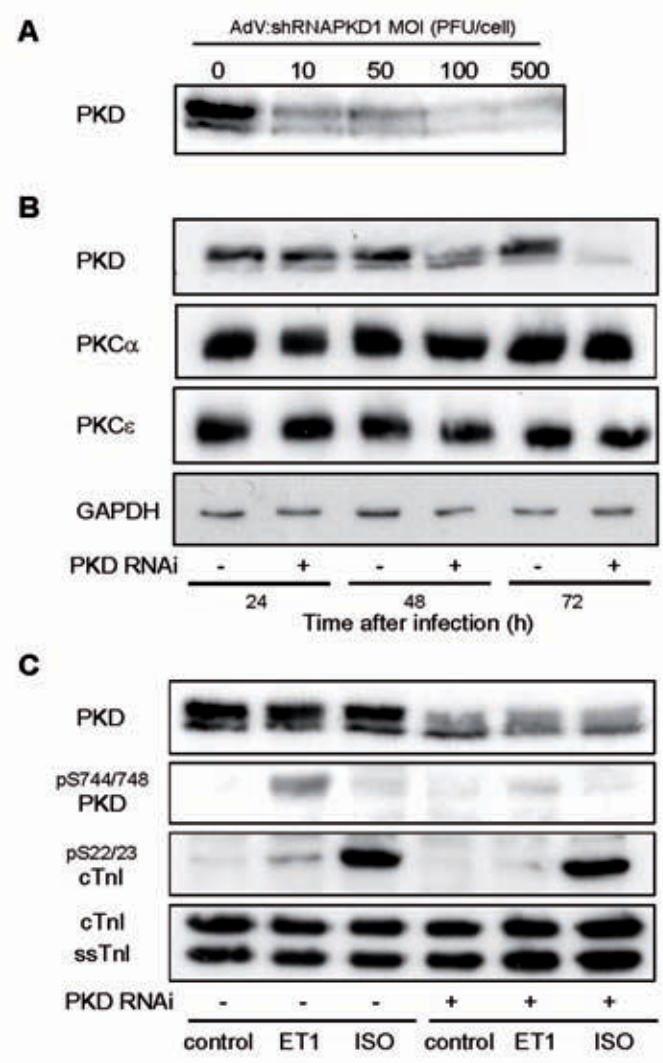


Figure 2. ***A:*** *MOI-dependent downregulation of PKD protein expression in NRVM by RNAi, through adenoviral shRNA delivery. PKD protein expression was assessed by immunoblot analysis 48 h after infection.*
B: *Selectivity of PKD silencing. PKD, PKCα, PKCε and GAPDH protein expression was determined by immunoblot analysis 24-72 h after infection with adenovirus encoding either EGFP shRNA (-) or PKD shRNA (+) at MOI 100.*
C: *Impact of PKD downregulation in NRVM on cTnI phosphorylation following exposure to ET1 (5 nmol/L) or ISO (10 nmol/L) for 10 min. Protein expression and phosphorylation were assessed by immunoblot analysis 48 h after infection with adenovirus encoding either EGFP shRNA (-) or PKD shRNA (+).*
(Figure adapted from Cuello et al, 2007).

Downregulation of PKD1 Protein Expression in Cardiac Myocytes

Recombinant adenoviruses were generated using the AdEasy system de–

(continued on page 15)

