



HEART NEWS AND VIEWS

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THE International Society for Heart Research has had many members who have enriched society both by their scientific contributions and their personality. One of these was Albrecht Fleckenstein, an imaginative scientist, a remarkable human being and a colorful personality. Fleckenstein is best known for his work on the relationship between calcium and the heart which has led to one of the most important advances in cardiac therapy, the use of calcium antagonists (calcium blockers).

Albrecht Fleckenstein was born in Aschaffenburg, Germany in 1917 and died in Freiburg in 1992. He studied medicine in Würzburg and Vienna. After the war he studied in Heidelberg where he completed his *Habilitation* (appointment to an academic rank). Later he spent a year with Professor Burn in Oxford, England. In 1956 he was appointed Chairman of the Department of Physiology in Freiburg where he remained the rest of his life.

As Fleckenstein describes it, the discovery of calcium

Past Truth & Present Poetry



16. Albrecht Fleckenstein

calcium flux through the cellular membranes, an idea which was confirmed by voltage clamp technique. The fast transmembrane sodium transfer was not affected.

Fleckenstein also discovered the relationship of calcium to necrotization of the heart muscle by isoproterenol, a relation-

antagonists occurred by chance. In 1964 he was asked to look at two newly

synthesized coronary vasodilators with unexplained cardiodepressant effects. One of these compounds was verapamil. Fleckenstein soon found that these compounds inhibit cardiac excitation-contraction coupling: they diminish contractile force, while failing to change the action potential. In addition, they reduce calcium dependent ATPase. Later it was found that these compounds are antianginal, antiarrhythmic and antihypertensive.

At the onset there were few explanations of the negative inotropic effects until Fleckenstein and another member of our society, Winifred Nayler, proposed the idea that these compounds act by blocking

September 11, 2001

Recent events here in America have sent a collective chill through the entire civilized world. The objective of these terrorists is coax the west into a war that would destabilize the middle-east in such a way that the terrorist leaders might rise to a position of power after all the smoke clears. To achieve this self-serving goal they don't care how much western or Islamic blood they shed. Now the dogs of war have been unleashed and we are being propelled into an uncertain future. Another consequence has been a fear of flying unlike any that has ever occurred before. As I write this, airplanes are flying with mostly empty seats and many flight are canceled. Let's hope that our governments can quickly restore confidence in the air travel system and that our membership will continue to support the ISHR meetings. A primary mission of the ISHR is to bring together scientists of all cultures from around the globe. I pray that these disastrous events will only serve to further unite us as scientists and friends. After all, unity is the enemy of world terrorism.

James M. Downey, Ph.D.

ship also proposed by another member of our society, George Rona. The crucial event in the development of these lesions is lack of high-energy phosphates resulting from excessive activation of calcium-dependent ATPase. The calcium antagonists block the effect, preventing necrosis.

It is interesting to compare the chance discovery of calcium antagonists to that of other antihypertensive compounds. The rationale of methyldopa as an antihypertensive compound was based on a false premise. It was first thought that methyldopa acts by inhibition of decarboxylation of amino acids. We now know that methyldopa acts primarily centrally. Chlorothiazide was a “design discovery” by Karl Beyer and his team from Merck, who synthesized derivatives of sulfanilamide molecules that were also carbonic acid inhibitors. The discovery of beta-blockers goes back to J. W. Black in England who synthesized propranolol (Inderal), which fulfills the criteria of a beta-blocker. Angiotensin inhibitors owe their discovery to L.T. Skeggs who found that the conversion of angiotensin 1 to angiotensin 2 is the result of a converting enzyme, ACE. The pharmacological industry soon synthesized specific COX-2 inhibitors, which amongst other functions effectively lower blood pressure.

What sort of a man was Fleckenstein? He disliked pretense and his approach to science was original and refreshing because he went directly to the point. I remember that prior to my presidential address at the international meeting of the International Society for Heart Research in Freiburg, Germany in 1973, I was told that a group of students wanted to complain about the visiting Americans who, when visiting a local museum, supposedly had deposited cigarette ashes into containers which the medieval sculptor had intended for a different purpose. It was the time of global student unrest with rebellion against all authority. As I was coming to the end of my talk, the rebel students marched noisily into the auditorium, thirsting for blood. Before they could

ask embarrassing questions, I was saved first by a lady who obviously was not a scientist nor was she a member of our society. She inquired about the relationship between coronary disease and airplane flights, a question totally out of place. Albrecht Fleckenstein rose and answered her politely. He then silenced the rebel students who were never given a chance to complain.

Scientists come in all shapes and sizes, like ordinary human beings. David Goodstein (“Conduct and Misconduct in Science”, *Annals New York Academy of Sciences*, 1996; **775**: 31-36) describes the dual personality of scientists: “The fact is that scientists are usually rigorously honest about the things that really matter to them, such as accurate reporting of procedures and data. In other arenas, such as disputes over priority or credit, they tend to behave like the ordinary mortals they are. Furthermore, scientists are not dis-

interested truth seekers; they are more like players in an intense, winner-take-all competition for scientific prestige, or perhaps merchants in a no-holds-barred marketplace of ideas.”

Now when I take my calcium blocker in the morning, I think of Albrecht Fleckenstein. Who could forget him!

I appreciate the help of Prof. Dr Eberhard Bassenge and Dr Lionel Opie in the preparation of this manuscript.

Richard J. Bing, M.D. ■

On page 5 and 6 we continue publishing brief biosketches of the 82 Founding Fellows of the ISHR. For a complete list of the Founding Fellows, see *HEART NEWS AND VIEWS* 2001;9(1):8.

