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Integrating the Life Sciences from Molecule to Organism

The Physiologist

INSIDE

21st Century Physiology: Organisms as Integrated Systems

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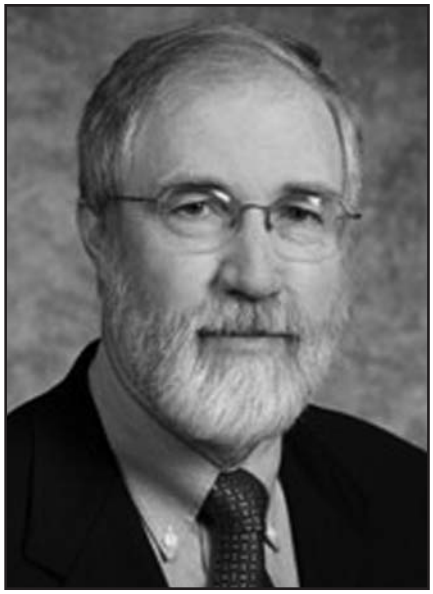

James P. Collins

"What role does life play in the metabolism of planet Earth?" asks a 2007 National Academy of Sciences (NAS) report *The Role of Theory in Advancing 21st Century Biology: Catalyzing Transformative Research*, which goes on to note: "Metabolic pathways, which are the means by which organisms acquire the energy and material components they need to survive and reproduce, have a profound global impact."

Physiology is often linked with the study of the human body, but basic research questions in physiology extend well beyond biomedicine. Physiologists have a unique set of perspectives and integrative skills for answering a range of fundamental questions in biology.

At a time when Earth's climate is changing rapidly as a result of global warming, physiologists will play an important role in advancing our understanding of what aspects of climate change stress organisms, and how such organismal changes in turn will drive global processes. Responses to a changing environment will include altered metabolic pathways and networks in individuals, and in populations. Our ability to cope with and forecast the changes associated with global warming will require scientists of all kinds who want to study the intricacies of Earth's complex systems.

We need to improve our understanding of the nonlinear relationships of Earth's systems in order to predict which biological components will be robust in the face of change in physical or biological variables and which will be resilient. Developing these predictive capabilities requires identifying the fundamental rules governing emergent properties of organisms, determining whether the rules apply broadly to all organisms, and understanding whether these rules apply to multiple levels of biological organization: to cellular dynamics as well as to ecosystem structure and function.

We now have much greater insight into how the parts of organisms func-

(continued on page 243)

The Physiologist

Contents

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Celebrating 125 Years of Physiology at Michigan

2007 marks the 125th Anniversary of the appointment of Henry Sewall, as the first full-time Professor of Physiology at the University of Michigan. Physiology had been part of the curriculum at the University of Michigan Medical School from its beginning in 1850. However, physiology as a research discipline at the University dates back 125 years to when Sewall was hired. To mark the occasion, John A. Williams, Chair, Department of Molecular & Integrative Physiology, University of Michigan, and colleagues in the department organized a celebratory event on September 27-28 to mark the occasion.

In attendance were 23 PhD graduates, including 16 who traveled to Ann Arbor from out of town and seven who are current postdocs or faculty. Five former postdocs also came from out of town. Seven former faculty (Dave Dawson, Matt Kluger, Anita Payne, Jim Ranck, Jim Sherman, Harvey Sparks, and Arthur Vander) returned to recognize the contributions of the Department to the University of Michigan. In addition, Governor Jennifer M. Granholm sent a letter "to congratulate the University of Michigan on the Department of Physiology's 125th anniversary."

Throughout its 125 year history, physiologists have been an important part of Medical Education at the University of Michigan. In 1922, the Department graduated its first PhD in Physiology and, to date, has awarded 233 PhDs in Physiology. Many of these graduates, as well as the medical students who worked in the department, have gone on to be leaders in American medical science. Michigan Physiologists also played an important role in the founding of the American Physiological Society and have played a leadership role in the Society throughout its history. In 2002, the Department's name was changed to Molecular & Integrative Physiology to more completely reflect the Department's mission. Presently, the Depart-ment has over 50 faculty and about 60 graduate students and postdoctoral fellows.