DAVID J. HEARSE - AN APPRECIATION

DAVID HEARSE started his university education at the University of Wales in Cardiff, where he chose to study the newly emerging field of biochemistry, graduating with a first class degree. During his subsequent studies towards a PhD, he developed a strong interest in biochemical pharmacology and earned the opportunity of a summer studentship at New York University Medical Center. This, in turn, led to an invitation to join the faculty of the Department of Pharmacology at NYU, where he was introduced to the now fashionable world of pharmacogenetics. In 1970, whilst contemplating the opportunity to study for an MD in New York, David received an invitation from the Nobel Laureate Professor Sir Ernst Chain to return to the UK, to join the Department of Biochemistry at Imperial College. At Imperial, David was tasked with 're–placing' a young South African called Lionel Opie (the 1998 recipient of the Peter Harris Award), who had built a rat heart perfusion rig there but was moving on to pastures new. Lionel Opie could, of course, neither be 'replaced' nor cloned, but he did teach David the mysteries of the isolated working rat heart and the measurement of tissue metabolites. At that time, Ernst Chain urged David to pursue Chain's conviction (probably stimulated by Opie's classical metabolic studies) that glucose could offer a great deal to the ischemic heart, through its ability to support anaerobic ATP pro–duction. From these early days, David built up a perfusion facility and estab–lished a strong interest in the concept of cardioprotection, which led him to his well-known studies of 'reperfusion injury'. During these studies, David coined the phrase 'oxygen paradox'; indeed, he was one of the first to recognize that the adverse structural, contractile and electrophysiological consequences of reperfusion were directly attributable to the readmission of molecular oxygen and to propose that free oxygen radicals may be a culprit - a topic that he was to investigate extensively in the ensuing years.

In recognition of his exceptional contributions to the Society and his scientific achievements, **Professor David J. Hearse** received Honorary Membership of the ISHR during the XVIII World Congress in 2004 (Brisbane, Australia) and was awarded the Peter Harris Distinguished Scientist Award during the XIX World Congress in 2007 (Bologna, Italy).

During the mid 1970s, David had a chance meeting with a cardiac surgeon (Mark Braimbridge), which led to a visit to the operating theatre at St Thomas' Hospital, where he was subsequently given the opportunity of establishing a laboratory in the new Rayne Institute for Biomedical Research. This was a major turning point in David's career, in that it directed his work towards the field of cardiac surgery and transplantation. Indeed, David was a pioneer of "translational research" in its truest sense, in that his work culminated in the development and introduction into worldwide clinical use of the St Thomas' Hospital Cardioplegic Solution. This meticulously formulated solution, when infused into the coronary arteries of the human heart, extended the safe period of elective ischemic arrest from less than 1 to more than 4 hours. The result was a dramatic reduction in patient mortality during cardiac surgery and, in particular, the abolition of lethal ischemic con–tracture (the 'stone heart'), a phenom–enon whose molecular mechanisms David went on to investigate. His growing international recognition as an out–standing investigator led to David's appointment to a personal chair (as the inaugural Professor of Cardiovascular Biochemistry) and allowed him to expand his laboratory, which grew to a Depart–

David lecturing on one of his favourite topics.

ment of around 30 scientists and clinicians of various nationalities. These achieve–ments were aided by sustained fund raising from the British Heart Foundation, The Wellcome Trust and the Medical Research Council, plus David's rare success (as an investigator outside the US) in obtaining three consecutive NIH grants for his work on reperfusion, free radicals and anti-oxidants. Such success never turned David's head, however. As one of his recruits (as a raw post-doc in 1986), I know from first-hand experience that David never adopted a dictatorial, empire-building attitude (unlike some of his contemporaries!) and took particular care in nurturing the development of his younger colleagues. Indeed, the flour–ishing independent research careers of many of David's past trainees attest to his qualities as an outstanding mentor and are often cited by him as a source of great personal pride and satisfaction.

In his early days in London following his New York sojourn, David was to meet Peter Harris and it was Peter who encouraged him to become a member of the ISHR (1972) and, later, to propose that he join the ISHR Council (1980). This was the start of an incredibly long period of dedicated service to the ISHR, with David

