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HEART NEWS AND VIEWS

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FOCUS ON THE JAPANESE SECTION

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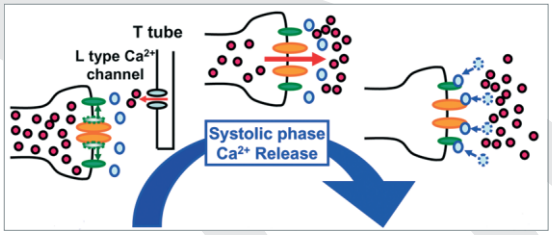

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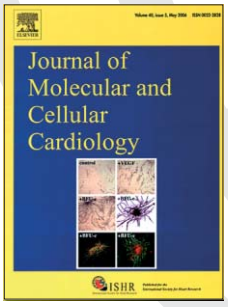

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THE HEART OF THE MATTER

A CAREER IN CARDIOVASCULAR RESEARCH

Joanne S. Ingwall, Ph.D.

DESCRIBING THE JOURNEY to my current positions of Professor of Medicine (Physiology) at Harvard Medical School and Senior Biochemist, Director of the NMR Laboratory for Physiological Chemistry and Vice Chair for Faculty Development in the Department of Medicine at Brigham and Women's Hospital is a challenge. At one level, it seems straightforward - early on I studied the structure of ATP-analogs using physical techniques and then became smitten with the beauty of studying ATP-dependent processes in contracting muscle cells and beating fetal mouse hearts. It all began with manipulating the energy pool required for protein synthesis in differentiating skeletal muscle cells, progressed to studying energy supply/demand mismatch in beating fetal mouse hearts in organ culture deprived of O_2 and oxidizable substrates to mimic ischemia and then to adult rodent hearts placed in a NMR spectrometer to study the relationship between energy supply and use in normal and hypertrophic development and in hypoxia, ischemia and heart failure. It would appear that I always studied ATP and the heart!

At a more detailed level, the path was hardly straight. I moved from being an honest protein chemist (my thesis was the first physico-chemical characterization of the blood clotting protein prothrombin) to being a cell biologist to becoming a biophysicist studying cardiac energetics. When introduced as professor of medicine (physiology), I always think that I am neither a physician nor a

THE HEART OF THE MATTER: A CAREER IN CARDIOVASCULAR RESEARCH

WE are pleased to present the second article in our autobiographical series entitled, "The Heart of the Matter: A Career in Cardiovascular Research". Dr Joanne S. Ingwall, Professor of Medicine at Harvard Medical School, Senior Biochemist, Director of the NMR Laboratory for Physiological Chemistry, and Vice Chair for Faculty Development in the Dept. of Medicine at Brigham and Women's Hospital, has provided an insightful account of her career path from protein chemist to cardiac biophysicist. We are grateful to Dr Ingwall for sharing the wisdom she acquired during her successful career in cardiovascular research.

Leslie Anderson Lobaugh, Ph.D.

physiologist – how did this happen? I will answer this by presenting a few career lessons that I have learned that may be useful to young investigators.

Be willing to learn new things and to use new tools, even if no one else is doing it

Lessons from a Career in Cardio–vascular Medicine

- *Go with the science. Focus on the problem and the hypotheses to be tested, not the tool or the model system. Be willing to learn new things and to use new tools, even if no one else is doing it.*

We put mouse hearts in the magnet housed in the chemistry department at UCSD in the spring of 1976 (we were the first to put a heart in a magnet). Who would have guessed that my lab would still be putting hearts in the magnet today. Originally, we did this to define how low intracellular pH fell during simulated ischemia, thinking that preserving ATP and phosphocreatine levels in intact hearts would be too difficult. We knew that the traditional approach required isolating and perfusing beating rat hearts and then freeze clamping them to measure metabolite concentrations using heart extracts. We saw the potential for respecting the physiology of the system by making ^{31}P NMR measurements in the beating heart.

You are only as good as your students, so choose wisely and invest heavily in their career development

After moving from UCSD to Harvard Medical School in 1977, Howard Morgan and the late Jim Neely taught us how to make good perfused hearts. We taught ourselves how to interface the NMR experiment with the perfused heart preparation, and what we could learn from it. It was fun to be a pioneer in this field. I still get excited to monitor biochemical events such as phosphoryl transfer and Na accumulation in the intact beating heart in the magnet. Imagine how exciting it is to measure in real time the velocity of the creatine kinase reaction in an intact beating heart and how it changes in hypertrophy and failure! We observed that energy reserve is decreased in the hypertrophied/failing heart in real time. This led us to our current understanding of why ATP falls in the failing heart.

Physiologists view the heart as a black box, sacrificing biochemical information in order to preserve intact the physiology of the system, while biochemists actually think they know how a reaction proceeds based on measurements of dilute extracts and solutions. By combining NMR and heart preparations, we can have the best of both worlds, sacrificing neither the physiology nor the biochemistry. This is a good example of how not being afraid to try new things can change your entire career.

- *You are only as good as your students, so choose wisely and invest heavily in their career development. Take pride in their accomplishments. They are the standard bearers of the field for the future.*

One of the plusses of being on the ground floor of a new and exciting field is that it attracts the best and the brightest young minds. I have been truly fortunate to have as post-doctoral colleagues such stars in cardiovascular medicine as Stefan Neubauer and Kieran Clarke, now full professors at Oxford; Monique Bernard, Luce Van der Elst and Marianna Bak in Europe; John Bittl, Stan Perry, Sam Goldhaber, Rong Tian, Jim Balschi and Luigi Nascimben who are or have been distinguished faculty at HMS, to name some of them. Their intelligence and dedication to science has pushed the field forward. This is why we lead research groups.

- *Choose collaborators wisely – they can change the course of your research career.*

Collaborating with Charles Springer, then at SUNY Stony Brook and now in Oregon, set us on the path defining the energetics of cation movements in the intact heart. What fun it was to watch Na accumulate in the ischemic heart perfused in the magnet using Charlie's shift reagent to discriminate between intra- and extra-cellular Na^+ and also K^+! This allowed us to test a whole new set of hypotheses such as whether the Na pump was under thermodynamic control and whether Na accumulation in hypoxic hearts could predict whether the hearts fibrillated. Collaborating with Cricket Seidman here at HMS, Jil Tardiff at Einstein and Joe Metzger at Michigan opened an entire new line of research defining the energy

cost of contraction in hearts bearing single amino acid substitutions in sarcomeric proteins (some related to familial hyper–trophic cardiomyopathy). Each mutation has a unique phenotype affecting thick and thin filament interaction, which changes the cost of contraction.

■ *Give back to the field. Say yes!*

It is difficult to strike a balance between professional activities and research and family. Some succeed without "giving back", but usually the experience gained and contacts made when you accept grant and manuscript review assignments and leadership positions in professional societies offer a large payback. I cannot say that I "enjoyed" my service to the ISHR as treasurer of the American Section because I inherited a society essentially bankrupt and about to lose its status as a non-profit organization. But I did learn a lot working with the pro bono lawyers to rescue the Section administratively, helped by the profits from the first molecular biology of the heart meeting chaired by Bernardo Nadal-Ginard and myself. It was worth it!

From left to right: Paul C. Lauterbur, Thomas F. Budinger, Sir George Radda, Gerald M. Pohost, and in the front is Joanne. This picture with some of the pioneers in NMR was taken at a meeting in New York City in 1990.