W. Glen Pyle (Chicago, IL, USA) was the winner of the Richard J. Bing Award for Young Investigators Competition, which was one of the highlights at the XVII World Congress of the International Society for Heart Research (Winnipeg, Canada; July 6-11, 2001). See page 7-9 for his report. The other three finalists of the competition were:

Koshiro Monzen (Tokyo, Japan): Smads, TAK1, and their common target ATF-2 play a critical role in cardiomyocyte differentiation;

Timothy D. O'Connell (San Francisco, CA, USA): 1 B/C-Adrenergic receptor double knockout mice have smaller hearts: A direct effect on myocyte hypertrophy during postnatal development;

Shi-Qiang Wang (Baltimore, MD, USA): Intermolecular signaling mechanisms of Ca²⁺-induced Ca²⁺ release in cardiac myocytes.

An extensive report on this highly successful Congress will be published in the next issue of *HEART NEWS AND VIEWS*. In following issues the winners of the Peter Harris Distinguished Scientist Award, the Research Achievement Award, the American Section Young Investigators Award and the European Section Young Investigators Award, the ISHR-ES / SERVIER Research Fellowship, as well as the new Honorary Members will be featured.

PRESIDENT'S LETTER



It's the science, stupid!

In Winnipeg the mantle was passed from David Hearse to myself. It was indeed an honor to return to Mobile aboard the stately elegance of ISHR-One. Not to be too pretentious the ISHR staff had cleverly disguised it by painting Northwest Airlines on its side and hiring a hundred strangers to ride along with me. I assumed that I could bask in the glory of David's tenure but already some weighty issues are confronting our Society. The first is our rather stagnant membership. At the last count we have around 2000 members world wide. The membership in the three big sections, North America, Japan and Europe have been hovering around 500 members each for several years. Compare those numbers to the almost 6000 members of the American Heart Association's new combined Council on Basic Cardiovascular Sciences. Our records for North America alone shows over 500 active scientists who were members but have let their dues lapse.

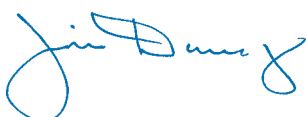
Last year Litsa Kranias and Michael Schneider did an in depth look into the reasons why our membership remains so small and what we might do to increase it. Basically they identified the problem as simply too few benefits from belonging to the Society. What does the ISHR actually do? Our official mission statement is to promote the discovery and dissemination of knowledge in the cardiovascular sciences on a world wide basis through publications, congresses and other media. That makes us essentially marketers of scientific information. We do this through ISHR sponsored meetings and our Journal, the JMCC. The latter is doing very well thanks to the capable editorship of Rick Walsh and before him Norman Alpert. Unfortunately, you don't have to be an ISHR member to read the JMCC. That brings us back to the meetings. That is our sole marketable product. Our hook is that members get a break on registration that more than covers the price of joining the Society. The one-year membership syndrome derives from the individual that attends a single meeting and does not return. If he doesn't return then there is no incentive to renew the membership. Litsa and Michael concluded that since meetings are our only product they have to be first class so members will return year after year.

Last year Pawan Singal made a passage to India to try to revive the Indian Section which had been suffering from some serious organizational problems. His mission was a resounding success and last winter a well attended meeting was held in Delhi. We have seven active sections, not counting the CIS (former Soviet Union) section which is currently on life-support due to severe economic problems in that part of the world. All of these sections hold an annual or biannual meeting. That essentially means there will always be an ISHR meeting coming soon to a location near you. This take-the-mountain-to-Mohamed approach is unique among the world's societies and in concept should be a winner. It only works, however, if the meetings are worth attending. Take for example the American Heart Association's Scientific Sessions. Every November forty thousand cardiac scientists migrate from all corners of the globe to attend this meeting. When Bill Clinton decided to run for president of the US a decade ago he asked himself what is the most burning issue. He allegedly said to himself: "It's the economy, stupid!" and that became his famous campaign slogan. So, why are scientists choosing to religiously attend the AHA meeting and not ours? The answer seems simple, "It's the science, stupid!" The Scientific Sessions have the best science on this planet and as a result people come.

The ISHR is a 100% volunteer organization. We do not have a single paid employee. Many scientists generously expend great effort to do the business of the Society. The real heroes among those volunteers are the meetings organizers. These people go out and raise huge sums of money and work long hours tending to the thousands of details involved in planning such a meeting. Unfortunately, many are organizing such a meeting for the first time. Also, no man can be conversant in all areas of cardiac science. While some ISHR meetings have been a resounding success, such as the extravaganza organized by Naranjan Dhalla in Winnipeg this summer, or last year's Louisville meeting, others have admittedly suffered from weak programs and last year the mother of all

disasters struck when the European section meeting actually had to be canceled.

In an attempt to improve the scientific quality of the section meetings we have constituted an international program committee. All of the members are seasoned scientific programmers. It is also diverse with members from all disciplines. The new committee will serve as a resource to the future section and world congress organizers to give aid and council in designing a program. The committee will be there from the conception of the meeting to give advice on what needs to be done and when. Most importantly they can help the organizer get the right people on the program talking about important and timely topics. This committee will even have the power to infuse cold cash into a sinking program if really needed. It is hoped that meetings organizers will take advantage of this important resource. When our only product is scientific meetings then we should do everything in our power to ensure that they include the best possible science. Only time will tell whether our efforts will have an impact on the quality of the future ISHR meetings or, more importantly, on the future membership.



