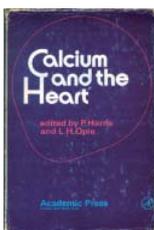




## THE NEWS BULLETIN OF THE INTERNATIONAL SOCIETY FOR HEART RESEARCH



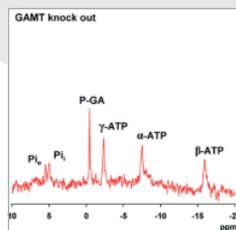
**HISTORY OF THE EUROPEAN SECTION**

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**PRESIDENT'S LETTER**

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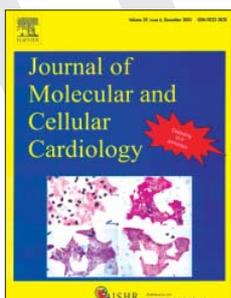


**NO PCR IN HEARTS FROM GAMT KNOCK OUT MICE**

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### HISTORY OF THE EUROPEAN SECTION OF THE ISHR

#### HOW EVEN EUROPEANS CAN'T GET THEIR NUMBERS RIGHT

by Lionel H. Opie  
(one of the founding members)



The International Society for Heart Research started off as the International Study Group for Research in Cardiac Metabolism, in a small meeting in the beautiful stone-built city of Dubrovnik, then part of Yugoslavia. That was in 1968 and I was one of the few English-speaking persons that attended (the prevailing language was German), another being the organizer, Dr Eörs Bajusz (1926-1973), a farsighted Hungarian then working in the USA. The German preponderance was a credit to their very vigorous interest in cardiac metabolism, at least in part sparked by the pioneering work of Richard Bing (*see page 4*).

#### Early Days

The Dubrovnik meeting was supported by a German pharmaceutical company that was interested in marketing potassium-magnesium aspartate infusions. There was a complex constitution written in appropriately complex German. This constitution had to be abandoned because, being incorporated in West Germany as it was then, there could be no participation of the East Germans nor any others of the Soviet group of nations. Apart from these legal complexities, Dubrovnik was a meeting of enthusiasts and it was clear that a wider meeting should be held in the near future. That led to the 1969 meeting in Gargnano, on the shores of Lake

Garda in Italy, with a much wider international representation. The scientific part of the meeting was excellent but we were all surprised by the absence of any organisers and leaders. Of note, the Secretary-Treasurer, previously appointed by the pharmaceutical company that had sponsored the Dubrovnik meeting, had disappeared, and so it seemed had most or all of the finances. This gave the Americans the idea that the Europeans were not trustworthy and it gave the Europeans the idea that the founding fathers of the Society, coming from America, were also not trustworthy as they also seemed to have vanished (in reality, Dr Bajusz was suffering from bad health).



Eörs Bajusz

The actual scientific highlight of the Gargnano meeting was the talk by Professor Albrecht Fleckenstein, the innovative German physiologist who had discovered calcium antagonist drugs and postulated a major role for calcium overload in cardiac pathology. His problem was that he had so much data to present that he could not remotely keep to time. However, this was ingeniously solved by the fact that the Italians who organised the meeting had anticipated the problem and given him a projector that thoughtfully burnt up each of his slides if he spoke too long. That got him through his speech almost on time.

The Iron Curtain was responsible for the creation of an East European Section of the Study Group. Only a few members, like Felix Meerson from Moscow and

Albert Wollenberger from Berlin (see page 4), were allowed out, whereas others went on “holiday” in their little Škoda’s to get across the border into Austria. A combination of personal risk and determination was required.

We soon came to realise that we would have to act swiftly and decisively to avoid the demise of the International Study Group, and to keep the interest of Europeans. We therefore drew up a conjoint letter, signed by 31 of the attendees, strongly suggesting that there should be a meeting of the Europeans just before the World Congress of Cardiology in London in 1970. We also called for a European-organized international meeting in Switzerland in 1971, asked for clarification of relations between the European and American Study Groups, and put out feelers to the nascent *Journal of Molecular and Cellular Cardiology*, of which Richard Bing and I were about to become editors at the invitation of Eörs Bajusz.

### The birth date of the European Section of the ISHR was unequivocally 1970

#### First European Meeting, London, 1970

From the Gargnano meeting, and armed with the letter signed by 31 attendees, Wolfgang Kübler, a brilliant young cardiologist from Düsseldorf and by now a close friend of mine, decided with me to press Professor Peter Harris of London to undertake a meeting specifically aimed at



Wolfgang Kübler

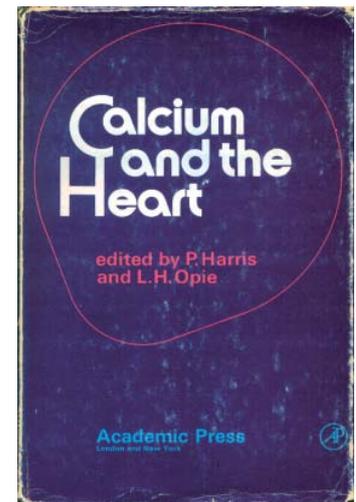


Figure 1. Proceedings of the meeting of the European Section of the International Study Group for Research in Cardiac Metabolism held at the Institute of Cardiology, London, on 6 September, 1970.

the Europeans. The topic would be the regulatory role of calcium in health and diseases of the heart. I was working at the

Royal Postgraduate Medical School at Hammersmith Hospital in London and Wolfgang was a Fellow in the group of Peter Harris at the National Heart Hospital in London, so our communication with Peter was easy. In those days it was safe to travel across London by bicycle, so we met in Peter’s office in central London. The fruits of our labours resulted in the Calcium meeting that took place in London in September 1970 and had 77 attendees. It is very clear from the published book that this was indeed a meeting of the European Section of the Study Group (Figure 1). The book, entitled *Calcium and the Heart*, edited by Peter Harris and myself, gave in detail the major talks of the meeting and clearly established the academic credentials of the European Section of the Study Group. The birth date of the European Section was unequivocally 1970.

### Geneva, 1971 and Paris, 1972

At the London meeting, the plans for the next meeting in Switzerland went ahead, and Dr Pierre Moret (*see page 4*) was asked to be the organizer. He undertook this in conjunction with the International Society of Cardiology and the World Health Organization. The topic was: The Metabolism of the Hypoxic and Ischemic Heart. At the business meeting of the Study Group, Professor Pierre Hatt



Pierre Hatt

of Paris was nominated to hold the next meeting in Paris in 1972. At the Geneva meeting I also convened the European Section of the Editorial Board of the *Journal of Molecular and Cellular Cardiology*, which was thus closely related to the Study Group. This tradition of joining the European Editorial Board and Study Group meetings continued for many years, and had the consequence of fostering a strong European interest in the *Journal*.

The Geneva meeting was basically European-organized but international in character, and led to the 1972 meeting in Paris. On March 15, 1972, Professor Hatt made several proposals “to members of the European Section of the International Study Group for Research in Heart Metabolism.” Fortunately I have kept a photocopy of the proposals, which can be summarized as follows: Members of the Study Group were defined as all those who attended the last two meetings (London 1970, Geneva 1971) and the Paris meeting (*Figure 2*). Every year the Chairman, who could invite new members, should come from a different country and should organize the meeting in conjunction with the international committee. A

1. Membership of the Study Group shall consist of all those who attended the last 2 meeting (London 1970, Geneva 1971) and the present meeting (Paris 1972). New members shall be invited at the discretion of the Chairman and shall become members on presentation of at least a paper. Preference will be given to young research workers actively engaged in the field of heart metabolism. Young workers will receive preference in allocation of travel funds.