going on to become the Secretary General in 1989 (when, amongst other things, he orchestrated the launch of *Heart News and Views* and persuaded Tom Ruigrok to become its enduring and excellent Editor) and the President in 1998. He has also served the Society's official journal, the *Journal of Molecular and Cellular Cardiology*, as an Editorial Board member (continuously since 1977) and an Asso–ciate Editor (1983-1992). During his academic career, David also attained an international reputation as a creative host of truly outstanding conferences, organizing (with Derek Yellon and Philip Poole-Wilson) the famous 1988 ISHR European Section meeting in Oxford (no-one who attended will ever forget the surprise appearance of the Irish Guards' marching band at the end of a sumptuous dinner at Blenheim Palace!) and (with Roberto Ferrari) the equally successful 1998 ISHR World Congress in Rhodes. Beyond the ISHR, in 1972 David founded what was to eventually become the British Society for Cardiovascular Research (BSCR) and, at various times, served as the Society's Treasurer, Secretary and Chairman.

Created in 1986, the **Peter Harris Distinguished Scientist Award** is the highlight of each World Congress of the ISHR. It is conferred in recognition of a lifetime of distinguished scientific achievements in the field of cardiovascular research.

Previous recipients are:

- **Setsuro Ebashi**, *Japan* (Melbourne, Australia; 1986)
- **Albrecht Fleckenstein**, *Germany* (Ann Arbor, USA; 1989)
- **Robert B. Jennings**, *USA* (Kobe, Japan; 1992)
- **Howard E. Morgan**, *USA* (Prague, Czech Republic; 1995)
- **Lionel H. Opie**, *South Africa* (Rhodes, Greece; 1998)
- **Robert J. Lefkowitz**, *USA* (Winnipeg, Canada; 2001)
- **Arnold M. Katz**, *USA* (Brisbane, Australia; 2004)

David building a pond at his Oast House.

In addition to publishing over 400 papers and 10 books and providing visionary leadership to the ISHR and the BSCR, David also found time to take on the challenge of becoming the Editor-in-Chief of *Cardiovascular Research* in 1992. He and his in-house team of Associate Editors transformed the Journal and its impact factor during their tenure. They demonstrated that manuscripts could be reviewed rapidly *and* expertly, and published quickly following acceptance, which stimulated other cardiovascular journals to get their 'acts into order'. As a result, waiting times for editorial decisions and publication plummeted from many months to just weeks; a time-scale that we expect today but was unheard of in the early 1990s. More recently, with Roberto Ferrari, David founded *Dialogues in Cardiovascular Medicine*, a unique journal that he and Roberto have edited for the past 10 years.

Not surprisingly, David has lectured extensively throughout the world and has been the recipient of numerous awards and distinctions, including a DSc, an Honorary Fellowship of the Royal College of Physicians and several other Fellow–ships. He also has many interests outside academia, including food (eating, cooking and growing - particularly tomatoes), wine (only the finest, from Burgundy to Cloudy Bay) and … carpentry. Indeed, over the past several years, David has accom–plished the remarkable feat of restoring a derelict agricultural oast house in rural Sussex into a stunning home. With typical ingenuity, he has managed to incorporate a little bit of science even into this project, by manufacturing the teak floorboards (with his own hands) from the discarded laboratory bench-tops of a venerable British university! Speaking of ingenuity, perhaps I will get another opportunity to recount an earlier story of how he studied the impact of oxidative stress on cardiac function, using an Indian decorative dye and equipment that he adapted from an airport signboard... A truly remarkable individual and scientist, with whom it has been my good fortune and privilege to work for so many years and to whom the ISHR in particular owes a great deal.

Metin Avkiran, PhD DSc
London, UK ■

THE PRESIDENT'S LECTURE 2007

GENETIC MANIPULATION OF THE MAMMALIAN HEART: WHAT HAVE WE LEARNED?