James M. Downey

Liaison of the ISHR with the AHA

Over the past 3 years, I have spearheaded the development of a formal liaison between the ISHR and the Council on Basic Cardiovascular Sciences (BCVS) of the American Heart Association (the second largest Council of the AHA). This liaison was formally approved by both the International Council of the ISHR and the Executive Committee of the Council on BCVS at their meetings in November, 1999, in Atlanta, Georgia. By joining forces, the two Societies will create significant synergy and momentum, resulting in mutual benefits. This liaison will entail the following:

- (i) Joint sponsorship of scientific symposia and scientific conferences. This was inaugurated during the 22nd Annual Meeting of the ISHR-American Section in Louisville, Kentucky, which was co-sponsored by the BCVS. The XVIIth World Congress of the ISHR was also co-sponsored by the BCVS;
- (ii) Cross representation for the two Councils, whereby at least one ISHR representative attends the Executive Committee meetings of the BCVS and at least one BCVS representative participates in the ISHR Council meetings. This cross representation is presently even stronger, since several members of the BCVS Council (Drs Marbán, Hintze, Murphy, Hasenfuss, and Schneider) are also members of the ISHR Council;
- (iii) Each Society now has access to the entire membership database of the other Society. With over 4,500 members, the database of the BCVS will prove very invaluable for announcing meetings or other activities of the ISHR;
- (iv) The websites of the two Societies have been linked. Among other things, this will enable ISHR members to have instantaneous access to the membership database of the BCVS and vice versa;
- (v) Each Society will be allowed to advertise meetings or publish ads in the other Society's newsletter. An ad inviting BCVS members to join the ISHR has already been published in the BCVS newsletter.

It is apparent that this partnership will be mutually beneficial to both Societies. I look forward to strengthening the liaison with the BCVS and, hopefully, other cardiovascular societies as well.

Roberto Bolli, M.D.

Arnold M Katz

ISHR member since 1969. International Advisory Comm. 1976-92; President, Amer. Section 1986-88. JMCC Assoc. Editor 1979-86; Editor-in-Chief 1986-92. *Current position:* Professor of Medicine Emeritus, Univ. Conn.; Visiting Professor of Medicine, Dartmouth Med. School.

Training: Univ. Chicago (BA), Harvard (MD), Mass. General Hosp. NIH, Nat. Heart Hosp. (London).

Research emphasis: Calcium, cardiac contractile proteins & sarcoplasmic reticulum, heart failure.

Major research contributions: *J Biol Chem* 1959; **234**: 2897-2900 (Science Citation "Classic"); *J Biol Chem* 1964; **239**: 3304-3311; *J Biol Chem* 1974; **249**: 6174-6180; *N Engl J Med* 1990; **322**: 100-110.

Single-authored books: Physiology of the Heart (3 editions, latest in 2001), Heart Failure: Pathophysiology, Molecular Biology, Clinical Management (2000).

Most admired scientists: Louis N. Katz, Paul Wood.

Relaxation: Springer spaniels; bucking, splitting, stacking wood.

Favorite dish: Everything cooked by Phyllis, especially curries.

Favorite author: J.R.R. Tolkien.

Favorite composer: W.A. Mozart.



Litsa Kranias

Member of ISHR/American Section Council: 1997-2003. Member of ISHR Council: 1998-2004. *Current post:* Professor and Director of Cardiovascular Biology, Department of Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine, Cincinnati, OH.

Trained: University of Chicago and Northwestern University in Chicago, IL
Qualifications: BA, MS, PhD, FISHR, FAHA.

Research emphasis: Regulatory mechanisms and signaling pathways in calcium homeostasis, contractility, and remodeling of the mammalian heart.

Major research contribution: Defining phospholamban as a major regulator of basal myocardial contractility and a key determinant of the heart's responses to beta-agonists, using genetically altered models.

Publications: Over 150 research papers.

Most cited article: Targeted ablation of the phospholamban gene is associated with markedly enhanced myocardial contractility and loss of β -agonist stimulation. *Circ Res* 1994; **75**: 401-409.

Most admired scientist: Ketty Schwartz.

Relaxation: Classical music; reading mystery novels; swimming in Greek beaches; shopping.



Michihiko Tada

ISHR member since 1973. Member of ISHR Council since 1980. Secretary General ISHR Jap. Section 1995-96. Chairman Programme Comm. XIV ISHR World Congress, 1992, Kobe. President, 17th Annual Meeting of ISHR Jap. Section, 2000, Osaka.

Current post: Professor and Chairman, Dept. of Medicine and Pathophysiol., Osaka Univ. Med. School, Osaka, Japan.

Trained: Osaka Univ. Med. School and Graduate School of Med.; Dept. of Biol., Osaka Univ. Fac. of Science; Inst. of Muscle Disease and Mount Sinai School of Med., New York. *Qualifications:* MD, PhD (Osaka University), FACC.

Research emphasis: Molecular biological aspects of calcium cycling proteins in cardiomyocytes; Mechanisms of preconditioning in myocardial ischemia-reperfusion.

Major research contribution: Establishing and defining the role of phospholamban (PLN), which functions to control Ca pump ATPase (SERCA2) of cardiac sarcoplasmic reticulum.

Publications: Six books and over 300 refereed papers.

Most cited paper (SCI): *J Biol Chem* 1975; **250**: 2640-2647.

Most admired scientist: Yuji Tonomura.

Relaxation: Seeing operas and playing golf.