Another way to "give back" is to nurture young investigators. We all need mentors to help us make wise decisions about career paths. One of my most rewarding activities professionally has been my work with post-doctoral fellows and faculty providing career development advice. It should be an obligation of every senior faculty member to work with others to promote careers and contribute to the well being of our institutions. The rewards are enormous.

To conclude, if you choose wisely and well, you will enjoy going to the lab every morning and have opportunities to do new and –one hopes- important experi–ments.

Joanne S. Ingwall, Ph.D.
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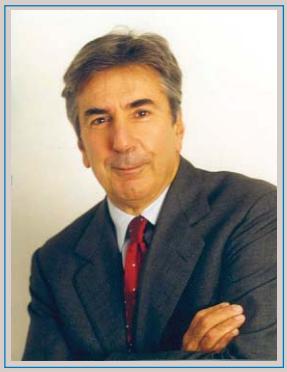
Dr INGWALL obtained her Ph.D. in biophysical chemistry from the Chemistry Department at Cornell Uni–versity, where she was the first to define the physico-chemical properties of a blood clotting protein. As a postdoctoral fellow at the Cardiovascular Research Institute at UCSF and Stanford Medical School, she extended her interest in protein chemistry to the control of muscle protein synthesis in differentiating skeletal muscle cells in culture, a project that earned her the third Louis Katz Award for Young Investigators from the AHA. Her initial faculty level appointment was in the Cardiology Division of the Department of Medicine at UCSD. She was recruited to the (then) Peter Bent Brigham Hospital in 1977, and has risen through the ranks from assistant to full professor. Her current major research interest is cardiac energetics using hearts of transgenic mice designed to mimic specific molecular defects known to occur in ischemia and heart failure. She is a pioneer in the use of magnetic resonance spectroscopy to study cardiac energetics and function.

Dr Ingwall has held many positions of leadership in professional organizations including the International Society for Magnetic Resonance in Medicine (board member and president), the International Society for Heart Research, American Section (board member and 2 terms as treasurer), the American Heart Association (basic science councilor, co-organizer of the first meeting on the molecular biology of the heart, AHA program committee member and chairman of exhibits, contributing author to the *AHA Mentoring Handbook*), and the Stanley J. Sarnoff Endowment for Cardiovascular Research (board member and all office positions). In 2001, she received the Distinguished Service Award from the International Society for Magnetic Resonance in Medicine.

Dr Ingwall's commitment to faculty development is well recognized. Since 1997, she has served as the co-chair of the Research Career Development Committee of the BWH Research Council. The goal of this committee is to develop programs providing career guidance and skills enhancement for the research community at the hospital, with a focus on junior faculty and fellows. This work was acknowledged by awarding its co-chairs the John MacArthur Research Service Award at BWH, in 1999. Also, in what was most likely a unique experiment, Dr Ingwall served as Faculty Development Coordinator in the Department of Radiology at the Beth Israel Deaconess Medical Center, matching a Ph.D. scientist with clinical faculty. Expanding on these experiences, Dr Ingwall became the first director of the Office for Faculty Development at the Beth Israel Deaconess Medical Center. She has also served as Partners HealthCare System consultant for Ph.D. Career Development where she oversaw a multi-faceted program focused on issues specific to Ph.D.s working in a hospital setting. Dr Ingwall is now Vice Chair for Faculty Development in the Department of Medicine at Brigham and Women's Hospital. In recognition of her long-term commitment to mentoring faculty and students, Dr Ingwall received the 2000 A. Clifford Barger Excellence in Mentoring Award from Harvard Medical School.

PRESIDENT'S LETTER



Dear Reader,

This is a very hectic time for me. Cardiology is progressing, and my department is about to move to a new hospital (although, we have been planning this move for four years). The XIX World Congress is getting closer, and the website is now live (www.ishr-italy2007.org) , and I am pleased to report that there have been a lot of hits and enquiries. This is promising.

We are in the final stages of the scientific programme, and about to send out the official invitation letters. I can also confirm that the Satellite meeting in Pavia will be held in conjunction with the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. This is excellent news for the ISHR because I believe that in Europe we should collaborate with other societies, while still retaining our identity. We are also hoping to have a "white evening" in Bologna, thanks to the Foundation Cassa di Risparmio di Bologna, where they will open their unique historical buildings for you to visit.

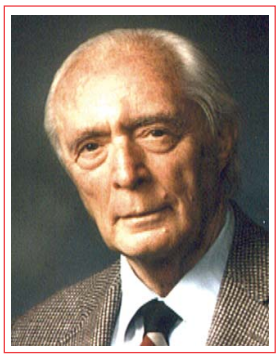
I do not want to forget to mention the other meetings that are taking place this year. The 26th European Section meeting in Manchester, UK will take place in June. I am looking forward to the meeting, not only for the science, but as I have never visited this city. I am especially looking forward to being able to visit the 15th Century Cathedral, as I have been told on many occasions of its beauty. In addition to the usual symposia and posters, a novel feature of the Manchester Meeting will be the introduction of "How To" sessions where experts in various fields will talk about methods they use in research. A scientific highlight of the meeting will be the Plenary Lecture by Sir Peter Mansfield (Nobel Laureate for magnetic resonance imaging). Befitting the fact that this meeting will be held while the Football World Cup ("soccer" for the benefit of North Americans) is in full swing, the conference dinner will be held at Old Trafford - the stadium of Manchester United. June is a very hectic month this year, as there is also the 28th Annual Meeting of the North American Section in Toronto, Canada. This also promises to be an exceptional meeting, on a subject close to my own heart – Molecular Advances. Toronto is one of my favourite cities, one of the largest in North America, and it also boasts a wonderful shoreline around Lake Ontario. The climate is wonderful, and I am ashamed to admit (as a pure Italian) that the wine is exceptional!

I wish you all a fantastic start to the Summer, and look forward to updating you again shortly.

Roberto Ferrari

PAST TRUTH & PRESENT POETRY

31. BRUNO KISCH'S GRANULES IN THE HEART



RICHARD J. BING

IN 1963, an article by Bruno Kisch entitled "A Significant Electron Microscopic Difference Between the Atria and the Ventricles of the Mammalian Heart" appeared in the journal *Experimental Medicine and Surgery*. Amongst the 21 illustrations, figure 8 and 9 demonstrate the presence of "dark microbodies". As Kisch writes, "there are also great masses of bodies of a diameter of about 1/20 up to 1/30 of a micron, some of them showing a kind of granulation." The article created little interest, in contrast to a paper published by Jamieson and Palade one year later with similar findings. The discovery of these microbodies was the beginning of a long and intense search for their significance, a search which has led to a new clinical test for the diagnosis and prognosis of heart failure.

Kisch's discovery was based on morphological evidence. The next step, the discovery of the pharmacology of these microbodies, used classical physiological methods. In 1981, de Bold of Toronto, Canada, speculated that the granules described by Kisch resembled those present in polypeptide-hormone producing cells. After intravenous injection of supernatants of atrial muscle homogenates into rats, he found a 30-fold increase in sodium and chloride excretion, while urine volume rose 10-fold. As de Bold wrote, "It is tempting to speculate that the cardiac atria, which are known to be a monitoring site of intravascular volume, may also be the source of a factor affecting the volume regulatory function of the kidney."