HONORED SPEAKER: JEFFREY ROBBINS, PH.D. (JUNE 2007; BOLOGNA, ITALY)

JEFFREY ROBBINS received his Ph.D. in Genetics and Development in 1976 from the University of Connecticut and is currently Professor of Pediatrics, Division Chief of Molecular Cardio–vascular Biology and Associate Chair of the Research Foundation at Cincinnati Children's Hospital and Distinguished University Professor at the University of Cincinnati. Prior to assuming his present position, Dr Robbins was Professor in the Departments of Pharmacology and Cell Biophysics, Molecular Genetics and Biochemistry, and Molecular Physiology at the University of Cincinnati College of Medicine. He has won a number of teaching awards, including the Golden Apple. His early work in defining the elements necessary for cardiac specificity of the transcriptional apparatus led to the development of reagents that are currently used worldwide to affect the protein complement of the heart through transgenic manipulation. Dr Robbins, along with hundreds of other scientists, has used these tools to mechanistically explore the structure-function relation–ships of cardiac proteins. His work has focused on understanding the behavior of both the normal contractile proteins and the mutations that cause cardio–vascular disease. His current work focuses in part on moving these models into large animals that more closely reflect human cardiovascular behavior.

Dr Robbins has been publishing in the field of cardiovascular biology for approximately 13 years. With over 140 peer-reviewed publications during this period, his contributions have changed the way that basic cardiovascular research is done, by allowing the research com–munity to carry out "gain-of-function" approaches specifically in the myocardium via cardiac-specific transgenesis. In a series of landmark papers, Robbins first defined the promoter elements needed to drive high levels of gene expression in the mammalian heart. Identifying the cis-trans interactions was what drove the basic research but, understanding the im–plications, Robbins then took the work further and explored the utility of cardiac-specific gene expression as a method of doing defined genetics in the mammalian four-chambered heart.

After the initial proof-of-principal that cardiac specific transgenesis was feasible, he defined, built and tested a set of reagents that are now routinely used by hundreds of laboratories to carry out genetic experiments in the mouse cardiovascular system. Robbins unambiguously showed the utility of the general approach and developed a set of robust reagents that could be used by relatively inexperienced investigators to create animal models of cardiovascular disease. Robbins' work has changed the way in which we explore the basic pathology of cardiovascular disease. With well over 300 different models being developed and published using his reagents, the work that Robbins published has allowed the entire field to move forward at a pace undreamed of only 10 years ago. A contributing factor to the rapid spread of the technology was Robbins' early decision to make the reagents freely available, allowing the rapid dissem–ination of the needed tools, free from the confines of university intellectual property concerns.

Robbins went on to use gain-of-function approaches to further his own investigations into the underlying pathologies of hypertrophic cardio–myopathy, as well as defining the structure-function relationships in a number of the contractile proteins. His recent experiments have established the importance of mutations in the inter–mediate filament protein desmin and the chaperone alpha B crystallin as causative for a class of cardiomyopathies, which has recently led to establishing a role in cardiovascular disease for intracellular pre-amyloids.

Dr Robbins is a Fellow of the International Society for Heart Research and the American Heart Association. He has served on and chaired numerous national research review committees for the National Institutes of Health and the American Heart Association. He currently serves on 11 Editorial Boards, is Associate Editor for a number of journals and has been Cardiovascular Section Editor for the *Annual Review of Physiology* for the past seven years. He has won numerous research awards and, in 2005, he was the recipient of the American Heart Asso–ciation's highest honor for lifetime contributions to basic research; the Research Achievement Award. ■

ISHR MEETINGS CALENDAR

- **September 1-5, 2007.** **XXIX Congress of the European Society of Cardiology.** Vienna, Austria. **Inquiries:** *E-mail* congress@escardio.org; *Website* www.escardio.org
- **September 7-11, 2007.** **XVI Meeting of the Latin American Section.** Sao Paulo, Brazil. **Inquiries:** Dr Paulo Tucci. *E-mail* tucci@fcr.epm.br
- **November 4-7, 2007.** **Scientific Sessions of the American Heart Association.** Orlando, FL. **Inquiries:** *Website* www.scientificsessions.org
- **May 28-31, 2008.** **XXVIII Annual Meeting of the European Section.** Athens, Greece.
- **June 17-20, 2008.** **XXX Annual Meeting of the American Section.** Hilton Cincinnati, Netherland Plaza, Cincinnati, OH.