Favorite dishes: Shabu-shabu and sukiyaki; *composer:* Felix Mendelssohn; *painter:* Johannes Vermeer; *authors:* Yasunari Kawabata and John Steinbeck.



Gerd Heusch

ISHR member since 1991. Member of ISHR International Council since 1995. President Elect of the European Section.

Current position: Professor and Chairman, Department of Pathophysiology, University of Essen Medical School, Germany.

Training: Universities of Düsseldorf and Bonn, MD; University of Düsseldorf, PhD; research cardiologist, UCSF.

Qualifications: MD, PhD, MD (hon), FESC, FACC, FISHR. *Research interests:* Coronary blood flow, myocardial ischemia/reperfusion, sympathetic nervous system, heart failure.

Major research contribution: Characterization of α -adrenergic coronary vasoconstriction and its role in myocardial ischemia in animals and man; characterization of short-term hibernation.

Publications: 7 books, more than 130 original peer-reviewed papers, more than 80 review articles.

Representative publications: α -Adrenergic coronary vasoconstriction and myocardial ischemia in humans. *Circulation* 2000; **101**: 689-694; Hibernating myocardium. *Physiol Rev* 1998; **78**: 1055-1085.

Most admired scientist: John Ross Jr.

Relaxation: Family, jogging, reading.



Howard E. Morgan

ISHR member since 1973. Member of ISHR Council 1976-1989; President ISHR 1983-1989; Peter Harris Award, ISHR, 1995.

Current Position: Evan Pugh Professor of Physiology, Emeritus, Pennsylvania State University, Winfield, PA.

Trained: Johns Hopkins, Vanderbilt University and Cambridge University.

Qualifications: MD, DSc (Hon), FACC, FISHR

Research interests: Regulation of glucose, glycogen, and protein metabolism by hormones, increased work of the heart, anoxia and ischemia. Early studies focused on glucose transport and phosphorylation and the regulation of phosphorylase b activity. Developed the isolated working rat heart preparation to study cardiac work in vitro. In regard to protein metabolism research centered on unraveling the intracellular signaling systems responsible for accelerated growth and hypertrophy of cardiac muscle cells.

Publications: Two texts, 250 research publications, 3 named as "Citation Classics" by Current Contents.

Positions in scientific organizations: President, American Heart Association (1987-88), American Physiological Society (1985-86), Cardiac Muscle Society (1976-77) and Association of Physiology Chairmen (1975-76). Member, Institute of Medicine, National Academy of Science (1987).



Heinz-Gerd Zimmer

ISHR member since 1973. In the past, member of the Board of the German Cardiac Soc., Council Member of the ISHR (Internat. and Eur. Section), member of the Executive Scientific Comm. of the Eur. Soc. of Cardiol. (ESC) as representative of the ISHR Eur. Section, Chairman of the ESC Working Group "Pathophysiology of the Cardiac Myocyte" (1982-86). Since 1999 member of the committee for exp. cardiol. of the German Cardiac Soc. Fraenkel Award of the German Cardiac Soc., 1977.

Position: Professor and Chairman of Physiol., Director of the Carl-Ludwig-Inst. of Physiol., Univ. of Leipzig, Germany. *Training:* MD, University of Marburg, Germany; *Habilitation,* Ludwig-Maximilians-University Munich, Germany.

Research interests: Cardiac adenine nucleotide and protein metabolism, evaluation of cardiovascular function in small laboratory animals by heart catheterization, metabolic support of the heart (ribose), molecular biological effects of catecholamines on the heart, extracellular matrix and remodeling.

Publications: See PubMed and <http://webmed.zmai.uni-leipzig.de/~cliphys/>

Most admired scientists: Carl Ludwig, Albrecht Fleckenstein.

Other interests: History of physiology and medicine, German literature of the 19th century, piano music, skiing.



James M. Downey

ISHR member since 1983. North American Section Council 1988-97, Internat. Council since 1994, currently President ISHR.

Current post: Professor of Medical Physiol., Univ. of South Alabama, Mobile Alabama, USA.

Trained: Manchester Coll., Indiana; PhD: Univ. of Illinois; Post Doctoral: Harvard Med. School.

Research emphasis: My research began with an engineering approach to the interaction between mechanical forces in the heart wall and coronary flow which led to the "Waterfall" hypothesis of that interaction. I eventually concluded that it would not be clinically feasible to augment flow to ischemic tissue using this approach so my interest turned to preservation of the ischemic myocardium. I first explored antioxidants but soon became interested in the ischemic preconditioning phenomenon. Our studies revealed that signal transduction pathways such as adenosine receptors and PKC can markedly protect the heart.

Publications: Over 200 refereed articles and over 40 book chapters. Most cited article: *Circulation* 1991; **84**:350-356.

Positions in scientific organizations: NIH Cardiovasc. and Renal Study Section 1989-93 and 1998-2000. Amer. Physiol. Soc. Governance Comm. 1985-91, elected to APS Circulation Group 1976, AHA Circulation Council Exec. Comm. 1993-97.

Relaxation: Restoring antique motorcycles and saltwater fishing.



Kenneth D. Philipson

Current positions: Professor of Physiology and Medicine, Chair of the Department of Physiology, Associate Director of the Cardiovascular Research Laboratories - UCLA School of Medicine.

Training: BS, University of Chicago; PhD, University of California, Berkeley.

Research interests: Structure and function of calcium transport proteins, transport of calcium across myocardial membranes, excitation-contraction coupling, Na/Ca exchange.