*Figure 2. Resolution proposed by Professor Pierre Hatt and adopted at the Paris meeting in 1972.*

conjoint meeting organized by Professor Albrecht Fleckenstein would be held with the International Study Group in Freiburg in September 1973. This meeting was opened by Richard Bing, who is of course the founding father of cardiac metabolism and Honorary Life President of the Society. He was often interrupted by vociferous students, for reasons which only they could understand. One of those students later mellowed into a well-respected and well-known leader of the cardiac metabolism research community. In 1974 the European Group meeting would be held in Prague, and Dr František Kölbl (*see page 4*) agreed to organize it. All these proposals were accepted (*Figure 3*).

### How the Error in Dates Occurred

Thus it is abundantly clear that the Prague meeting was the fifth meeting of the European Section of the Study Group. If London in 1970 was quite definitely the first meeting of the European Section and Prague in 1974 the fifth, how then in 1979,

all those years and many meetings later, did the normally very exact French come to designate the meeting in Dijon as the third meeting? It is because they regarded



Albrecht Fleckenstein

it as the third *International* meeting of the European Section of the Study Group. There had, in fact, been two prior “International” meetings, also meetings

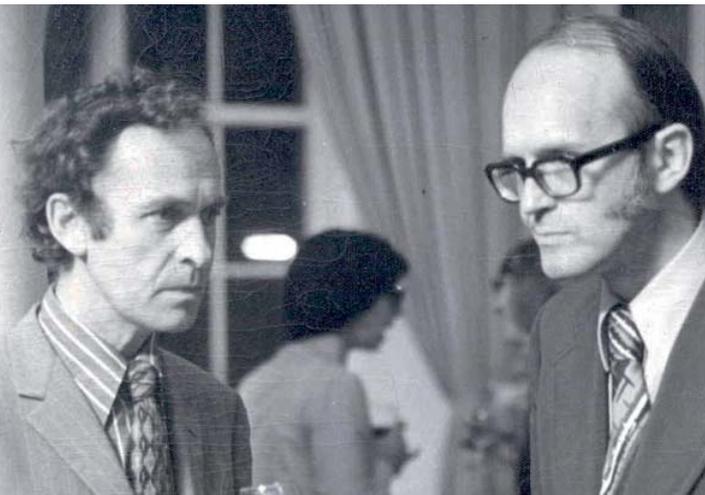
6. Every effort should be made to keep in close touch with all other groups, both in North America and in Europe, interested in heart metabolism. A conjoint meeting will be held with the International Study Group in Freiburg in September 1973.

7. Professor A. FLECKENSTEIN agree to organize the 1973 meeting and to act as chairman of the European Group till this meeting.

8. The 1974 European Group meeting should be held in Prague, Dr. F. KOLBEL agree to organize it.

These proposals were unanimously accepted by the members of the European Group present at the business meeting in Paris on March 15<sup>th</sup> 1972.

*Figure 3. Resolutions adopted at the Paris meeting in 1972.*



*Peter Harris and Lionel Opie sharing a hilarious joke (Dijon, 1979).*



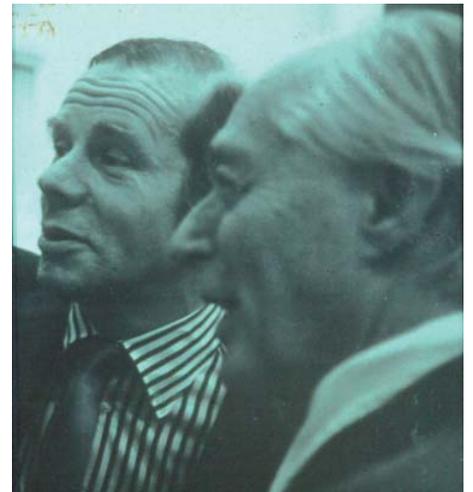
*Roberto Ferrari, (co-)organizer of the Bologna meetings (1981 and 1996) and the XXXII World Congress (2007). Currently President of the ISHR.*



*Pierre Moret, organizer of the Geneva meetings (1971 and 1984), and his wife Anne.*



*Bernard Swynghedauw, co-organizer of the Paris meeting (1972), with Lionel Opie.*



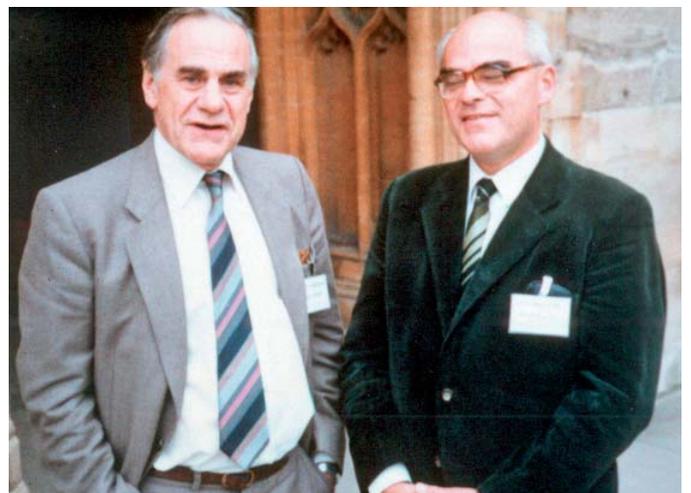
*Richard Bing (right) and Michael Oliver (Edinburgh, UK) in Dijon (1979).*



*Felix Meerson (Moscow)*



*Albert Wollenberger (Berlin)*



*František Kölbel (right), organizer of the Prague meeting (1974), with Andrew Henderson (Cardiff, UK).*

**Figure 4. The real count**

Combined international meetings are indicated in red

1970	I	London	
1971		Geneva (Int.)	5 European meetings not recognized
1972		Paris	
1973		Freiburg (Int.)	
1974	V	Prague	
1975		Brussels	
1977		Rotterdam	No number traced
1979		Dijon (Int.)	'Illrd International meeting' on programme
1981		Bologna	JMCC becomes official organ of the ISHR
1984	X	Geneva	V in JMCC
1985		Stockholm	VI in JMCC
1986		Reijkjavik	VII in JMCC
1987		Budapest	
1988		Oxford	
1989	XV	Rotterdam	
.			
.			
2005	XXX	Tromsø	

of the European Section, one being in Geneva in 1971 and another in Freiburg in 1973.

However, when somebody started to number all the meetings consecutively, the Dijon meeting was regarded, in error, as the third meeting, whereas, in fact, it was the eighth meeting of the European Section. We can now draw up a correct table of meetings, allowing for the first five meetings that had been ignored (Figure 4), and contrast it with the "wrong" official calendar (Figure 5). The complete list of European meetings is

represented in Figure 6.