(continued from page 11)

scribed by He and colleagues.[4] In order to validate the new adenoviral vectors and to determine the minimum virus dose that is required to achieve high-efficiency transduction with effective gene silencing, we infected cultured neonatal rat ventricular myocytes at MOI of 1-500 plaque forming units (PFU)/cell **(Figure 2A)**. At daily intervals for up to 72 h after infection, cellular protein was harvested for analysis of PKD expression using immunoblot analysis **(Figure 2B)**. Adenoviral expression of shRNA targeted at rat PKD1 achieved selective downregulation of PKD1 protein expression, which declined to approximately 15% by 48 hours after infection **(Figure 2B)**. To confirm specificity of action, we characterized the system further by: *(1)* Constructing and using adenoviral vectors that deliver additional gene-silencing DNA templates, which produce shRNAs that are homologous to different sites within the target message (data not shown). *(2)* Constructing and using in the experiments an adenoviral vector that delivers a "control" DNA template, silencing its own EGFP expression. *(3)* Demonstrating that downregulation of PKD protein expression did not affect the expression pattern of other, non-targeted, genes *e.g.* PKC isoforms **(Figure 2B)**.

Friederike Cuello (London, UK) was the winner of the ISHR-ES/SERVIER Research Fellowship 2005 at the XXV European Section Meeting (Tromsø, Norway; June 2005).

Functional Consequences of Reduced PKD1 Protein Expression in NRVM

We have shown previously that PKD phosphorylates cardiac troponin I (cTnI) at Ser22/23.[5] Using our novel *loss-of-function* tool, we explored whether native PKD might mediate an increase in cTnI phosphorylation in NRVM in response to endothelin-1 (ET1). In control-infected cells, ET1 induced a significant increase in cTnI phosphorylation at Ser22/23, with a greater increase observed in response to isoprenaline (ISO), which activates PKA but not PKD **(Figure 2C)**. The ISO-induced increase in cTnI phosphorylation was unaffected by PKD downregulation. However, PKD downregulation significantly attenuated the ET1-induced cTnI phosphorylation, indicating that this response occurred predominantly through native PKD. This finding added support to our complementary studies, suggesting that PKD activity regulates cTnI phosphorylation at Ser22/23 in ventricular myocytes.[6]

Conclusion

In the absence of specific pharmacological inhibitors of PKD activity, our development of an adenovirus-mediated RNAi approach for silencing PKD expression has provided a powerful new tool for performing *loss-of-function* studies, and will assist our efforts to determine the biological function(s) of this kinase in myocardial cells.

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XIX WORLD CONGRESS OF THE ISHR
Bologna, Italy 22-25 June 2007

Congress Venues

Palazzo della Cultura e dei Congressi
Piazza della Costituzione 1
Bologna

Santa Lucia
Aula Magna Alma Mater Studiorum Università di Bologna
Via Castiglione 36
Bologna

Friday June 22, 2007

	Palazzo dei Congressi						Holiday Inn	
	Hall Europa	**Hall Italia**	**Hall Rossa**	**Hall Verde**	**Hall Topazio**	**Hall Sagittario**	**Hall Bianca**	**Hall Azzurra**
15.30-16.30	*Peter Harris Distinguished Scientist Award* *David Hearse (UK): "Ischemia, reperfusion and cardioprotection: successes and failures in the journey from laboratory to man"*							
16.30-18.00	Frontier symposium **Statins treatment: beyond lipid lowering achievement**	Frontier symposium **Viability versus necrosis: new insights**	Frontier symposium **NADPH oxidases in cardiovascular signaling and disease**	Frontier symposium **Cardiac protein oxidation: from damage to redox signaling**	Frontier symposium **Connexin-43 in cardiovascular disease**	Frontier symposium **Matrix metallopro-teinases in the ischemic and failing heart**	–	–
18.00-19.15	*Transfer by bus to Hall Santa Lucia*							