Major research contributions: Molecular, functional, and physiological studies on the cardiac sarcolemmal Na/Ca exchanger; determination of many basic functional properties of the exchanger using isolated sarcolemmal vesicles; cloning and expression of each of the three known mammalian Na/Ca exchangers; determination of molecular regulatory mechanisms of the exchanger; structure/function studies on the transport properties of the exchanger; generation of mice with genetically altered levels of the Na/Ca exchanger. All with the help of many talented colleagues.

Most cited article: Molecular cloning and functional expression of the cardiac sarcolemmal Na⁺-Ca²⁺ exchanger. *Science* 1990; **250**: 562-565.

Relaxation: Playing golf at ISHR meetings, trying to beat my son at chess.



Downregulation of Actin Capping Protein: Anchors Aweigh for PKC?

Beginning under the ‘scope. Like so many scientists, my interest in basic research was sparked by laboratory work I was involved with as an undergraduate student. Typically, student volunteers carry out relatively safe and menial tasks, making solutions and running standard assays. I, however, was not the typical student. Instead of volunteering to do research, I volunteered to be researched. My experience as a scientific subject ranged from a psychological experiment in my first year, to crashing into walls in my third year in an effort to understand how shoe inserts cushion the impact, to skeletal muscle biopsies in my fourth year. Seeing science from both sides of the microscope was the catalyst for my career in biomedical research.

After graduating with a bachelor of science degree in human kinetics from the University of Guelph, I was accepted into the doctoral programme at the University of Tennessee. It was there, while working under the guidance of Dr Polly Hofmann, that I developed an interest in muscle mechanics and how intracellular signaling molecules regulate cardiac function. As part of my doctoral thesis I investigated how protein kinase C (PKC) was involved in κ -opioid receptor-dependent protection of heart muscle. In a series of experiments that made up the core of my thesis, we developed a model of “preconditioning” in which a PKC-dependent reduction in ATP consumption by the myofilaments attenuates ischaemic damage in the heart.

In December of 1999 I joined the laboratory of Dr John Solaro at the University of Illinois (Chicago) as a post-doctoral research associate. Initially it was my intention to focus on how the PKC-dependent phosphorylation of troponin I influences cardiac function. However, I quickly became interested in a transgenic mouse model that had recently been provided to us by collaborators at Washington University in St. Louis. This transgenic mouse, developed by Marilyn Hart (now at Minnesota State University) and John Cooper, had a

10% reduction in the sarcomeric actin capping protein. Hart and Cooper had actually generated three transgenic lines, two of which had much more severe reductions in the sarcomeric actin capping protein, but only mice with the more modest reduction survived more than 30 days.

Actin Capping Protein 101: An Introduction

In cardiac muscle, actin filaments are anchored at the Z-disc by the actin capping protein. Actin capping protein is a heterodimer composed of an α - and β -subunit. The actin capping protein β -subunit isoforms display subcellular specific expression patterns in cardiac myocytes: actin capping protein comprised of the β_1 -subunit is confined to the Z-disc (hence the name “CapZ”), whereas β_2 -subunit containing actin capping protein localizes to the intercalated disc and cell periphery. These two populations of actin capping protein cannot substitute for each other *in vivo*. Hart and Cooper found that by overexpressing the β_2 -subunit in the heart, the amount of capping protein containing the β_1 -subunit decreased proportionately. Thus, they produced transgenic mice deficient in CapZ by overexpressing the β_2 -subunit.

In 1999 Hart and Cooper published



W. Glen Pyle, Ph.D.

their work with the CapZ transgenic mice in the *Journal of Cell Biology*. They described how the downregulation of CapZ disrupted sarcomeric architecture in the two most severely affected transgenic lines. Their major findings were that the downregulation of CapZ in mouse hearts produced a gross myofibrillar disarray and hypertrophic cardiomyopathy that was 100% within 26 days post natal.

Prior to the start of my post-doctoral appointment, Cooper and Hart sent several of their remaining transgenic mice to the Solaro lab, with the intention of having the functional phenotype of the surviving transgenic line characterized. Preliminary work had shown that the gross myofibrillar disarray that typified the now defunct lines was not present with the 10% reduction in CapZ. Moreover, there was no difference in mortality rates between the cardiac CapZ transgenic and wild-type mice. As such, it was expected that there would be no significant functional deficiencies associated with the 10% downregulation of cardiac CapZ.

CapZ on the Side

By September of 2000, my project investigating the PKC-dependent regulation of myocardial function through troponin I phosphorylation was well underway. Like most post-doctoral fellows, I wanted to diversify my work in the lab, and began to look for a secondary project. Working with the CapZ transgenic mice offered a rather unique opportunity: to our knowledge, no one had examined the functional impact of

this protein in the heart. In fact, very little was known about CapZ beyond its ability to cap and anchor actin filaments in a variety of cell types. This provided me with the opportunity to investigate an area of cardiac physiology that was relatively unexplored.

The initial proposal was rather straight forward: using an experimental set-up in Dr Pieter de Tombe's laboratory at the University of Illinois, I would examine how the downregulation of cardiac CapZ altered myocardial mechanics and energetics. As I carried out these experiments I began to read what I could about CapZ in an effort to develop a more long term study. My review of the literature revealed how little is known about not only CapZ, but other Z-disc proteins as well. Despite its well known importance in the generation and propagation of force in muscle cells, Z-discs have been largely overlooked in the examination of muscle cell physiology.

CapZ as the missing link?