Thus, it is clear that the meeting held in 2005 in Tromsø was not the 25<sup>th</sup> Silver Jubilee meeting but, in fact, five meetings later, i.e. the 30<sup>th</sup> meeting. For these reasons I think we should get our history up to date and declare the next meeting in Manchester to be the 31<sup>st</sup> meeting and that this should get into place before the final programme is printed. There is no time like the present to remedy the past, especially when the past is incorrect. The European Section has a long and glorious history, but it is longer and more glorious than

*Thus, it is clear that the meeting held in 2005 in Tromsø was not the twenty-fifth meeting but, in fact, five meetings later, i.e. the thirtieth meeting*

**Figure 5. The official count**

1975		Brussels	No number on programme
1977		Rotterdam	No number traced
1979	III	Dijon	'Illrd International meeting' on programme
1981		Bologna	JMCC becomes official organ of the ISHR
1984	V	Geneva	V in JMCC
1985		Stockholm	VI in JMCC
1986		Reijkjavik	VII in JMCC
1987		Budapest	
1988		Oxford	
1989	X	Rotterdam	
.			
.			
2005	XXV	Tromsø	

**Figure 6. The complete list**

Meetings in conjunction with a World Congress are indicated in red

1970	I	London
1971	II	Geneva
1972	III	Paris
1973	IV	Freiburg
1974	V	Prague
1975	VI	Brussels
1977	VII	Rotterdam
1979	VIII	Dijon
1981	IX	Bologna
1984	X	Geneva
1985	XI	Stockholm
1986	XII	Reykjavik
1987	XIII	Budapest
1988	XIV	Oxford
1989	XV	Rotterdam
1990	XVI	Glasgow
1991	XVII	Leuven
1992	XVIII	Heidelberg
1993	XIX	Jerusalem
1994	XX	Copenhagen
1995	XXI	Prague
1996	XXII	Bologna
1997	XXIII	Versailles
1998	XXIV	Rhodes
1999	XXV	Maastricht
2001	XXVI	Winnipeg
2002	XXVII	Szeged
2003	XXVIII	Strasbourg
2004	XXIX	Dresden
2005	XXX	Tromsø
2006	XXXI	Manchester
2007	XXXII	Bologna/Padova
1980		Moscow
1983		London

ISHR World Congresses in Europe, without official involvement of the European Section:

many suppose.

**Those who Steered us Through**

I can't close without mentioning the name of Peter Harris, who took over the job of being the first official Secretary of the Society from 1973 to 1981. In 1974 he started actively to draw up a list of members. His winning smile, his sharp wit, his capacity to break the ice by a joke and, later as it became clear, his musical ability, all contributed to the growth of the Society. It became traditional to have a musical event and Tom Ruigrok was



From left to right: Peter Harris (violin), Jürgen Schrader (piano) and Tom Ruigrok (flute), during a rehearsal at Peter's place in Great Percy Street, London, on the evening before the start of the Oxford meeting (1988).

### **ISHR-ES/SERVIER RESEARCH FELLOWSHIP 2006**

This fellowship is to foster European cardiovascular research integration.

#### **Who may apply?**

Any ISHR-ES member, aged under 35 years on July 1, 2006. The doctoral thesis will have to be completed before the ISHR-ES annual meeting in Manchester, UK, on June 14-17, 2006.

#### **What is the ISHR-ES/SERVIER Research Fellowship?**

A 20 000 Euro grant is offered by SERVIER in partnership with the European section of the ISHR to support a cardiovascular research project within a European research group for a period of up to 1 year.

#### **How to apply**

Send 8 copies of the following:

- Curriculum vitae
- List of publications
- A description of your research program as a 1-page summary + no more than 6 pages of main text
- One letter of support from a supervisor
- Please refer to instructions on the ISHR Web site:  
[www.ishr-europe.org](http://www.ishr-europe.org)

#### **To:**

Prof. Fabio Di Lisa  
Dipartimento di Chimica Biologica  
Viale G. Colombo, 3  
35121 Padova  
Italy

**For more information:**  
[dilisa@civ.bio.unipd.it](mailto:dilisa@civ.bio.unipd.it)

#### **Deadline for applications:**

March 31, 2006

always prominent. In fact, prior to the Tromsø meeting, when Tom asked me to write up my talk for *Heart News and Views*, we had a short e-mail exchange with a proposal from me because I was

now I have to keep mine. I also cannot omit a strong word of appreciation for the personal skills and many talents of both Jutta Schaper, Secretary of the European Section from 1981 to 1992 and Ketty

### ***The European Section has a long and glorious history, but it is longer and more glorious than many suppose***

fearful that he might not play at the meeting. My message was "I will write if you will play." He kept his part of the bargain and

Schwartz, Secretary from 1993 to 1997. They steered the European Section of the Study Group (by now renamed as the International Society for Heart Research) towards a firm footing. There were many predators on the way and not a few times there has seemed to be competition with other societies who have claimed similar interests. In the end, the European Section has survived, grown strong and, as evident from the meeting in Tromsø, has triumphantly survived. Long may it survive and long may Tom Ruigrok continue to entertain our meetings with his musical talents.

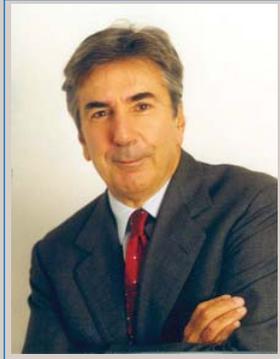
Lionel H. Opie, M.D., Ph.D.  
Cape Town, South Africa

[opie@capeheart.uct.ac.za](mailto:opie@capeheart.uct.ac.za) ■



Jutta Schaper (Bad Nauheim), Secretary of the European Section from 1981 to 1992.

**PRESIDENT'S LETTER**



*Dear Reader,*

**T**his has been an exciting time for me for a number of reasons:

**1.** I managed to attend the 22<sup>nd</sup> Annual Meeting of the Japanese Section in Osaka. I received an extremely warm welcome from everybody, and I particularly enjoyed meeting Professors Hiraoka, Hori and Komuro. I had the pleasure of attending a series of exciting sessions and symposia, and appreciating a first class level of organisation. I returned with the impression of a very healthy, active and vibrant Section. On a “non-scientific” note, I tried raw crab meat for the first time in my life, followed by at least 10 other crab dishes in Dotonbori. It was wonderful.

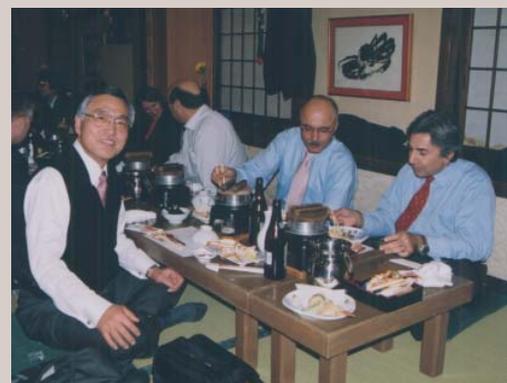
**2.** In Osaka, I also met with Tish Murphy, and she confirmed that the American Section, under the leadership of Rick Moss, is working on the program in Bologna. I hope to be able to provide you with symposia titles in the next letter.

**3.** I had a series of extremely productive meetings with Metin Avkiran regarding the program for Italy 2007. I would like to take this opportunity to thank him for his invaluable dedication, assistance and enthusiasm.

Thanks to the Scientific Programme Committee’s hard work, we have now confirmed 16 symposia and here are the titles:

- Basic biology of cell division and differentiation
- Translating the regenerative potential: focus on ischemia and angiogenesis
- Translating the regenerative potential: focus on heart failure
- Cardiovascular regeneration: embryonic versus adult stem cells
- Spatial organization of signalling pathways in cardiac myocytes
- Protein kinases as potential therapeutic targets
- NADPH oxidases in cardiovascular signalling and disease
- Cardiac protein oxidation: from damage to redox signalling
- A road map for cardiogenesis
- Injury and protection during myocardial ischemia and reperfusion
- Ways of the Moirae: signposts on the multiple roads of ageing
- Role of reactive oxygen species in the control of coronary blood flow
- Calcium dysregulation in arrhythmogenesis
- PKD: alphabetical progression or fundamental progress in signalling?
- Potential gene therapy targets in cardiovascular disease
- Open access publishing: what will the future be?

*Enjoying raw crab meat in Dotonbori, with Metin Avkiran (middle) and Meeting President Masatsugu Hori (left)*



We are working on accommodating additional symposia suggested by the ISHR Fellows, Council and Members. I will update you in the next bulletin.