These observations became the basis of future research on the endocrine function of the heart concerned with electrolyte and volume regulation. Later, it was found that the atrial natriuretic peptide (ANP) resembles a natriuretic peptide in porcine brain, and that this peptide (BNP or B-type natriuretic peptide) is also synthesized and secreted from the ventricular heart muscle. Like the atrial peptide, the ventricular peptide possesses diuretic, natriuretic and vasorelaxant activities. B-type natriuretic peptide is encoded on chromosome 1 and is translated into preproBNP, which is cleaved to form proBNP. The carboxy terminus of proBNP is again cleaved by a serine protease to form the biologically active BNP and the inactive N-terminal (NT). Both these peptides circulate in human plasma and are independent predictors of the severity of heart failure.

Gene expression of BNP in ventricular myocardium is influenced by stretch of the heart muscle. In the past, there were suggestions that this is an important factor in the production of cardiac hypertrophy and failure. Indeed, diastolic stretch (preload) or left ventricular end-diastolic wall stress also appear to be the factors responsible for the induction of BNP expression.

The recognition of BNP and NT-proBNP as markers for the severity, prognosis and diagnosis of heart failure has become one of the major landmarks in cardiology. Measurement of these two peptides in plasma improves the evaluation and treatment of patients with acute and chronic dyspnea. The two biomarkers are also of value in the clinical evaluation of ischemic heart disease. In stable ischemic heart disease they can rule out the presence of heart failure, while in acute coronary syndrome, measurement of BNP obtained after the onset of ischemic symptoms can inform on long-term risk.

Doctors Wolfgang and Jutta Schaper have published a scholarly and compassionate description of Dr Kisch's life and work. They mention the opposition Kisch had to face when, as an immigrant and refugee from Nazi Germany, he tried to continue his research on diseases of the heart. He encountered much hostility and prejudice.

Kisch became involved in the politics of American cardiology and the founding of the American College of Cardiology. W. Bruce Fye has given an account of the drama, even the tragedy of the role European refugees played in the history of American cardiology. According to Fye: In 1948 an official of a State Licensing Board characterized immigrant physicians as having an attitude of arrogance and superiority. "The majority has shown no friendliness or thankfulness for being allowed to reside in this free and democratic country." The American College of Cardiology was founded by some of these refugees out of frustration and Kisch was among those who formulated the college's policies. The American Heart Association, representing the native and elite group of American Cardiologists, was suspicious of this influx of alien upstarts and attempted to stifle their influence. Kisch, who had been a respected scientist in Germany, hoped to attract teachers and researchers to the College. Fortunately, he found diversion and respite from the political turmoil in his studies on the ultrastructure of the heart.

(continued on page 7)

BRIDGING THE GAP. WHERE CLINICAL AND BASIC SCIENCES MEET

BY KARL T. WEBER, M.D.

COMPLETE WITH ALL THE TRIMMINGS

IN 1925, Iod Basedow married Imma. The couple moved to rural Nebraska. Their sons, Ion and Iot, would later marry Irene and Imogene. Ion was employed at the local slaughtering/meat-packing plant, while Iot ran the Basedow farm. They each raised a family of healthy children.

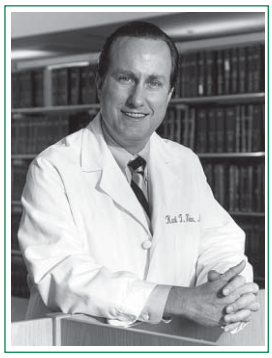
The Basedow clan gathered on Thurs–day evening, June 20, 1985, to celebrate Iod and Imma's 60th wedding anniversary. Irene and Imogene had prepared a sumptuous feast, complete with all the trimmings. Irene noted that "tomorrow afternoon the Scholastic Marching Band Competition begins in Kansas City. Imogene and I look forward to having the children participate. The awards cere–monies is Monday afternoon. All but Ignatz, who plays third base for the American Legion team and mows lawns for spending money, will be traveling with us."

"Ya," quipped Ion and Iot in unison, "We've stocked up."

"Ion bought 20 lbs of ground beef down at the plant," noted Iot. "There'll be outdoor barbecues at Ion's house Friday and Saturday and then the Annual Chili Barbecue down at the firehouse on Sunday."

It was near midnight on Monday evening when Irene, Imogene, and the children returned home. As Irene pulled into the drive, she found the living room was well lit. Strange, Ion's shift began at 5:00 a.m. Why was he not asleep? She found him pacing the living room complaining of restlessness since Sunday and the feeling his heart was racing. There was no calming him down.

Imogene, tired after the 8-hour trip, looked forward to a few hours' sleep before their rooster would register his wakeup call at daybreak. But Iot was tossing and turning. He normally was a sound sleeper. No sooner had she dozed off when she sensed Iot get out of bed. Perhaps nature's call, she reckoned. But when he did not return, she got up to find him seated at the



kitchen table devouring a Dagwood-like sandwich heaped high with leftover hamburgers.

"What's up, honey?" she asked.

"I don't know," Iot replied. "I'm so restless, and I haven't been able to sleep for the last few nights. I hope this sandwich cures my insomnia." He then added, "It's strange. Despite Ion and me eating nearly 20 lbs of ground beef, I am losing weight."

The following morning Irene and Imogene compared notes. Ion and Iot had the same affliction. Did this run in the family? Without any change in their husbands' restlessness, Irene and Imogene decided to take them to Dr Cotton on Friday.

Cotton obtained Ion and Iot's current symptoms, their negative past medical histories, and the fact neither had used over-the-counter preparations. Each had a rapid regular pulse, 110 bpm, while blood pressure was normal. Physical examinations were negative; however, each had a fine tremor of hands and palms were warm and sweaty. He obtained blood samples and prescribed propran–olol to control beta adrenergic receptor-related symptoms of tachycardia, sweat–ing, tremor, and restlessness.

Over the weekend, Cotton reached a diagnosis, and decided that, irrespective of Friday's test results, an additional study was indicated.

What is your diagnosis, what test would you order, and how would you go about solving the mystery?

Answer

The Basedows had skewed Cotton's expectations of age- and gender-related thyrotoxicosis. A familial tendency? Maybe. Serum thyroxine was increased; and thyroid stimulating hormone reduced. On Monday, he obtained radioactive iodine uptake test which was reduced in each case suggesting Ion and Iot were receiving exogenous thyroid hormone. How could this be? Neither gave such a history, and there was no reason to suspect devious intake. He needed more information and therefore orchestrated a family gathering on Wednesday evening.

"Ion and Iot have not been feeling well since Sunday," noted Cotton. "We need to do some detective work to determine why. It appears both men have factitious hyperthyroidism secondary to their receiving thyroid hormone. What have each of you been doing since last Friday?" Iod and Imma noted they had been at the farm since their anniversary dinner while Irene and Imogene were in Kansas City.

"So Ion and Iot were alone all weekend?" asked Cotton.

"No," reported Ignatz. "I never left town."

"How did you spend your time, Ignatz? With your father and uncle?" queried Cotton.

"Well, not exactly. You see, I had school on Friday, baseball games on Friday and Saturday evening, and several lawns to mow. But I did attend the barbecue down at the firehouse," noted Ignatz. This seemed to offer Cotton an insight he was searching for. He probed further.

"If I understand you, Ignatz, you did not partake of the barbecue your father

COMPLETE WITH ALL THE TRIMMINGS

and uncle held on Friday and Saturday? Did you eat the food they prepared when you returned from your baseball games?"