Information gathered from the literature, combined with what I had learned in the construction of my doctoral thesis, lead me to hypothesize that CapZ played a role in intracellular signaling. Several studies have shown that a variety of signaling molecules congregate at or near cardiac Z-discs, possibly forming signaling scaffolds. One of the more well characterized signaling pathways thought to involve interaction with the Z-discs is PKC. While some PKC isoforms have been shown to translocate to an area near cardiac Z-discs upon activation, exactly how PKC is fixed there is unknown. Work by Dr Daria Mochley-Rosen and others indicates that PKC is anchored in various subcellular compartments through isoform specific binding proteins, termed receptors for activated C-kinase (RACK). It is thought that the anchoring of signaling molecules near their target substrates facilitates interaction and modification of the target protein. Because CapZ is found in an area known to anchor activated PKC, I hypothesized that the capping protein either fixes or

aides in the anchoring of activated PKC isoforms at cardiac Z-discs.

The initial series of experiments designed to examine the impact of CapZ downregulation on myocardial function revealed that this modification increased myofilament calcium sensitivity. Although controversial, some previous studies have shown that certain PKC isoforms decrease myofilament calcium sensitivity. Thus, one explanation for these results could be that intracellular PKC signaling is disrupted in the CapZ transgenic mice, allowing for increased myofilament calcium sensitivity that would normally be depressed. While these results were interesting and could be explained by the proposed hypothesis, clearly more convincing evidence was required.

A more direct test of the hypothesis would be to examine how the transgenic hearts responded to PKC activation. If the hypothesis were correct and CapZ was in fact involved in PKC signaling, then myocardium deficient in CapZ would have a reduced response to PKC activation. Therefore, I treated cardiac muscle with agonists known to activate PKC-coupled membrane receptors. In wild-type muscle fibers, I found that these agonists (endothelin and phenylephrine) both decreased active tension and actomyosin MgATPase activity. By contrast, transgenic cardiac muscle fibers with downregulated CapZ did not respond at all to either agonist. While I was happy to see my hypothesis supported with experimental evidence, I was surprised to observe the *complete* blockade of myofilament regulation by PKC with only a 10% reduction in CapZ.

With evidence in support of the hypothesis, I refined my ideas and generated a model to explain how CapZ may be involved in PKC signaling. Given the total abolition of PKC-dependent control of myofilament activation already noted, I suggested that CapZ served as a PKC anchoring protein in addition to its role in maintaining normal sarcomeric architecture. The downregulation of CapZ would, according to this model,

prevent PKC-dependent control of cardiac myofilaments by precluding the anchoring of activated PKC isoforms to the Z-discs. To test this hypothesis, I again treated wild-type and transgenic myocardium with endothelin and phenylephrine and investigated how the various PKC isoforms present in the mouse heart responded to these agonists. Specifically, I was interested in how the reduction in cardiac CapZ affected PKC interaction with the myofilaments. According to my hypothesis, I expected that PKC would not interact with myofilaments deficient in CapZ, and that the increase in myofilament-associated PKC following receptor stimulation would be absent. Alas, this was much too simple. First, PKC- ϵ was able to associate with cardiac myofilaments even with the downregulation of cardiac CapZ. In fact, the amount of PKC- ϵ associated with the myofilament fraction prior to the application of receptor agonists appeared to be similar in wild-type and transgenic hearts. To further complicate matters, I found that whereas myofilament associated PKC- ϵ was increased following the application of endothelin or phenylephrine to wild-type cardiac muscle, PKC- ϵ associated with transgenic myofilaments actually decreased with the same treatment. Clearly these results did not fit neatly into my hypothetical model.

I spent the next few days pondering what I had found, trying to make sense of all the data. The most pressing and confusing question was, "why was the PKC- ϵ 'disappearing' from the transgenic myofibrils?" Still unable to decipher these results, I returned to the lab the following Monday and began to investigate the effects of CapZ downregulation on the other PKC isoforms. It was here, in results that I originally thought would be rather uninteresting, that I found a potential answer to my question. Immunoblot analysis revealed that some PKC-isoforms, namely PKC- δ and PKC- α , that in wild-type myocardium did not translocate to the myofilaments upon activation, did just that in transgenic myocardium. These new

findings allowed for the proposal of a revised hypothetical model. In this model I suggested that CapZ is still an important intermediary in the anchoring of activated PKC to cardiac Z-discs. When CapZ is present, activated PKC- ϵ strongly binds to the proteins of the Z-disc, possibly through direct interaction with CapZ. In transgenic myocardium deficient in CapZ, PKC- ϵ may still bind to cardiac Z-discs, but this interaction is weakened by the absence of the capping protein. The altered make-up of the Z-disc provides a binding site for PKC- α or - δ , which are normally not associated in significant amounts with the Z-disc. The stronger interaction between cardiac Z-discs and PKC- α or - δ allows these isoforms to bind and displace PKC- ϵ . But if these other isoforms can anchor near the myofilaments, why don't they modify myofilament activation? Although untested, I proposed two possible explanations. First, PKC isoforms interact with specific substrates. Thus, it is possible that PKC- α and - δ simply do not phosphorylate myofilament proteins. Previous studies have shown that these two PKC isoforms can phosphorylate myofilament proteins *in vitro*, but to date no work has repeated these findings *in vivo*. The second possibility is similar in that it too suggests that these isoforms are unable to phosphorylate myofilament proteins. However, instead of suggesting that PKC- α and - δ do not have

target substrates in the myofilaments, I hypothesize that their binding to cardiac Z-discs holds them in a conformation that does not allow for efficient interaction with their myofibrillar targets. Therefore, one hypothesis says that these isoforms can not regulate myofilament function and the other suggests that the anchoring of these isoforms in the absence of CapZ does not provide the optimal environment.