**4.** The Japanese Section has confirmed that they will hold their Annual Meeting in Ferrara in 2007, preceding the Italy 2007 Main Congress. Masayasu Hiraoka, the Section President, and his wife kindly visited Ferrara just before the New Year. We managed to visit the university, the castle, the theatre and the hotels. We met with the Rector, Prof. P. Bianchi, the Pro-Rector, Prof. R. Rossi, and the President of the Province of Ferrara, Cav. G. Dall’Acqua and they were all very, very helpful. Therefore, I believe that things are proceeding well.

On a “non scientific” note again, Massi enjoyed the Italian eels from “Comacchio” for the first time in his life. He told me they were bigger than the Japanese eels, and just as delicious.

**5.** I also met several times with Fabio di Lisa, and the European Section meeting preparations are progressing well and here are some symposium titles:

- Pre- and post conditioning: signalling and effectors
- Oxidative stress: sources and targets

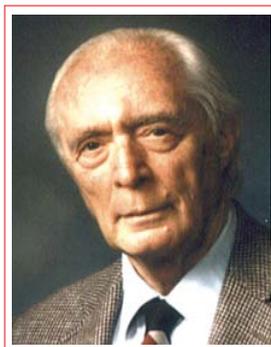
*(continued on page 10)*

## PAST TRUTH & PRESENT POETRY

**I**N THE LAST CENTURY, organic chemistry together with biochemistry have led to stunning successes in the development of new approaches to medical therapy. An example is the discovery of the synthesis of cholesterol, leading to the treatment of atherosclerosis and to a billion dollar industry, which produces and markets statins, the cholesterol lowering drugs. The transition from the bench to the clinic required many ideas, some successful, some leading nowhere. When statins are advertised on television with “Ask your doctor whether this or that statin is right for you”, the public is unaware of the torturous course of their discovery. As in the evolution of species there were ideas that withered while others grew, flowered and bore fruit. I describe here the road that led to the use of statins in the treatment of diseases of the heart and circulation.

In essay 21 [*Heart News and Views* 2002; **10** (3)], I have already referred to some of the work on the synthesis of cholesterol and referred to Konrad Bloch’s Nobel lecture of 1964, where he cited many contributing scientists. In this article I focus mainly on the development of statins. Robinson suggested that cholesterol arises by cyclization of squalene, Ruzicka proposed a common origin of steroids, and others showed that the feeding of squalene to animals increases the cholesterol content of tissues. But the most essential contribution came from the work of Schoenheimer who worked with Bloch in the department of Hans Clarke at Columbia University, New York. There, Bloch was introduced to the new tool of isotopic tracers, and with Rittenberg, began the study of the utilization of acetic acid for cholesterol synthesis, using  $^{14}\text{C}$  labeled compounds. Bloch mentions that he learned from the information obtained on rubber biosynthesis, where acetate is utilized for the biosynthesis of the macromolecule; Konrad Bloch was able to demonstrate that labeled squalene could serve as a precursor of cholesterol.

### 30. FROM THE BENCH TO TELEVISION: THE DEVELOPMENT OF STATINS



RICHARD J. BING

In the course of this work the arrangement of acetate carbons in the steroid skeleton was also established.

The pathway of cholesterol synthesis had to be known before discussion of HMGCoA reductase as a rate limiting enzyme. This came about in a round about way. In 1959, six years before the Nobel prize of Bloch, Nancy Bucher summarized her findings on cholesterol synthesis. She first described that the system for converting acetate to cholesterol resides in the microsomes. Then she stated, “Thus there appears to be a major rate limiting step which is dependent upon the microsomes and which lies between acetyl CoA- or probably acetoacetyl CoA- and the point at which mevalonic acid enters the pathway for cholesterol synthesis.”

While the discovery of the role of acetyl CoA was crucial in the further development of cholesterol lowering drugs, a chance discovery in Japan made possible a fresh and unexpected approach. In 1976, an article authored by Endo appeared in the *Journal of Antibiotics*; the work, concerned with antibiotics, was carried out in the Fermentation Research Laboratories, Tokyo Japan. The authors described that an antibiotic cultured from the fungus *Psathyrium Ultimatum*, penicillium

citrinum, lowered cholesterol in rat liver slices. They isolated three metabolites from the fungus and preliminary experiments showed that these compounds lowered cholesterol synthesis but had no effect on the conversion of  $^{14}\text{C}$ -mevalonate to cholesterol, therefore the inhibitory action must lie between acetate and mevalonate.

Two years after this discovery, Brown, Faust and Goldstein confirmed the Japanese findings using human liver cells. Compactin, a name given to one of these compounds was found to be a powerful inhibitor of HMGCoA reductase. Soon the pharmacological industry began to produce a series of statins, such as Zocor, Prevacor, Lipitor, Baycol and others.

The manufacture of statins and their marketing has now become a billion dollar business. The public which listens to the television commercials of these drugs, as well as physicians who prescribe them, know little of the work which led to their development. They are unaware of the painstaking effort to match the molecular skeleton of acetate with cholesterol, and the serendipitous discovery that the products of a penicillin mold act as cholesterol lowering compounds.

Why not anoint scientists as popular heroes and place them on equal footing with movie actors and rock musicians? They deserve it! Maybe it would lead to adequate funding of their research!

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(continued on page 10)

**BRIDGING THE GAP. WHERE CLINICAL AND BASIC SCIENCES MEET**

**BY KARL T. WEBER, M.D.**

**A** GENTLE SUMMER BREEZE blew across the North Sea as the *Fearless Eagle* (*der Adler*), prepared to depart Hamburg in July, 1898. This steamer would make its first voyage to East Asia, a nonstop journey to Hong Kong that would take several months. Standing at the helm was Captain Tritthart, his ordinarily stern face creased by the slightest of smiles on this important occasion. A plume of smoke wafted skyward from his trusty pipe as Tritthart gripped the tiller and scanned the navigator's map that would guide them into the North Atlantic. A knock at the door interrupted his concentration.

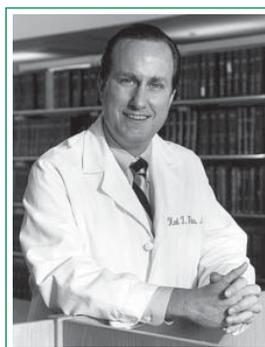
Twenty-eight-year-old Dr Bernhard Nocht made his way into the cabin. Nocht, a naval physician, would care for the ship's crew while satisfying his wanderlust to visit distant shores. He reported that rations on board, including citrus fruit from Spain, baked bread, fresh vegetables, and fresh as well as canned meats, had passed his personal inspection. Further, all hired men were fit for the long journey.

The arduous voyage on the high seas proved uneventful, and import goods were delivered on time in early September.

In Hong Kong, Tritthart searched for men who could serve as stokers, fueling the ship's hungry furnace. Twenty-three men would ultimately be hired, but only after Bernhard's physical examination had pronounced them fit; he had found no evidence of communicable illnesses, such as measles, scarlatina, tuberculosis or smallpox; jaundice; body lice or dermal eruptions; and none had cardiac murmurs, ascites, peripheral edema, or neurologic deficits. To accommodate their dietary preferences, Bernhard ordered crates of dried fish and white rice for the return journey. Because the Chinese crew would not begin work until the steamer was back in Hamburg, they would be passengers on this return voyage.