"No. I prefer chicken. And it was the same on Sunday at the firehouse. I don't eat chili." And so Cotton seemed to have narrowed the possibilities to Ion and Iot's weekend dietary extravaganza of ground beef.

"Ion, where did you buy the beef?"

"Down at the plant where I work," Ion responded.

"Did any of the rest of you have hamburgers prepared from the ground beef Ion purchased?" Cotton asked. There was a unanimous no. And there it was: an apparent answer to the dilemma.

But hamburgers were a dietary staple in this part of the Midwest. Why would there be a problem now? Were others living in or visiting the area affected? Cotton recommended the Basedows not eat ground beef until he had made several inquiries.

The next morning Cotton was on the phone with the State Health Department. He learned that other physicians had called to report a sudden increase in "painless thyroiditis" in their practices. A clustering of cases in surrounding counties would be found, which included southwest Minnesota and northwest Iowa. Subsequent Case Control Studies identified a total of 121 outbreak-associated cases of *thyrotoxicosis factitia* and the source of contaminated beef. There followed investigations of the implicated meat packing plant. An association was found between the occurrence of thyrotoxicosis and the consumption of ground beef prepared from sternothyroid and sternohyoid muscles of the neck. Known as "gullet trimmings," this procedure was intro–duced in 1993. Prior to that time, thyroid glands had been removed and sold for the manufacturing of thyroid extract. In April, 1993, this trimming procedure was used to enhance the yield of meat for ground beef. The inadvertent inclusion of thyroid gland tissue in this harvesting procedure was attributed to two factors: a dis–continuation of the kosher killing procedure, in which exsanguination creates a pale thyroid gland that contrasts with red neck muscles; and the relocation of the involved work area to another section of the plant.

The appearance of hyperthyroidism in previously euthyroid patients as a result of iodine exposure is referred to as the *Iod Basedow* phenomenon. It has occurred in areas of endemic iodine deficiency and can accompany ingestion of excess iodine and iodine-containing drugs and the use of radiographic contrast agents. Amio–darone, for example, a drug used in the management of arrhythmias, can be associated with hyperthyroidism. A 200 mg amiodarone tablet supplies 74 mg of iodine while recommended daily iodine intake is 0.15 mg.

Abridged from Weber KT. Complete with all the trimmings. *Cardiovasc Res* 1998; **40:** 235-238.

Karl T. Weber, M.D. ■

BRUNO KISCH'S GRANULES IN THE HEART

(continued from page 5)

Kisch was, as the Schapers called him, "a super intelligent man, who scientifically was far ahead of his time." But he was also a heroic figure, whose fight for recognition motivated him to make one of cardiology's significant discoveries.

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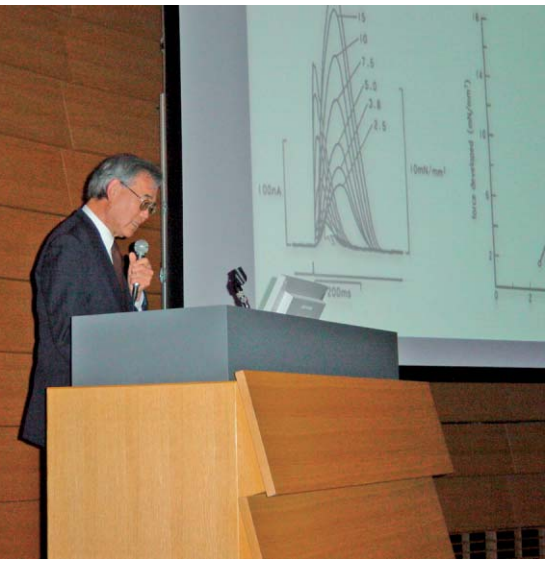
Richard J. Bing, M.D. ■

REPORT ON THE XXII ANNUAL MEETING OF THE JAPANESE SECTION
(DECEMBER 15-17, 2005; OSAKA, JAPAN)

Professor Masatsugu Hori and his colleagues from Osaka University Graduate School of Medicine hosted the 22nd Annual Meeting of the ISHR Japanese Section in Osaka, on 15-17 December 2005. The venue was the Osaka International Convention Centre, otherwise known as Grand Cube Osaka (on account of the building's shape, we presume) and the meeting attracted over 220 participants. Anyone who has attended an ISHR meeting in Japan has first-hand experience of the legendary hospitality of our Japanese colleagues, and this meeting certainly more than lived up to that reputation. However, what made the meeting really stand out was the breadth and quality of the science being presented, particularly by the rising stars of Japanese cardiovascular research (more on this topic later).

We were fortunate to participate in this meeting as members of an invited international faculty, which also included David Eisner (UK), Roberto Ferrari (Italy), Rick Kitsis (USA), Tish Murphy (USA) and Kai Wollert (Germany). Our principal task was to speak in the International Satellite Session, entitled "Stress Adaptation and Cell Death", held on the first afternoon of the meeting on 15 December, but members of the international faculty also participated in the Panel Discussion sessions that were held on subsequent days, as co-chairs and introductory speakers. The overseas speakers in the International Satellite Session focused on a range of topics, including the mechanisms and consequences of calcium dysregulation in heart failure, oxidative stress in myocardial ischaemia, mechanisms of cell death, cardioprotective signalling via GSK3β and VDAC, ischaemic preconditioning, and regulation and functions of PKD. The session was enriched by an introductory talk by Masatsugu Hori and presentations by three other local speakers, in the persons of Kinya Otsu (Osaka University), Michihiro Yoshimura (Kumamoto University) and Takayuki Shindo (Shinshu University), who discussed the roles of oxidative stress and aldosterone in heart failure, and the roles of adrenomedullin in a variety of cardiovascular diseases.

Professor Masao Endoh delivering the 2005 ISHR Keith Reimer Distinguished Lecture.



Without wishing to upset any of the participants in other sessions, we believe that a particular highlight of the meeting was the Panel Discussion sessions. The format of these was the brainchild of Masatsugu Hori and involved members of the international faculty and established international figures from Japanese cardiovascular science, including Hisayoshi Fujiwara (Gifu University), Issei Komuro (Chiba University), Seibu Mochizuki (Jikei University), Ryozo Nagai (University of Tokyo) and Munekazu Shigekawa (Senri-Kinran University), as chairmen or keynote presenters, but gave prominence to younger faculty members from various Japanese Universities, as speakers or commentators. The topical subjects discussed in these sessions were the mechanisms underlying the transition from cardiac hypertrophy to failure, the contribution of various forms of cell death to cardiac disease, emerging concepts in regenerative therapy, and the potential of calcium-regulatory proteins as therapeutic targets. The talent on show was breathtaking and the various assistant and associate professors who participated certainly rose to the challenge. Other sections of the ISHR would do well to consider including sessions of similar format in their meetings.

It would be remiss not to mention two other highlights. A reminder that Japanese investigators have been making key contributions to international cardiovascular research for a long time came in the form of a masterful lecture by Masao Endoh (Yamagata University), who has dedicated his entire career to the study of the physiological and pharmacological regulation of cardiac contractile function, on "Regulatory mechanisms of Ca^{2+} signalling in intact myocardial cells". This plenary lecture was in fact the 2005 ISHR Keith Reimer Distinguished Lecture and Masao Endoh was presented with the plaque and honorarium associated with this award by one of the authors (MA), in his capacity as the ISHR Secretary General. Another highlight, also initiated by Masatsugu Hori, was the Young Investigator Award competition; we were very relieved not to be on the selection panel for this, since it would have been a formidable job to select between the ten excellent presentations (indeed, the reason there were ten presentations was that the panel felt none of the entries could be eliminated to create a short-list!). In the end, there had to be a winner, however, and this was Toshihiro Takeda (Osaka University), for his work on the regulation of cardiac systolic function by presenilin 2. The award was presented by Ryozo Nagai, chair of the selection panel, at the superb reception held on the Friday evening, at which the sake flowed (some all over several members of the inter–

national faculty [they know who they are…], due to their over-enthusiastic hammering of the sake barrel during the traditional "Kagami-Biraki" ceremony!).