To Cap it all off

In July of 2001 I presented these findings at the XVIIth World Congress of the International Society for Heart Research as part of the Richard J. Bing Young Investigator's competition. I was one of four finalists selected to present their work on the first day of the meeting. The early presentation time was welcome as it allowed me to complete my work and concentrate on the outstanding science that was presented in the following days. While this was an excellent theory, it wasn't quite perfect. Although the presentations were over by early Saturday morning, the announcement of the winner was not made until several days later at the awards banquet. This allowed me plenty of time to go over (and over) my presentation. Did I make my points clear? Were the judges satisfied with my answers? Should I have added or removed some slides? These were all thoughts that crept into my head as I tried to concen-

trate on the meeting. By the time the awards banquet rolled around I was just glad to have a final decision made. The results were announced starting with the runners-up and ending with the winner. Having a keen sense of the obvious, I realised that when the first runner-up was announced and I was the only one of the competitors not on the stage, that I had won! Actually, it was that and the fact that my wife Frances, who was sitting next to me at our table, excitedly hugged me and said, "You won!".

While I am honoured to have received this award, I think it reflects the efforts of a much larger group of people than just myself. First and foremost in this group are my advisors, past and present. Drs Polly Hofmann, Pieter de Tombe, and John Solaro, who have all provided the perfect balance of instruction and independence. My colleagues in the Solaro and de Tombe labs, whose expertise in a wide range of fields is invaluable and whose personalities make work enjoyable. The American Heart Association, from whom I have received a post-doctoral fellowship. And finally, and most importantly, my wife Frances Roesch. Her support and encouragement are rivaled by none, and for that I am blessed.

W. Glen Pyle, Ph.D.
Chicago, IL, USA

Report on the Australasian Section Meeting (September 2-4, 2001; Brisbane)

The Australasian Section held its annual meeting this September in Brisbane, Australia. The aim of the meeting was to generate discussion on appropriate experimental models for cardiovascular research and this aim was fulfilled! There were 85 attendees who enjoyed the bucolic setting of The

Bardon Conference Center in the foothills of Mount Coot-Tha overlooking the city of Brisbane. The format was 2 1/2 days of plenary sessions. International guests included David Hearse *UK*, Jim Downey *USA*, Ed Lakatta *USA*, Anne-Marie Seymour *UK*, Joachim Herzig *South Africa*, Ted Kurtz *USA*, Michal Pravanec *Czech Republic*, Qingbo Xu *UK*, Dimitri Scholz *Germany*, Thomas Eschenhagen *Germany*, Bruce Smaill *New Zealand*, Alberto Kaumann *UK* and Teruhiyo Toyo-Oka *Japan*. The standard of the presenta-

tions was superb with Powerpoint a clear winner over slides presentations. The Winifred Nayler Prize for best student presentation was won jointly by Amanda Flood and Vincent Chan for their studies on adenosine responses in ischaemia-reperfusion and the ageing SHR as a model of human heart failure, respectively.

Except for one downpour on Saturday night which drenched the speakers' dinner (and several of the speakers), the weather was perfect with temperatures in the low 20's and sunny

skies. A highlight of the meeting was a dinner/debate on the subject: "The human is a poor model of experimental cardiovascular disease". At debate time, the members of the two teams were still trying to work out exactly what they were debating. The pro team consisted of Ed Lakatta, Ted Kurtz and Stephen Harrap while the con team boasted the talents of Alberto Kaumann, Thomas Eschenhagen and Robert Di Nicolantonio. To help limber the tongues of the two teams, the chairman, David Hearse, uncorked a bottle of Australian bubbly and requested that each debater drain a glass prior to speaking. Timing was strictly but delicately enforced with the aid of a bull horn. The world has already forgotten what was said at the debate but what was done will live in the annals of ISHR frivolity for years to come.

Another interesting social aspect of the program was a late afternoon walk up the mountain to Slaughter Falls. This was listed in the program simply as Researchers to the Slaughter. There, refreshments awaited us while we watched parrots, cockatoos and kookaburras frolic in the trees. Slaughter Falls by the way was only a dry creek bed since this is the drier time of the year in Brisbane so spirits were the only thing flowing. The following night found the conferees at King's College at the University of Queensland for a tasty dinner and a slice of Australian college life. Thanks go out to Lindsay Brown and



Conferees enjoy coffee between sessions on the terrace of the Bardon Conference Center

his organizing team for a job well done "down under".

Brisbane is the chosen site for the 2004 World congress and it is an ideal venue. The city is a clean, modern and prosperous city of over a million people on Australia's east coast. The city abounds with recreational infrastructure including the expansive Southbank facility where the congress will be held, the downtown botanical gardens and Eagle Street pier. Brisbane is situated on the head of a large bay with a river winding through downtown. A casino in a beautiful colonial style building dominates the downtown riverfront. The city runs a fleet of inexpensive launches,

the CityCats, allowing you get around the city by water in lieu of the bus. In addition, Brisbane is the gateway to spectacular Australian scenery such as the well-known beaches and the Great Barrier Reef. Much to the chagrin of Australians traveling overseas, the Australian dollar at the time of this writing is very weak against most currencies. However, this makes Brisbane a real bargain for international visitors. We all are looking forward to a stimulating congress in 2004.