By mid-December, the *Fearless Eagle* was back in Hamburg. No illnesses had appeared among European or Chinese

**DARK VOYAGE OF THE  
FEARLESS EAGLE**



crews during the uneventful 8-week voyage. The Hong Kong-based crew were now actively involved in their physically demanding chores aboard the steamer. It was on December 26 that Bernhard found Li Ming and Song Yang had taken ill. Each complained of poor appetite, malaise, nausea and generalized weakness. There was a loss of power in lower extremities, and with a slow, deliberate gait each hobbled about using ropes, hatches, or dockhouses to steady themselves. They further reported numbness and a prickling sensation to the soles of their feet. In recent days, Li Ming had also developed swollen facies and legs, a bounding, rapid pulse and neck vein distention. Bernhard arranged for both men to be admitted to a hospital. Li Ming died soon after admission.

Captain Tritthart summoned Bernhard to his cabin to ascertain why these men had taken ill. Bernhard was saddened and surprised at these unexpected events. The Chinese crew were presumptively healthy, and each had been carefully examined for illness prior to their hire. Food had not spoiled and water tanks were well maintained. The steamer was in good sanitary condition and did not harbor pestilence. If these

men had been ill with infection when they came on board in Hong Kong, he could not discern what disease had a latency period of some 70 days, and why others had not taken ill. Tritthart and Nocht could only guess at the possibilities, but infection seemed improbable.

The *Fearless Eagle* departed for Boston on December 27. Out to sea but a few days, the steamer was engulfed by the first of several hurricane-like storms. The Chinese crew, barefoot and without proper clothing, were not prepared for these adverse conditions. Their exposure to the elements was constant as they traversed the flooded front deck several times daily to reach their living quarters. They frequently suffered upper respiratory infections.

It was January 8, 1899, two weeks after their departure from Hamburg and 13 weeks since leaving Hong Kong, that Wong Shown reported ill. His legs and face were swollen and he noted pains in both calves and chest. Bernhard found Wong to have a rapid but regular, bounding pulse. Over ensuing days, Wong developed a progressive paralysis of his lower extremities and remained confined to his quarters for the remainder of the journey.

Perplexed and frightened, Bernhard struggled to contain his sense of helplessness. Crew members asked him to see Wong San on the evening of January 19. San was the fourth member of the Chinese crew to fall ill and the third with swollen facies and leg edema. Pitting edema also involved the abdominal wall and thorax, and there was percussion dullness in keeping with bilateral pleural effusions. San suddenly collapsed and died days later.

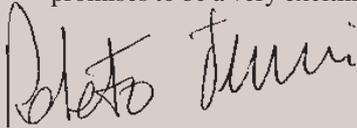
On January 29, yet another crew member, Wong Sui, was stricken in the same way as his coworker. His symptoms were less advanced, but his fear overwhelming. Violent storms again appeared to further

(continued on page 10)

(continued from page 7)

- Alterations in ion homeostasis: causes and consequences
- Cell therapies for diseased hearts

In the meantime, Christmas has come and passed, and the New Year has begun. I wish you all a fantastic start to what promises to be a very exciting year!



Roberto Ferrari

## **DARK VOYAGE OF THE FEARLESS EAGLE**

(continued from page 9)

prolong the journey. On February 8, Wong Sui, his feeble voice barely audible, attempted to speak with fellow crew members as they left guard duty. He was found dead in his berth an hour later. Bernhard noted that he had developed marked edema of face, trunk and legs.

Between February 16 and mid-March, 1899, five additional members of the Chinese crew would be stricken with the ailment that featured facial and peripheral edema. Most had rapid heart rate. All told since the departure of the *Fearless Eagle* from Hong Kong on 15 October, ten cases had appeared, of which 5 died. By early April, out of desperation, Captain Tritthart arranged for the remainder of the Chinese crew to be placed aboard a steamer bound for East Asia, and so ended the epidemic aboard this steamer.

### **What is your diagnosis and what is its causality?**

Chinese crew members who took ill presented with generalized weakness, unsteady gait, and numbness of the lower extremities suggestive of peripheral

neuropathy. Some developed jugular venous distention, peripheral edema and a rapid bounding pulse suggestive of salt and water retention. Others had rapid deterioration with onset of anasarca, paralysis, and death. Most of these patients had a rapid bounding pulse. The combination of increased extravascular volume manifested by edema, pleural effusions, and anasarca, increased intravascular volume presenting as raised jugular venous pressure and a hyperdynamic heart with rapid bounding pulse is strongly suggestive of high cardiac output circulatory failure.

Dr Nocht was initially searching for an infectious agent. But the latency period of 70 days or more, the absence of fever and constitutional symptoms, and the nontransmissibility of the disease to the European crew make infection unlikely. The second possibility is the presence of a toxin ingested with food. Fish can concentrate methyl mercury at high levels. Such contamination and subsequent ingestion can cause neurotoxicity and cardiovascular collapse. However, the absence of severe gastrointestinal symptoms and the presence of hyperdynamic heart failure prior to collapse make mercury toxicity unlikely. Contamination of beef with thyroid gland tissue

can cause high cardiac output circulatory failure, but the crew ate only fish. The long latency period and the separate source of food for the Chinese crew make a nutritional deficiency likely in our patients. Selenium deficiency, endemic in the Keshan province of Southeast Asia, causes cardiac necrosis and severe cardiomyopathy with low cardiac output making its clinical presentation different from affected crew members. The food consumed by the Chinese crew consisted of high quality polished rice, which is very poor in thiamine compared with unpolished or hardboiled rice. The latency of the disease certainly fits with thiamine deficiency because the liver stores of this vitamin generally last 2 to 3 months. The clinical syndrome of hyperdynamic circulatory failure and neuropathy can be caused by thiamine deficiency. Dried and half-cooked fish as well as tea, coffee and some vegetables are rich in thiaminases which quickly deplete thiamine stores and can worsen the disease known as beriberi.

Abridged from: Weber KT. Dark voyage of the *Fearless Eagle*. *Cardiovasc Res* 1998; **39**: 263-266.

Karl T. Weber, M.D. ■

## **FROM THE BENCH TO TELEVISION: THE DEVELOPMENT OF STATINS**

(continued from page 8)

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Richard J. Bing, M.D. ■

## REPORT ON THE XIV MEETING OF THE LATIN AMERICAN SECTION (OCTOBER 29, 2005; LA PLATA, ARGENTINA)

**T**HE Latin American Section of the ISHR held its XIV meeting which was organized together with the Argentinean Society of Physiology. The meeting was held on the campus of the School of Medicine of La Plata. The aim of the organizing committee was two-fold: first, to offer basic scientists, clinical cardiologists, fellows, interns and students grounds to interact in the setting of the most stimulating basic and clinical cardiac research performed in Latin America and second, to call an assembly in order to elect new officers of the Latin American Section.

The decision to hold the meeting in the relaxed atmosphere of the School of Medicine of La Plata proved to be an excellent choice, given that the reunion was crowded with an outstanding number of enthusiastic students. The joint reunion with the Argentinean Society of Physiology permitted the interaction with professionals from other fields of research which made discussions more generous and fruitful. There were at least 100 attendees and the format was a one day meeting with two morning and two afternoon symposia. During the Latin American Section's assembly, Dr Paulo Tucci from Brazil was proposed and elected president for the upcoming term. Dr Tucci has proposed several innovative ideas, including a proposal to distribute a

*Dr Eduardo Escudero, the scientist (top) and the musician (bottom)*

monthly report on the activities of the Latin American Section of the ISHR to the members of the Section with the idea of maintaining closer contact and interaction between members.



The event culminated with a charming closing cocktail party, featuring local wines and cheeses and highlighted by the warm hands of Dr Eduardo Escudero at the piano, who delighted the attendants with the most wonderful tangos and popular tunes.