The meeting of course also included poster presentation and oral commu–nication sessions, in the traditional format. And therein lies a funny episode. We were excited to see listed among the Japanese abstracts an oral communication by an eminent Canadian investigator, who is renowned for his outstanding work on cardiomyocyte apoptosis, on the last day of the meeting. Now, this investigator is not exactly a shrinking violet and we were surprised that we had not seen or heard him until then. Several of us went to the relevant meeting room to hear his talk, only to be disappointed by a no-show. About two hours after the closing ceremony, as we were leaving the hotel to go to dinner (actually, to yet another party organised by our host, Masatsugu Hori…), who should we spy, just arriving from the airport, but the said investigator, looking very much like he had just walked across the frozen hinterland of Manitoba! We are sure there is a story waiting to be told there…

In respect for Tom Ruigrok's word limit, we should now draw this report to a close. On behalf of the ISHR and the inter–national participants in the meeting, we would like to express our sincere thanks to Masatsugu Hori, Kinya Otsu (who was also heavily involved in the meeting's organization and management) and the ISHR Japanese Section for a great meeting that combined superb science with excellent organization and outstanding hospitality. We would also like to take this opportunity to thank Yoshiko Fukuura, the administrative assistant for the meeting, who handled all of the challenges thrown in her direction before and during (and most likely after) the meeting with impeccable efficiency and not inconsiderable charm. *Arigato gozaimashita!*

Metin Avkiran (London, UK)
Jim Downey (Mobile, USA)

1

1. Toasting Professor Masao Endoh's award. From the left are David Eisner, Tohru Izumi, Masao Endoh, Keitaro Hashimoto, Metin Avkiran and Tish Murphy.

2

2. Professor Ryozo Nagai (left) presenting the Young Investigator Award to Dr Toshihiro Takeda.

3. A presidential summit at the meeting reception: Professor Masayasu Hiraoka (Section President) on the left and Professor Masatsugu Hori (Meeting President and Section President-Elect).

3

Photo on page 1: *Kagami-Biraki (barrel opening) at the Reception as a traditional ceremony with Japanese wine. From the left: Professors M. Hori (President), M. Avkiran, M. Hiraoka, K. Wollert, E. Murphy, J. Downey and D. Eisner.*

PRESENILIN 2 REGULATES THE SYSTOLIC FUNCTION OF HEARTS BY MODULATING Ca^{2+} SIGNALING

Toshihiro Takeda, M.D., Ph.D.

IT was my great honor to receive the 2005 Young Investigator Award at the 22nd Annual Meeting of the Japanese Section in Osaka for my work on the role of presenilin 2 (PS2) in hearts. I have just completed my doctoral degree in the Department of Cardiology, Osaka University Graduate School of Medicine, and I am continuing my research as a postdoctoral fellow under Prof. Masatsugu Hori. I was the last graduate student of Prof. Michihiko Tada, who passed away last summer. I joined Prof. Tada's laboratory after completing my cardiology residency, because I was interested in the regulation of excitation-contraction (E-C) coupling in hearts. My research goal was to elucidate a novel regulatory mechanism involving PS2, a modulator of the cardiac ryanodine receptor (RyR2). PS2 is reported to be the gene responsible for the development of early-onset familial Alzheimer's disease (***Ref. 1***). PS2 is ubiquitously expressed in various tissues, including the heart. In brain, PS2 localizes predominantly to the endoplasmic reticulum and interacts with sorcin which serves as a modulator of RyR2 (***Ref. 2***). We hypothesized that PS2 in the heart localizes to the sarcoplasmic reticulum (SR) and modulates E-C coupling. To test this hypothesis, we examined the cardiac phenotype of PS2 knockout (PS2KO) mice.

Physiological Characteristics of PS2KO Hearts

The PS2KO hearts showed no evidence of any cardiac morphologic defects. There was no evidence of cardiac hypertrophy or heart failure. Hemodynamic data did not indicate any differences in heart rate, left ventricular (LV) systolic pressure, LV end-diastolic pressure or the minimum first derivative of the LV pressure (-dp/dt) between PS2KO and wild type (WT) mice. However, the first derivative of the maximum LV pressure (+dp/dt) was significantly higher in PS2KO than that in WT mice (7143 ± 311 mmHg/sec for WT and 8629 ± 358 mmHg/sec for PS2KO), suggesting that cardiac contractility significantly increased in PS2KO mice.

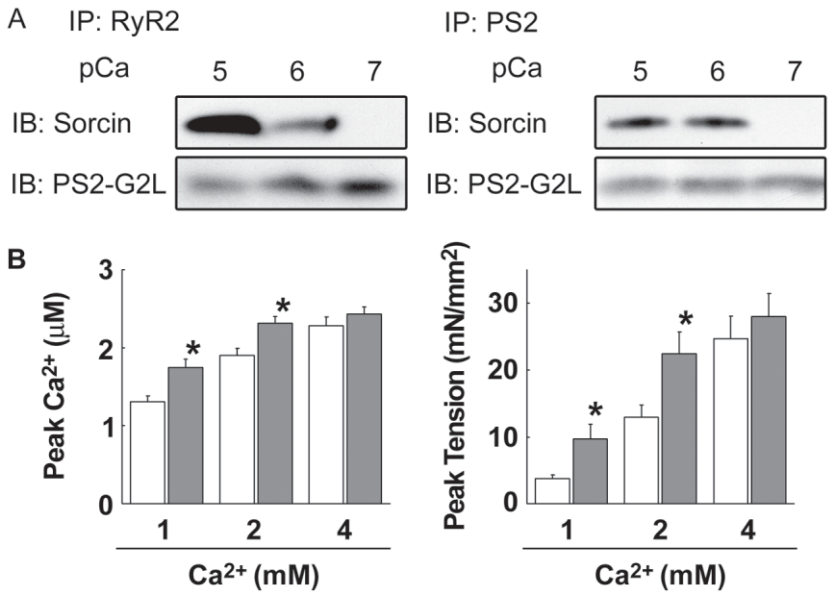


Figure 1. A: *Effects of intracellular Ca^{2+} concentration on the physical interaction of PS2 with RyR2 or sorcin. Calcium was added to the immunoprecipitation buffer to yield free Ca^{2+} concentrations in the range of 0.1 to 10 μM (pCa 7 to 5) and immunoprecipitation with anti-RyR2 or anti-PS2 antibodies was performed in HEK-293 cell homogenates. PS2 and sorcin antibodies were used for immunoblotting.* ***B:*** *The effect of extracellular Ca^{2+} concentration on the Ca^{2+} transient and tension (n = 8 for WT and 10 for PS2KO). *P<0.05 vs WT.*

Measurement of Ca^{2+} Transients and Tension in Left Ventricular Papillary Muscles

We measured intracellular Ca^{2+} kinetics and contractile properties in aequorin-loaded papillary muscles in 2 mM $[Ca^{2+}]_o$. The peak amplitude of the Ca^{2+} transient was significantly increased in PS2KO mice compared to that in WT mice (***Fig. 1B***). Isometric tension measurements performed on the papillary muscles from PS2KO mice indicated an increase in peak tension per cross-sectional area compared to that from WT mice. The times to the peak of the Ca^{2+} transient and to peak isometric tension in PS2KO and WT mice were not noticeably different, nor were the decay times of the Ca^{2+} transient and the relaxation of isometric tension.