Hall Santa Lucia

19.15-19.30	*"Welcome to Bologna" **Roberto Ferrari (IT), Luigi Tavazzi (IT)***
19.30-20.15	***Nobel Laureate Lecture: Louis J. Ignarro (USA):** "Nitric oxide as a unique signaling molecule in the cardiovascular system"*
20.15-20.45	***Cultural lecture: Philippe Daverio (IT):** "Such a wonderful contemporary old place. Talking about Bologna"*
20.45-21.00	*Incoming President's Address **Roberto Bolli (USA)***
	Followed by a "Pasta" dinner

Saturday June 23, 2007

	Palazzo dei Congressi						Holiday Inn	
	Hall Europa	Hall Italia	Hall Rossa	Hall Verde	Hall Topazio	Hall Sagittario	Hall Bianca	Hall Azzurra
8.00-9.00	*Poster mounting*							
9.00-10.30	***Plenary session** The complexity of the heart beat*							
10.30-11.00	*Coffee-break*							
11.00-12.30	Frontier symposium **The I*f* current: a new therapeutic target**	Frontier symposium **Endothelial dysfunction in hypertension and heart failure: from bench to bedside**	Frontier symposium **Revisiting the role of Ins(1,4,5)P³ in myocardium**	Frontier symposium **Z-disc and M-band proteins and their implications for human heart disease**	Frontier symposium **Cholesterol: are statins enough?**	Frontier sysmposium **Role of reactive oxygen species (ROS) in myocardial physiology and pathology**	Frontier symposium **Basic biology of cell division and differentiation**	Frontier symposium **Carotid artery disease: addressing therapeutic options**
12.30-14.00	***Lunch symposium** Recent developments on the role of ARBs in protecting the heart and the brain and **Moderated posters** with lunch*							
14.00-15.00	***Research Achievement Award: Martin J. Lohse (DE):** "Finding targets for heart failure therapy"*							
15.00-16.30	***Plenary session** The complexity of device therapy*							
16.30-17.00	*Coffee-break*							
17.00-18.30	Frontier symposium **Aldosterone and heart failure**	Frontier symposium **Biomarkers and inflammation**	Frontier symposium **From bench to bedside: the challenge of managing acute thrombosis**	Frontier symposium **Spatial organization of signaling pathways in cardiac myocytes**	Frontier symposium **New understanding and treatments in atrial fibrillation**	Frontier symposium **Angiotensin - growth and functional modeling in the heart**	Frontier symposium **Cardiovascular regeneration: embryonic versus adult stem cells**	Frontier symposium **Rebuilding the cardiac vessels**
18.30-20.00	*free time and walk to Hall Santa Lucia*							

Hall Santa Lucia

20.00-20.45	***Landmark Scientific Lecture: Eric Olson (USA):** "Towards a molecular blueprint of heart development and disease"*
20.45-21.15	***Cultural lecture: Anna Ottani Cavina (IT):** "Discovering Bologna. The secret charme of a city"*
	free evening