Once again, we feel that this year's meeting of the Latin American Section met its goals. The meeting brought together outstanding researchers and excellent clinicians who generously shared their knowledge with the younger crowd permitting a most fertile scientific exchange. In addition, the Section's presidency passed to the hands of a man who is committed to increasing the Section's popularity while at the same time maintaining the high standards that this International Society demands.

*Alicia Mattiuzzi, M.D. and  
Martín Vila Petroff Ph.D.  
La Plata, Argentina*



## HEARTS FROM GAMT KNOCK OUT MICE, LACKING (PHOSPHO)CREATINE, SHOW REDUCED CONTRACTILE RESERVE AND ARE MORE SUSCEPTIBLE TO ISCHEMIC INJURY

In 1997 I joined the laboratory of Tom Ruigrok and Cees van Echteld in Utrecht (The Netherlands) as an undergraduate student. My then direct supervisor, Jan van Emous, had just won the ISHR-ES Young Investigator Award; clearly something to live up to! The excitement of seeing an isolated heart beating, and the possibility of getting biochemical information out of it in a non-destructive way using NMR spectroscopy, triggered my enthusiasm for heart research and I stayed in the field. After I graduated, I did a PhD project in the same lab. Using simultaneous  $^{23}\text{Na}$  and  $^{31}\text{P}$  NMR spectroscopy, I could measure intracellular  $\text{Na}^+$ , phosphocreatine (PCr), ATP, inorganic phosphate and intracellular pH all at the same time. This was very useful as I studied intracellular  $\text{Na}^+$  overload during ischemia and reperfusion, a process tightly related to intracellular pH. After I finished my PhD in 2003, I joined Stefan Neubauer's group at the University of Oxford (UK). Oxford is, of course, a great place to do research with its rich scientific history and many excellent research groups. It is also particularly exciting as it is the place where cardiac NMR was born. Here in Oxford I did the research that I presented last summer in Tromsø (*Ref. 1*), and for which I too was to receive the ISHR-ES Young Investigator Award.



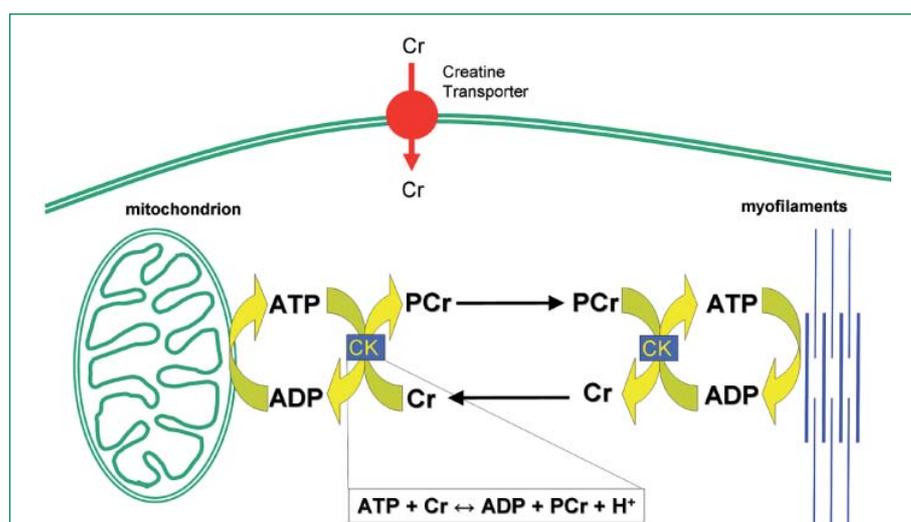
Michiel ten Hove, Ph.D.

thought we would have a creatine free mouse. When the first hearts of these mice were perfused,  $^{31}\text{P}$  NMR spectroscopy clearly showed PCr, alongside an additional peak. The PCr, of course, puzzled us, as we did not understand where the creatine came from. Just as we started the project I met Hermien Kan from Nijmegen (The Netherlands) at a meeting. She studied skeletal muscle of the same mice. She had found a similar  $^{31}\text{P}$  NMR spectrum in skeletal muscle. However, when she studied a batch of animals that had been housed individually, she did not see any PCr in the spectra. We then

### GAMTKnockOutMice

In our group we are working on the PCr/creatine kinase system and its role in congestive heart failure. Creatine kinase catalyzes the transfer of a high energy phosphate group from ATP to creatine, forming phosphocreatine and ADP (*Fig. 1*). It has been known for many years that myocardial creatine, PCr and ATP levels are reduced in patients with severe heart failure. In recent years, the creatine kinase system has been extensively studied using creatine kinase knock out mouse models, but many questions remained unanswered. We took a different approach and instead of targeting the enzyme, we targeted the substrate creatine. Creatine is synthesized in two steps. In the second and last essential step, guanidinoacetate is converted into creatine, a reaction catalyzed by the enzyme guanidinoacetate-*N*-methyl transferase (GAMT). In collaboration with the group of Dirk Isbrandt in Hamburg (Germany), we created a GAMT knock out mouse. Thus, these mice are unable to synthesize

creatine themselves. By feeding them vegetarian, that is creatine free, food we had a creatine free mouse. At least, we



**Figure 1.** Schematic representation of the 'creatine kinase/phosphocreatine energy shuttle' in a cardiomyocyte. Creatine kinase (CK) catalyzes the transfer of a high energy phosphate group from ATP to creatine, forming phosphocreatine (PCr) and ADP. This system has two functions: it acts as a high energy phosphate buffer, maintaining high ATP and, importantly, low ADP levels. The second function is the intracellular transport of the high energy phosphate bound from the mitochondria to the site of ATP utilization, for example the myofilaments. The heart does not synthesize creatine itself, but instead takes it up from the blood via a specific creatine transporter. The creatine in the blood either originates from food intake or is made in the liver or kidney.

realized that mice have the habit of coprophagia: they eat faeces. Our mice were bred by intercrossing heterozygous mice, using the wild type littermates as control. So, the GAMT knock out mice ingested creatine via the faeces of their wild type (and heterozygous) littermates that were housed in the same cages. Since then, we house the mice per genotype, and we have creatine free animals, suitable to study.

### Baseline Cardiac Function

Measuring heart weights, myocyte cross sectional area and mRNA of hypertrophy markers, we found that GAMT knock out mice did not develop substantial left ventricular hypertrophy. Using *in vivo* hemodynamics we measured left ventricular systolic and diastolic function, as well as blood pressures. In addition, we used *in vivo* cine MRI to measure systolic and diastolic left ventricular volumes. We found that baseline systolic and diastolic function and volumes as well as baseline ejection fraction were essentially the same in GAMT knock out and control mice. So, under baseline conditions, hearts lacking creatine function completely normally. To explain this puzzling result, we isolated hearts and perfused them in Langendorff mode in the NMR spectrometer and performed  $^{31}\text{P}$  NMR spectroscopy. As shown in **Fig. 2**, we found no PCr in these hearts, but instead an additional peak showed up just next to where PCr normally appears. This peak originates from phosphorylated guanidinoacetate. Guanidinoacetate, as mentioned above, is the precursor of creatine and accumulates in these hearts. Guanidinoacetate can be used in the creatine kinase reaction but only at a very slow rate (<1% of creatine). We hypothesized that guanidinoacetate is being used instead of creatine in these mice, explaining the mild cardiac phenotype. To test this, we administered isolated, perfused hearts a  $\beta$ -adrenergic

agonist; isoproterenol. In normal hearts, administration of isoproterenol leads to a decrease in PCr levels. In hearts from GAMT knock out mice we found a decrease in phosphorylated guanidinoacetate, similar to the decrease in PCr in controls, proving our hypothesis was correct.