PS2KO hearts exhibited no change in expression of calcium regulatory proteins. The SR Ca^{2+} content, estimated by releasing Ca^{2+} with the addition of caffeine, showed no significant difference between PS2KO and WT. These data suggest that PS2 ablation accelerates Ca^{2+}

release from SR by modulating RyR2 activity.

PS2 Interacts with RyR2 and Sorcin *in vitro* and *in vivo*

Since a previous study demonstrated that PS2 in brain interacts with sorcin (***Ref. 2***), we tested whether PS2 also interacts with RyR2. Immunoprecipitation analysis showed that PS2, sorcin and RyR2 interact with each other in HEK-293 cells overexpressing these proteins and in mouse hearts and brain. Immuno–histochemistry of heart muscle indicated that PS2 co-localizes with RyR2 and sorcin at the Z-lines. These results indicate that PS2, RyR2 and sorcin co-localize and interact with each other *in vivo* as well as *in vitro*.

Effects of Ca^{2+} Concentration on Physical and Functional Interaction among PS2, RyR2 and Sorcin

An increase in intracellular Ca^{2+} concentration by treatment of cells with Ca^{2+} ionophore was found to enhance the sorcin/PS2 interaction. Therefore, we tested the effects of Ca^{2+} concentration on the interaction among PS2, RyR2 and sorcin. Elevation of Ca^{2+} from *p*Ca 7 to 5 resulted in a concentration-dependent decrease in the amount of PS2 which was immunoprecipitated with an antibody against RyR2, but in an increase in the amount of sorcin associated with RyR2 (***Fig. 1A***). PS2/sorcin interaction was enhanced by elevation of Ca^{2+} concen–tration as previously described. Finally, we examined the effect of extracellular Ca^{2+} concentration on the Ca^{2+} transient and tension. We found significant increases in peak Ca^{2+} transient and tension at 1 and 2 mM of $[Ca^{2+}]_o$ in PS2KO compared to those in WT mice, but not at 4 mM $[Ca^{2+}]_o$ (***Fig. 1B***).

Conclusions and Future Perspective

In this study, we demonstrated the interaction between PS2, RyR2 and sorcin. PS2 inhibits cardiac contractility by reducing the Ca^{2+} transient. Further studies will be necessary to elucidate the detailed molecular mechanism for the dynamic regulation of RyR2 activity by PS2; however, we propose the following hypothesis (***Fig. 2***): At low intracellular Ca^{2+} concentrations, PS2 interacts with RyR2. The inactivation of RyR2 by PS2 would prevent depletion of Ca^{2+} in the SR and maintain a high concentration of Ca^{2+} in its lumen. Upon depolarization of the sarcolemmal membrane, Ca^{2+} enters into the cells through the L-type Ca^{2+} channel. With the increase of Ca^{2+} concentration, PS2 dissociates from RyR2 and activates RyR2 to release a large amount of Ca^{2+} from the SR, leading to muscle contraction. At high Ca^{2+} concentrations, sorcin interacts with RyR2 to stop the Ca^{2+}-induced Ca^{2+} release by inhibiting RyR2 activity.

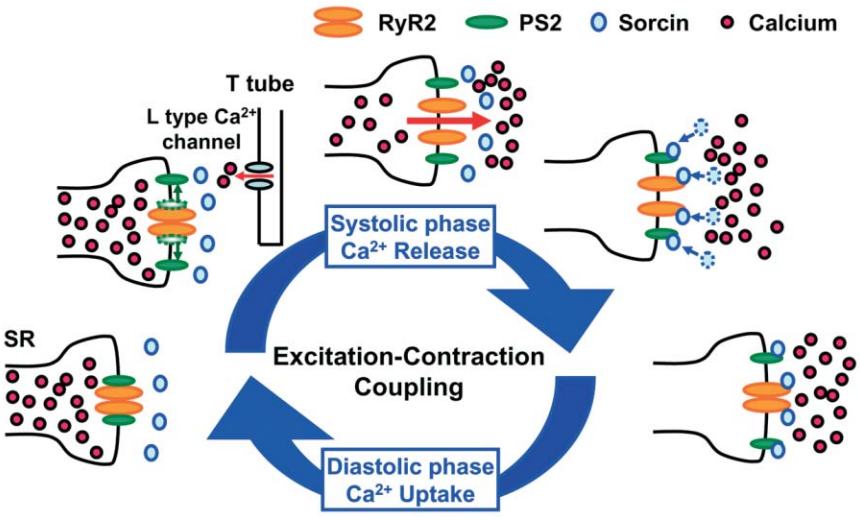


Figure 2. *Regulation of Excitation-Contraction coupling by PS2. At the end-diastolic phase (low Ca^{2+}), PS2 interacts with RyR2, while sorcin dissociates from PS2 and RyR2. PS2 may inhibit RyR2 activity to maintain a high Ca^{2+} concentration in the SR lumen. Upon depolarization of the sarcolemmal membrane, Ca^{2+} enters into the cells through the L-type Ca^{2+} channel. With the increase of Ca^{2+} concentration, PS2 dissociates from RyR2 and activates RyR2 to release a large amount of Ca^{2+} from the SR. At the end-systolic phase (high Ca^{2+}), sorcin interacts with RyR2 to stop the Ca^{2+}-induced Ca^{2+} release by inhibiting RyR2 activity.*

Toshihiro Takeda (Osaka, Japan) was the winner of the Young Investigator Award at the XXII Annual Meeting of the Japanese Section (Osaka, Japan; December 15-17, 2005).

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IN MEMORIAM

MICHIHIKO TADA
1938-2005

MICHIHIKO TADA, who died on August 5, 2005, was among the 20th-century's leaders in cardiovascular research. His scientific accomplishments centered on the dis–covery of phospholamban, its role in regulating calcium transport by the cardiac sarcoplasmic reticulum, the elucidation of its molecular structure, and the molecular mechanisms of its physio–logical actions. In addition, his studies of myosin, adenylyl cyclase, thromboxane, neutrophil function, myocardial protec–tion, and the gap junction made major contributions at the interface between biochemistry and clinical medicine.

Dr Tada was born on June 25, 1938, and received his M.D. in 1963 and his Ph.D. in 1968, both from Osaka University. His thesis work, carried out with Professor Yuji Tonomura, focused on the initial phases of the myosin ATPase reaction and mechanism of actomyosin super–precipitation. From 1968 to 1970, as a research fellow at the Institute for Muscle Disease in New York City, he examined the proteolytic fragments released from heavy meromyosin. It was there, in 1970, that I first met Michi when he visited my laboratory at the Mount Sinai School of Medicine. This visit began an extra–ordinarily productive collaboration that lasted four years. Michi's first project was to examine the interaction between calcium and cyclic AMP, then—and now—the two most important regulators of myocardial contractility. Together we decided that he should begin by examining the role of calcium in regulating adenylyl cyclase activity. Working virtually entirely on his own, using methods with which he had no prior experience, he carried out an elegant study of the effects of calcium on adenylyl cyclase and the sodium pump in the heart.[1] An unexpected consequence of this project was that it drew Michi's attention to the importance of cyclic AMP-dependent protein kinase in cellular regulation, which was to play a seminal role in his work on the cardiac sarcoplasmic reticulum.