Sunday June 24, 2007

Palazzo dei Congressi

Holiday Inn

	Hall Europa	Hall Italia	Hall Rossa	Hall Verde	Hall Topazio	Hall Sagittario	Hall Bianca	Hall Azzurra
8.00-9.00	*Poster mounting*							
	***Plenary session** The complexity of the metabolic syndrome*							
10.30-11.00	*Coffee-break*							
11.00-12.30	Frontier symposium **Managing the metabolic syndrome: a multi factorial approach**	Frontier symposium **ACE inhibition: still a long way to go for a full understanding**	Frontier symposium **Trials and tribulations of p38-MAPK**	Frontier symposium **Potential gene therapy targets in cardiovascular disease**	Frontier symposium **Update on SCD prevention in dilated cardiomyopathy**	Frontier symposium **PKD signaling: alphabetical progression or fundamental progress?**	Frontier symposium **Translating the regenerative potential: focus on ischemia and angiogenesis**	Frontier symposium **Nutritional strategies to prevent cardiovascular disease: a current review**
12.30-14.00	***Lunch lecture** JIKEI HEART STUDY - Results and relevance in context of existing morbi-mortality data and **Moderated posters** with lunch*							
	Lunch symposium *The heart of the matter: a career in cardiovascular research and **Moderated posters** with lunch*							
14.00-15.00	***Keith Reimer Distinguished Lecture: Eduardo Marbàn (USA):** "Stem cells for cardiac regeneration"*							
15.00-16.30	***Plenary session** The complexity of diabetes*							
16.30-17.00	*Coffee-break*							
17.00-18.30	Frontier symposium **How best to control CV risk in diabetes patients**	Frontier symposium **Role of the angiotensin II AT2 receptors in cardiovascular disease**	Frontier symposium **Signaling mechanisms regulating apoptosis**	Frontier symposium **Role of reactive oxygen species in the control of coronary blood flow**	Frontier symposium **Heart failure: what have we understood so far?**	Frontier symposium **Heart rhythm and arrhythmias**	***Richard J.Bing Award for Young Investigators***	Frontier symposium **A road map for cardiogenesis**
18.30-20.00	*free time and walk to Santa Lucia Hall*							

Hall Santa Lucia

20.00-20.45	***Landmark Scientific Lecture: Salim Yusuf (CA):** "Cardiovascular diseases: a maladaptation to societal progress?"*
	ISHR fellows dinner

Monday June 25, 2007

	Palazzo dei Congressi						Holiday Inn	
	Hall Europa	Hall Italia	Hall Rossa	Hall Verde	Hall Topazio	Hall Sagittario	Hall Bianca	Hall Azzurra
8.00-9.00	*Poster mounting*							
9.00-10.30	***Plenary session** The complexity of heart failure*							
10.30-11.00	*Coffee-break*							
11.00-12.30	Frontier symposium **Potential conflicting data relating the use of statins in CHF**	Frontier symposium **Injury and protection during myocardial ischemia and reperfusion**	Frontier symposium **Signposts on the multiple roads of ageing**	Frontier symposium **New paradigms in G protein-coupled receptor signaling**	Frontier symposium **How to optimize cardiac energy metabolism?**	Frontier symposium **Protein kinases as potential therapeutic targets**	Frontier symposium **Translating the regenerative potential: focus on heart failure**	Frontier symposium **Critical limb ischemia: from clinical aspects to therapeutic options**
12.30-14.00	***Lunch symposium** Role of late (persistent) sodium current in cardiac pathophysiology and* **Moderated posters** *with lunch*							
14.00-14.45	***Janice Pfeffer Distinguished Lecture: Joanne Ingwall (USA):** "Energetics of the failing heart: new tools yield new insights"*							
14.45-15.45	***ISHR General Assembly***							
15.45-16.30	***President's Distinguished Lecture: Jeffrey Robbins(USA):** "Genetic manipulation of the mammalian heart: what have we learned?"*							
16.30-17.00	*Coffee-break*							
17.00-18.30	Frontier symposium **From ischemia to lethal arrhythmia**	Frontier symposium **Statins and cardiovascular disease: oddities and unexpected findings**	Frontier symposium **New insights into plaque vulnerability**	Frontier symposium **Pharmacogenetics: impact of adrenoceptor polymorphisms**	Frontier symposium **Remodeling, the heart returns to childhood**	Frontier symposium **Prostanoid pathways in atherosclerosis**	Frontier symposium **Metabolic aspects of CAD and CHF**	Frontier symposium **Calcium dysregulation and therapeutic manipulation in heart failure**
18.30-19.15	***HALL EUROPA*** *Nobel Laureate Lecture: Aaron Ciechanover (IL): "The ubiquitin proteolytic system: from basic mechanisms and onto human disease and drug targeting"*							
19.15-19.45	***Cultural lecture: M Montanari (IT):** "The culture of food, between identity and exchange"*							
	followed by the "white"closing night							