### Increased Workload and Ischemia

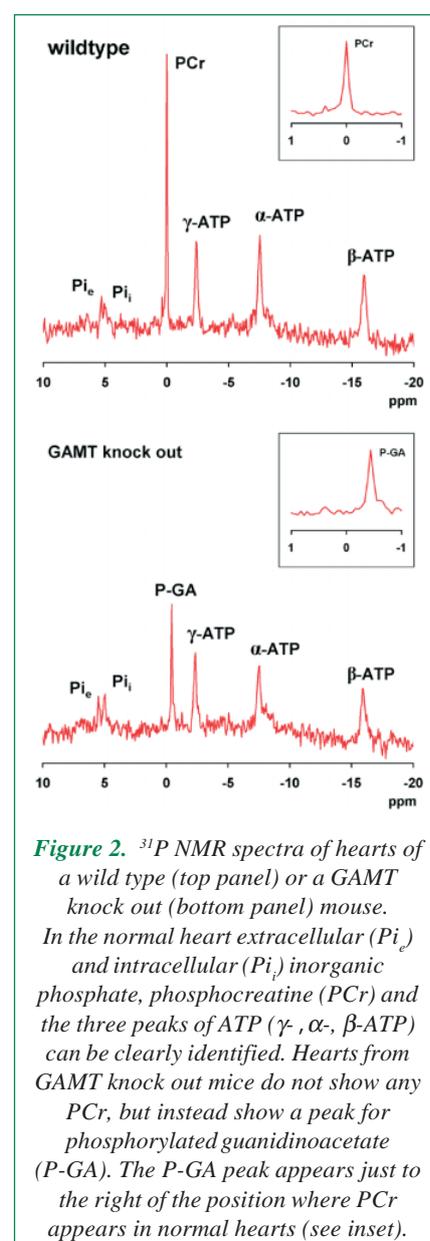
The normal baseline function we found in these mice, could mask limitations in the ability of these hearts to cope in situations of stress. Therefore, we subjected these hearts to two different types of stress; increased workload and ischemia. We increased the *in vivo* workload using dobutamine infusion and measured left ventricular contractile reserve with *in vivo* hemodynamics. GAMT knock out mice showed a reduced contractile reserve compared to controls. Finally, we subjected isolated perfused hearts to global ischemia and reperfusion. During reperfusion, hearts from GAMT knock out mice showed a significantly reduced contractile recovery.

### Conclusions and Future Directions

Altogether, we found that hearts from GAMT knock out mice, lacking (phospho)creatine maintain normal contractile function. This can be explained by the accumulation of the precursor of creatine, guanidinoacetate, despite a >100 fold reduction in the maximum flux through the creatine kinase reaction. However, hearts from these mice show a reduced contractile reserve and an increased susceptibility to ischemia and reperfusion, underscoring the importance of a high capacity PCr/creatine kinase system under conditions of acute stress. To further study the PCr/creatine kinase system, a truly creatine free (without guanidinoacetate) model would be of great interest. In addition, we recently reported on a mouse model with increased (phospho)creatine levels (**Ref. 2**), which offers a completely new way of studying the PCr/creatine kinase system. Hopefully, next year I can present more data from this model at the ISHR-ES meeting in Manchester.

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**Figure 2.**  $^{31}\text{P}$  NMR spectra of hearts of a wild type (top panel) or a GAMT knock out (bottom panel) mouse. In the normal heart extracellular ( $\text{P}_i^e$ ) and intracellular ( $\text{P}_i^i$ ) inorganic phosphate, phosphocreatine (PCr) and the three peaks of ATP ( $\gamma$ ,  $\alpha$ ,  $\beta$ -ATP) can be clearly identified. Hearts from GAMT knock out mice do not show any PCr, but instead show a peak for phosphorylated guanidinoacetate (P-GA). The P-GA peak appears just to the right of the position where PCr appears in normal hearts (see inset).

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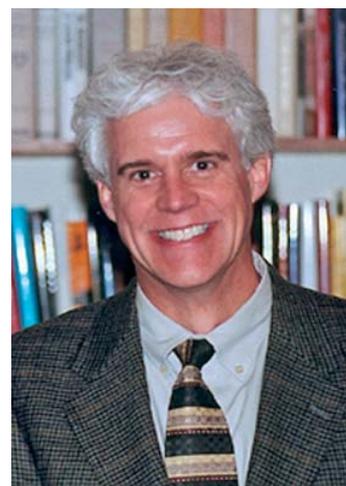
Michiel ten Hove, Ph.D.  
Oxford, UK

michiel.tenhove@well.ox.ac.uk

**Michiel ten Hove** (Oxford, UK) was the winner of the Young Investigator Award at the XXV European Section Meeting (Tromsø, Norway; June 21-25, 2005).

**ERIC N. OLSON, PH.D.**  
**WINNER OF THE 2005 OUTSTANDING  
INVESTIGATOR PRIZE**

**TRANSCRIPTIONAL CONTROL OF HEART  
DEVELOPMENT AND DISEASE  
(MAY 2005; NEW ORLEANS, LOUISIANA)**



**E**RIC OLSON was born on September 27, 1955 and grew up in North Carolina. He received a B.A. in chemistry and biology from Wake Forest University in 1977 and a Ph.D. in biochemistry at Wake Forest University School of Medicine in 1981. After a postdoctoral fellowship at Washington University School of Medicine, Dr Olson joined the Department of Biochemistry and Molecular Biology at The University of Texas M. D. Anderson Cancer Center in 1984 as an Assistant Professor where he rose to the rank of Professor and Chairman in 1991. In 1995, he moved to The University of Texas Southwestern Medical Center at Dallas, where he is Professor and Chairman of the Department of Molecular Biology and Associate Director of the D. W. Reynolds Center for Clinical Cardiovascular Research. He holds the Robert A. Welch Distinguished Chair.

Dr Olson has dedicated his career to understanding the mechanisms that control muscle gene expression. Dr Olson has used a sophisticated combination of biochemistry and genetics to discover many of the key transcription factors known to be important for cell fate determination, differentiation, growth, and patterning of cardiac, vascular and skeletal muscle cells. His work exposed a cascade of cardiac transcription factors that function in organisms as diverse as mice and fruit flies, and his demonstration that developmental control genes are redeployed in the adult heart to drive pathologic cardiac enlargement leading

to heart failure has provided new therapeutic targets and directions for cardiovascular medicine.

Beginning in the early 1980's, Dr Olson laid much of the groundwork of our current understanding of muscle gene regulation through the discovery of the basic helix-loop-helix (bHLH) transcription factor myogenin and the MEF2 transcription factor, which he showed to be essential coregulators of skeletal muscle development. Using a combination of *Drosophila* and mouse genetics, Dr Olson demonstrated that MEF2 was required not only for skeletal muscle differentiation, but also for differentiation of all muscle cell types. It is therefore a fundamental myogenic transcription factor. Dr Olson also discovered the bHLH transcription factors *paraxis*, *MyoR* and *capsulin*, which he showed to be required for patterning of different skeletal muscles of the head and body.

Based on the central role of bHLH proteins in skeletal muscle development, Dr Olson and his colleagues searched for and discovered the cardiac bHLH proteins *HAND1* and *HAND2*, the first transcription factors found in different cardiac chambers. Expression of *HAND2* is confined to the right ventricular chamber, and knockout mice showed that *HAND2* controls the formation of this specific cardiac compartment, providing the first evidence that a single gene defect could result in ablation of a specific region of the heart. Dr Olson also showed that *HAND1*

expression is confined to the left ventricular chamber and is essential for ventricular growth, as well as development of the cardiac valves.