In an effort to confirm reports that cyclic AMP stimulated calcium uptake by the cardiac sarcoplasmic reticulum, my colleague Doris Repke and I had been working to identify a significant effect of this second messenger on the calcium pump, but we had little success; although we occasionally observed minor stimu–lation, most of our findings were negative. Michi, with whom we shared our frus–tration regarding these inconclusive results, came up with the solution at the FASEB meeting in April 1971. I vividly recall the two of us walking through a tunnel connecting the buildings at McCormick Place in Chicago, when Michi turned to me and suggested that Doris and I were not seeing a consistent effect because our reaction mixtures lacked cyclic AMP-dependent protein kinase. My response was to ask: "What is a protein kinase?" After Michi explained, I suggested that he try to make some of this enzyme to see if he was correct. This led him to spend many weeks in the cold room working with beef heart extracts in an effort to purify this enzyme—my major contribution was to lend him an old, moth-eaten, but very warm sweater. Using histone as a substrate, Michi confirmed that his preparations were active, and early in 1972 we did our first experiment with the cardiac sarcoplasmic reticulum. In carrying out this work, in which we were joined by Madeleine Kirchberger, we chose not to begin in the most logical manner, which would have been to demonstrate that cardiac sarcoplasmic reticulum, like histone, is a substrate for Michi's enzyme—had we done so, we could have been scooped by three other groups that, unknown to us and to each another, were also working on this problem.[2] Because of our long experience studying cardiac sarcoplasmic reticulum, which at that time was very difficult to prepare and tricky to study, we chose instead to see if the calcium uptake reaction could be stimulated by cyclic AMP when we included the protein kinase that Michi had prepared. In carrying out this experiment, we followed advice I had received 15 years earlier when, as a research fellow, I was told by C.B. Anfinsen Jr. that the best way to find a regulatory effect was to "poise" the system. Accordingly, we carried out our first experiment at an ionized calcium concentration at which calcium uptake velocity was half-maximal, and found that transport velocity was doubled in the presence of cyclic AMP and the protein kinase. We subsequently learned that had we done this experiment at a saturating calcium concentration, as others were doing, we would have seen no effect because a major mechanism for the stimulatory effect is an increase in the calcium-sensitivity of the pump.

We had no difficulty replicating the positive result, which dramatically confirmed Michi's prescience, so that on May 8, 1972 we submitted our initial findings for publication as a rapid communication. To our surprise, this turned out to be more difficult than we had expected because, as is often the case, reviewers tend not to believe an important new finding. Our initial efforts to publish this finding in a prestigious journal that publishes early communications of new findings were unsuccessful, in part because neither of the two reviewers felt that stimulation of calcium uptake by cyclic AMP-dependent protein kinase was important; one reviewer wrote: "[this effect] seems to me a rather small

contribution." The other stated: "…how [this effect] relates to a possible enhancement of contractility is unclear." Accordingly, the first report of our finding was submitted to the *Journal of Molecular and Cellular Cardiology* and accepted on August 7, 1972,[3] and at a meeting held in Germany on October 18-20, 1972,[4] we presented a diagram suggesting mechanisms by which stimulation of calcium uptake by cyclic AMP-dependent protein kinase could explain the ability of β-adrenergic agonists both to abbreviate systole and to increase myocardial contractility.

The results of our initial experiments made clear what we would all be doing for the next few years. Michi, Doris, Madeleine, and I began by characterizing the substrate for Michi's protein kinase and defining the mechanism by which the calcium transport reaction was stimulated. Our results, which were published in 1974,[5-7] completed the initial phase of this work. It is amusing that the editors of the *Journal of Biological Chemistry* refused to allow us to give the regulatory protein a name, but instead insisted that this be referred to only as a "22,000-Dalton component of the cardiac sarcoplasmic reticulum." Although with my wife's help we had decided to name this protein phospholamban, we had no choice but to accept their decision. Of course, our name has been widely accepted, is included as a keyword in more than 1200 publications, and is even listed in some dictionaries.

In 1974, I offered Michi a faculty position in cardiology at Mount Sinai, but he decided instead to return to Japan where, after taking a year to complete his clinical training, he joined the faculty as an assistant professor in the First Department of Medicine at Osaka University Medical School. In 1980 he was promoted to associate professor in the Department of Medicine and Pathophysiology, and in 1984 to full professor. During this time he pursued his work on phospholamban and in 1980 published a landmark study of the effects of phospholamban phosphorylation on the transient state kinetics of the cardiac sarcoplasmic reticulum calcium pump.[8] He and his colleagues then purified phospholamban[9] and by 1985 had determined its structure first in canine[10] and then in human hearts.[11] This made it possible for Dr. Tada's group to characterize the molecular interactions between phospholamban and the calcium pump ATPase (SERCA2a) within the sarcoplasmic reticulum membrane bilayer.[12-16] These papers on phospholamban, which extend over a period of almost 30 years, represent a remarkable accomplishment. I can think of few modern scientists who, using a series of methods that advanced with the state-of-the-art, pursued a major problem and achieved such spectacular results, yet Dr. Tada's work on phospholamban is only a part of a lifetime of work that is published in 125 *peer-reviewed* articles.

Dr Tada was an active member of the Japanese Section of the International Society for Heart Research since its establishment in 1977, and from 1992 to 1998 was a member of the International Council of the ISHR. From 1984 to 2005 he served on the editorial board of the *Journal of Molecular and Cellular Cardiology* and was associate editor from 1990 to 1993. He was chairman of the Scientific Committee for the 14th World Congress of the ISHR held in Kobe in 1992, president of the 17th Meeting of the Japanese Section in 2000, and on the occasion of his 65th birthday was nominated as the Meritorious Member of the Japanese Section of the ISHR.

Throughout his lifetime as a scientist, Dr Tada made enormous contributions to our understanding of cardiac function in health and disease. Working at a time when the focus in cardiology was shifting from efforts to understand the mechanisms of disease to emphasis on technologic approaches to diagnosis and treatment, he remained a strong advocate of the importance of pathophysiology. Dr Tada's monumental productivity stands as a lasting tribute to the insight and efforts of this wise and effective clinical scientist.

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THE 2005 KEITH REIMER DISTINGUISHED LECTURE

REGULATORY MECHANISMS OF CA^{2+} SIGNALING IN INTACT MYOCARDIAL CELLS

HONORED SPEAKER:

MASAO ENDOH, M.D.

(DECEMBER 2005; OSAKA, JAPAN)

MASAO ENDOH graduated with an MD from Tohoku University School of Medicine in Japan in 1966 and received postgraduate training at the same institution. His postgraduate training was initially in surgery, but Dr Endoh's interest was soon drawn to cardiovascular pharmacology and his research effort has focused on this area since that time. Dr Endoh worked as a visiting scientist at the Sandoz Pharmaceutical Research Institute in Basel, Switzerland (1972-1973) and at the Institute of Pharmacology, University of Essen, Germany (1973-1975), before returning to Tohoku University School of Medicine, as an Associate Professor, in 1975. He remained at Tohoku (including a sabbatical at the Mayo Foundation, Rochester, Minnesota, USA, in 1983-1984) until his move to Yamagata in 1985. His position since September 1, 2005 is vice president of Yamagata University.