*James M. Downey, Ph.D.
Mobile, AL, USA* ■

Dear Colleagues and Friends,

About eight months before the XXII European Section Meeting of the ISHR, which will be held from 3 to 6 July, 2002 in Szeged, Hungary, I felt it would be a good idea to report to you about the current status of the organization. Let us start with the principles and aims that were settled by the Council of the ISHR-ES and by the local organizers.

Our primary aim is to have a good



meeting both scientifically and socially! Of course, to reach such an aim requires your help and cooperation; thus, we

would like to have all of you here in Szeged! Of course, we are conscious that we need to attract you by offering outstanding science and a good social programme at low cost. We are also aware that there is a strong competition between meetings. Using the example of Mozart, when once he was asked to show one of his scores to an amateur music lover. Seeing the score this person exploded "there are too many notes!" We can certainly say that "there

ISHR MEETINGS CALENDAR

- February 1-3, 2002. **Annual Conference of the Indian Section.** Kerala, India. **Enquiries:** Dr C.C. Kartha, Division of Cellular and Molecular Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram - 695011, India. *Tel.* +91 0471 524608; *Fax* +91 0471 446433; *E-mail* cckartha@sctimst.ac.in
- June 30 - July 2, 2002. **The Failing Heart: From molecular mechanisms to clinical applications - Satellite Symposium of the XXII Meeting of the European Section.** Stara Lesna, The High Tatras, Slovak Republic. **Enquiries:** Dr T. Ravingerova, Institute for Heart Research, Slovak Academy of Sciences, Dubravska cesta 9, 84233 Bratislava, Slovak Republic. *Tel.* +4217 5477 4405; *Fax* +4217 5477 6637; *E-mail* usrdravi@savba.sk; *Website* <http://nic.savba.sk/sav/inst/usrd/usrdconfer>
- July 3-6, 2002. **XXII Meeting of the European Section.** Szeged, Hungary. **Enquiries:** Dr A. Végh, Department of Pharmacology and Pharmacotherapy, University of Szeged, Faculty of Medicine, Dóm tér 12, H-6720, Szeged, Hungary. *Tel.* +36 62 545 673; *Fax* +36 62 544 565; *E-mail* vegh@freemail.hu; *Website* www.cardiovasc.com/ishr2002
- July 24-27, 2002. **Translational Approaches to Cardiovascular Disease - XXIV Annual Meeting of the American Section.** Madison, Wisconsin. **Enquiries:** Dr R.L. Moss, UW Cardiovascular Research Center, Department of Physiology. *Tel.* +1 608 262 1939; *Fax* +1 608 265 5072; *E-mail* rlmoss@physiology.wisc.edu; *Website* www.ishr2002conf.org/
- November 4-9, 2002. **Meeting of the Chinese Section.** Guangzhou, China. **Enquiries:** Dr X.Y. Yu, Guangdong Provincial Cardiovascular Institute, 96 Dongchuan Road, Guangzhou 510080, China. *Fax* +8620 8387 5453; *E-mail* xiyongyu@yahoo.com
- November 17-20, 2002. **Scientific Sessions of the American Heart Association.** Chicago, IL, USA. **Enquiries:** American Heart Association, Meetings and Councils, 7272 Greenville Avenue, Dallas, TX 75231. *Tel.* +1 214 706 1543; *Fax* +1 214 373 3406; *E-mail* scientificconferences@amhrt.org
- August 7-11, 2004. **XVIII World Congress of the International Society for Heart Research.** Brisbane, Australia. **Enquiries:** ISHR 2004 Congress, PO Box 164, Fortitude Valley QLD 4006, Australia. *Tel.* +61 7 3854 1611; *Fax* +61 7 3854 1507; *E-mail* heart2004@ozaccomm.com.au; *Website* www.baker.edu.au/ISHR

are too many meetings!" But ISHR meetings are something special; for many years they have provided an opportunity to meet with old friends and discuss science in an informal atmosphere. Now we want to meet these old friends again and especially we would like to involve our younger colleagues in the life of our Section.

We have prepared a draft scientific programme which includes six plenary lectures given by eminent scientists on various topics of cardiovascular research. There will also be 18 symposia during the four days of the meeting. Here I would like to take the opportunity to express my thanks to all of our symposia organizers who have helped us over the last few months, not only by putting together a fascinating scientific programme but by making every effort to provide financial support for their invited speakers. At each symposium there will be a short introductory lecture

given by one of the chairmen, two keynote lectures by the invited speakers and a summary lecture by the other chairman. However, and this is probably the most important facet of the programme, four abstracts will be selected for oral presentation and included in the programme for each of the symposia. This will allow our younger colleagues to present their work orally before experts in the field. But do not be upset if you are not selected for oral presentation! The poster section will be an even greater challenge than the oral one! We plan to invite outstanding scientists to lead the poster sections and ask several questions on your work. We believe such discussion to be the best and most profitable for those who are at the beginning of their careers.

We also plan to provide you with a good social programme. The weather in July in Szeged is pretty hot (around 30°C). The swimming pool is just oppo-

site the congress venue, so do not forget to bring your bathing costume. Also, tennis courts are available next door to the meeting venue. The official social programme includes a half day excursion to Opusztaszer (approximately 30 km from Szeged). This is an open air historical museum - with many facilities for good social gathering.

So please continue to support your Society by coming to this relaxed city, described in the Michelin guide as a 'little Paris'; without you the meeting will be less successful than it might otherwise be. See you there!

You can find further information at our website: www.cardiovasc.com/ishr2002.

Agnes Végh, Ph.D.
Szeged, Hungary

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HEART NEWS AND VIEWS

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