Dr Olson's laboratory showed that *MEF2C* is required for cardiac and vascular development whereas *MEF2A* is required for postnatal growth of the heart. His group also discovered the hairy-related transcription factor (*HRT*) family, which mediates the action of the notch receptor on cardiovascular development.

Many congenital heart defects in humans affect only specific regions of the heart. Dr Olson's analysis of the phenotypes of mouse mutants lacking cardiac transcription factors revealed that the heart is assembled in a modular fashion, with each compartment governed by a distinct genetic program.

Dr Olson discovered the cardiovascular transcription factor *myocardin*, which regulates both cardiac and smooth muscle genes by associating with serum response factor (*SRF*), a MADS-box transcription factor related to *MEF2*. The activity of *myocardin*/*SRF* is repressed by an unusual homeodomain transcription factor, called *HOP*, which Dr Olson discovered as a modulator of cardiomyocyte proliferation and differentiation.

Dr Olson's contributions have also directly impacted on understanding the

## ISHR MEETINGS CALENDAR

- **June 14-17, 2006.** **XXVI European Section Meeting.** Manchester, UK. **Inquiries:** *Scientific Secretariat:* Mrs R. Poulton, The University of Manchester, Room 1.302, Stopford Building, Oxford Road, Manchester M13 9PT, UK. *Tel.* +44 161 275 1628; *E-mail* [rpoulton@fs1.scg.man.ac.uk](mailto:rpoulton@fs1.scg.man.ac.uk) *Meeting Secretariat:* The University of Manchester, ConferCare, Barnes Wallis Building, Sackville Street, Manchester M60 1QD. *Tel.* +44 161 306 4068; *E-mail* [mcc.reg@umist.ac.uk](mailto:mcc.reg@umist.ac.uk); *Website* [www.meeting.co.uk/confercare/isshr2006](http://www.meeting.co.uk/confercare/isshr2006)
- **June 13-16, 2006.** **XXVIII American Section Meeting.** Toronto, Canada. **Inquiries:** Dr P. Liu, Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto, Rm 78A, 150 College Street, FitzGerald Building, Toronto, Ontario M5S 3E2. *Tel.* +1 416 946 8543; *Fax* +1 416 946 7545; *E-mail* [hsrcentre.excellence@utoronto.ca](mailto:hsrcentre.excellence@utoronto.ca); *Website* [www.isshr2006.com](http://www.isshr2006.com)
- **September 2-6, 2006.** **World Congress of Cardiology.** Barcelona, Spain. **Inquiries:** *E-mail* [congress@escardio.org](mailto:congress@escardio.org); *Website* [www.worldcardio2006.org](http://www.worldcardio2006.org)
- **November 12-15, 2006.** **Scientific Sessions of the American Heart Association.** Chicago, IL. **Inquiries:** *Website* [www.americanheart.org](http://www.americanheart.org)
- **June 22-26, 2007.** **XIX World Congress of the ISHR.** Bologna, Italy. **Inquiries:** Dr R. Ferrari, Department of Cardiology, University Hospital of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. *E-mail* [info@isshr-italy2007.org](mailto:info@isshr-italy2007.org); *Website* [www.isshr-italy2007.org](http://www.isshr-italy2007.org)

pathophysiology of heart failure. His work has shown that many of the same transcription factors and regulatory mechanisms that control heart formation are called into play in the adult heart as a consequence of pathological stress. Dr Olson's group discovered two stress-response pathways that connect abnormalities in myocyte function to maladaptive changes in cardiac gene expression. His laboratory was the first to recognize the importance of the calcium-sensitive phosphatase, calcineurin, in cardiac hypertrophy and failure. His work

showed that calcineurin induces hypertrophy via a biochemical cascade that targets the NFAT and GATA transcription factors and that calcineurin inhibition prevents hypertrophy. In addition, Dr Olson and his colleagues identified a key role for class II histone deacetylases (HDACs) as negative regulators of cardiac growth. Hypertrophic stimuli cause phosphorylation of HDACs leading to dissociation from MEF2 and nuclear export, thereby allowing MEF2 to activate genes involved in cardiac stress. Dr Olson's discovery of stress signaling pathways mediated by calcium-dependent signaling molecules, recipient transcription factors and chromatin remodeling enzymes has spawned new areas of investigation and has provided novel therapeutic targets for treatments of hypertrophic and atherosclerotic heart failure.

Dr Olson's lab has provided a training ground for a long succession of students and postdoctoral fellows, many of whom have gone on to become leaders in the field. Dr Olson's prior awards include the Edgar Haber Cardiovascular Research Award (1998), the Basic Research Prize (1999), and the Distinguished Scientist Award (2003) from the American Heart Association, the Gill Heart Institute Award (1999), the Pasarow Award in Cardiovascular Medicine (2000), the Louis and Artur Lucian Award for

Research in Cardiovascular Diseases (2003), the Pollin Prize (2005), and a MERIT Award from the National Institutes of Health (2000). In 2003, he received an honorary doctorate from his *alma mater*. He is a member of The National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine. Dr. Olson is the Editor-in-Chief of *Developmental Biology* and a member of numerous editorial boards. He also serves as a consultant for Myogen, Inc., a biotechnology company he co-founded, and is a member of the Scientific Review Board of the Howard Hughes Medical Institute.

Olson spends as much time as possible with his wife and three children and enjoys playing guitar and harmonica in a rock band, *The Transactivators*, with colleagues from his department. Following a recent benefit concert by Willie Nelson, he was named the Annie and Willie Nelson Professor of Stem Cell Research. ■

### The Outstanding Investigator Prize

The purpose of this Prize is to recognize an outstanding scientist who is making major and independent contributions to the advancement of cardiovascular science, and is likely to further develop his/her research in the future. The main criteria for selecting awardees are scientific excellence, independence, and potential for future research contributions. While the Peter Harris Award recognizes lifelong accomplishments and the Richard Bing Award recognizes young investigators, the Outstanding Investigator Prize is similar to the Research Achievement Award; the major difference between the two is that the latter is presented during the ISHR World Congress while the former is given at Section meetings.

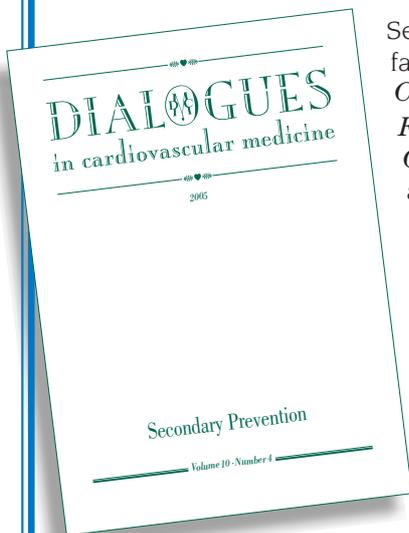
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## HEART NEWS AND VIEWS

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## HEART NEWS AND VIEWS

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### Editor

**T.J.C. Ruigrok**  
Utrecht, The Netherlands  
E-mail [t.j.c.ruigrok@xs4all.nl](mailto:t.j.c.ruigrok@xs4all.nl)

### Deputy Editor

**L. Anderson Lobaugh**  
Durham, NC, USA  
E-mail [llobaugh@nc.rr.com](mailto:llobaugh@nc.rr.com)

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**Dr Cuyppersstraat 15** **NEW**  
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The Netherlands.  
Tel.: +31 343 597 555  
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