Dr Endoh has made key contributions to the understanding of the mechanisms that regulate cardiac contractile function, particularly in response to neurohormonal factors and pharmacological agents. In the course of his productive research career, Dr Endoh has developed and applied several innovative techniques to address specific questions. He developed a blood-perfused canine papillary muscle model, which allowed a detailed analysis of the force-frequency relationship, assessment of the effects of novel inotropic agents, and study of the autonomic control of cardiac contractility.

Dr Endoh's work has helped delineate the mechanisms underlying receptor-mediated regulation of myofilament calcium sensitivity, particularly in response to α_1-adrenoceptor stimulation, and the mechanisms of action of calcium sensitising drugs. He was one of the first to use the bioluminescent protein aequorin to monitor intracellular calcium in intact cardiac muscle, in order to study the roles of receptor-mediated mechanisms in the regulation of calcium mobilisation during excitation-contraction coupling. Dr Endoh was also one of the first to describe the inhibitory effects of pertussis toxin, then known as islet-activating protein, on myocardial responses to adenosine and muscarinic receptor stimulation. His more recent work has revealed novel cross-talk mechanisms in the regulation of cardiac contractile function, such as that between endothelin-1 and norepinephrine, and has explored the underlying signalling mechanisms, focusing on the roles of protein kinases and phosphatases.

Dr Endoh has published more than 220 papers, including over 175 original articles. He has served or continues to serve on the Editorial Boards of numerous national and international journals, including the *Journal of Cardiovascular Pharmacology*, *American Journal of Physiology*, *Circulation Research* and *Journal of Molecular and Cellular Cardiology*. In addition to being an active member of many professional organi–zations, Dr Endoh is a Founding Fellow of the ISHR, Fellow of the American Heart Association, and Fellow, Cardiovascular Section, of the American Physiological Society. ■

The Keith Reimer Distinguished Lecture

Each year, the International Council selects a speaker to deliver the Keith Reimer Distinguished Lecture at the World Congress or speaker's section meeting. The purpose of this lecture is to honor the memory of Dr Reimer and to recognize his contributions to cardio–vascular research. The topic of the lecture must be in the field of ischemia, coronary hemodynamics, cardiac metabolism, or contractile mechanisms. This award is funded by a generous contribution from Chugai-Pharmaceutical Co.

Previous honored speakers are:

- **Roberto Bolli**, *USA* (Madison, USA; 2002)
- **Gerd Heusch**, *Germany* (Strasbourg, France; 2003)
- **R. John Solaro**, *USA* (Brisbane, Australia; 2004)

ISHR MEETINGS CALENDAR

■ **August 4-7, 2006. XXX Annual Meeting of the Australasian Section,** in conjunction with the **Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand.** Canberra, Australia. **Inquiries:** Dr Lea Delbridge, Department of Physiology, University of Melbourne, VIC 3010, Australia. *Tel.* +61 3 8344 5853; *Fax* +61 3 8344 5897; *E-mail* lmd@unimelb.edu.au; *Website* http://www.csanz.edu.au/

■ **September 2-6, 2006. World Congress of Cardiology.** Barcelona, Spain. **Inquiries:** *E-mail* congress@escardio.org; *Website* www.worldcardio2006.org

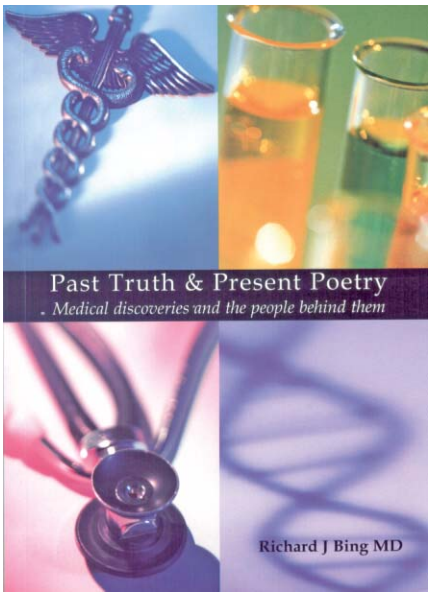
■ **November 12-15, 2006. Scientific Sessions of the American Heart Association.** Chicago, IL. **Inquiries:** *Website* www.americanheart.org

■ **December 1-2, 2006. XXIII Annual Meeting of the Japanese Section.** Chiba, Japan. **Inquiries:** Dr Toshiaki Sato, Department of Pharmacology, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. *Tel.* +81 43 226 2051; *Fax* +81 43 226 2052; *E-mail* 23ishr@graduate.chiba-u.jp; *Website* www.m.chiba-u.ac.jp/class/pharmacology/23ishr

■ **June 22-26, 2007. XIX World Congress of the ISHR.** Bologna, Italy. **Inquiries:** Dr R. Ferrari, Department of Cardiology, University Hospital of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. *E-mail* info@ishr-italy2007.org; *Website* www.ishr-italy2007.org

REVIEW
BOOKS BY RICHARD BING

RICHARD BING has discovered the secret of longevity and creativity. Though well over 90 by now, indeed approaching his 97th birthday, Richard has now published in book form a series of articles which appeared in *Heart News and Views.* Each article is focused on a



development of historical importance in the evolution of our concepts of modern research cardiology. This is the mind of a scholar, but also of a creative artist. He reminds us of the great discoveries of the past, of the great minds that worked in stringent conditions and of the great thoughts and hypotheses that came into being. With his multi-lingual background, he is able to bring to life many important texts written in German and not readily available to most English readers.

But this is not his only book. *Fifteen Lives and a Cat's Story* is a delightful collection of short stories, showing Richard's depth of human understanding. His *The Winds of Time and other stories* explores ultimate realities: is there a God, is there Good, is there a Satan? He takes the reader along each line of thought in such a way that one is simply compelled to read more.

In summary, Richard is a compelling, enchanting and creative writer. Add this to his capacities as the man who first described cardiac metabolism in humans, who explored congenital heart disease, who was intimately involved with the founding of our Society and became its first Life-President, who put the *Journal of Molecular and Cellular Cardiology* into high gear as Editor-in-Chief, and who has composed several major musical works, including a mass, and he is a challenge to all of us. I do not think we can come near to his accomplishments. Added to all of that, his newly disclosed writing skills come as a delightful surprise.

Past Truth & Present Poetry - Medical discoveries and the people behind them, by Richard J. Bing. *TFM Publishing Ltd, Harley (Nr Shrewsbury) UK*, 2006.
ISBN: 1 903378 44 3. US$ 35.

Fifteen Lives and a Cat's Story, by Richard J. Bing. *Xlibris Corporation, Philadelphia, USA*, 2004.
ISBN: 1 4134 5924 2 (Hardcover); 1 4134 5923 4 (Softcover).

The Winds of Time and other stories, by Richard J. Bing. *Xlibris Corporation, Philadelphia, USA*, 2005.
ISBN: 1 4134 9399 8 (Hardcover); 1 4134 9398 X (Softcover).

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CALL FOR NOMINATIONS

Nominations for the 2007 **Research Achievement Award** (deadline: December 2006), the **Peter Harris Distinguished Scientist Award** (deadline: January 2007), and the **Richard J. Bing Young Investigator Award** (deadline: January 2007) are now being accepted. Details can be found at www.ishrworld.org .

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