To commemorate the Department of Physiology's 125th Anniversary, a number of events were planned including a scientific symposium showcasing the diversity of contemporary physiology. Invited speakers included Kevin Campbell, Univ. of Iowa; Benita Katzenellenbogen, Univ. of Illinois; Joseph Takahashi, Northwestern Univ.; and Andrew Marks, Columbia Univ.. The symposium was followed by a banquet at which Joel D. Howell presented "Some Reflections on the History of Physiology at Michigan." In addition, David F. Bohr, Professor Emeritus of Molecular and Integrative Physiology, received the Physiology Lifetime Service Award. Hannah V. Carey, APS President, and Martin Frank, APS Executive Director, were present at the banquet to present a Proclamation (see shaded box) to John Williams and the Department. On Friday, September 28,

The American Physiological Society
Proclamation
125 Years of Physiology at the University of Michigan
September 27, 2007

Whereas, physiology is the study of how molecules, cells, tissues and organs function to create health or disease;

Whereas, physiology as a science has been in existence at the University of Michigan since 1882 when Henry Sewell became the first full time Professor of Physiology;

Whereas, over 230 individuals have been awarded the Ph.D. degree in physiology at Michigan from the Department;

Whereas, the Department has made important and substantial contributions to physiological discoveries that have advanced human and animal health;

Whereas, eleven Presidents of the American Physiological Society have been associated with the Department and/or the University;

Therefore, we hereby provide our congratulations to the University of Michigan in honor of the physiological achievements of this Department and University as they celebrate their 125th Anniversary.

The American Physiological Society

Hannah Carey, APS President — Martin Frank, Executive Director

John Williams presents the Lifetime Service Award to David Bohr.

John Williams Accepts the APS Proclamation from Martin Frank and Hannah Carey.

the Department held a Research Forum with oral and poster presentations from the graduate students and postdoctoral fellows in the department. This was followed by alumni leading roundtable discussions on Careers in Academic Research, Careers in Teaching, and Careers in the pharmaceutical industry. The festivities concluded with a pub-night including a band made up in part by alumni and a faculty bagpiper."

Howell's banquet talk tracing the history of the Department was enlightening (and often humorous). He noted that the following individuals have led the Department over its 125 year existence: 1882–1889: Henry Sewall; 1889–1892: William Howell; 1892–1923: Warren Lombard; 1923–1954: Robert Gesell; 1956–1978: Horace Davenport; 1979–1986: Jack Kostyo; 1987–present: John Williams.

As noted in the proclamation, the University of Michigan has played an important role in the history of the American Physiological Society. To date, eleven of the Society's Presidents have been associated with the department and/or the University. They include: 1905–1910: William H. Howell; 1919–1920: William Plimpton Lombard; 1949–1950: Carl J. Wiggers; 1951–1952: Ralph W. Gerard; 1961–1962: Horace W. Davenport; 1965–1966: John M. Brookhart; 1978–1979: David F. Bohr; 1983–1984: Alfred P. Fishman; 1987–1988: Harvey V. Sparks, Jr.; 1996–1997: James A. Schafer; 2003–2004: John A. Williams.

Readers interested in a partial history of physiology at the University of Michigan are invited to read Horace Davenport's article in the 1982 issue of *The Physiologist* on "Physiology at the University of Michigan, 1850-1923" [http://www.the-aps.org/publications/tphys/legacy/1982/Physiology_1850-1923.pdf]. ❖

APS News

APS Bylaw Change

The APS Council has voted to approve a recommendation to eliminate the at-large members of the Joint Program Committee. This will require a change to the bylaws as stated below:

ARTICLE V. ***Standing Committees.*** SECTION 5. *Joint Program Committee.* A Joint Program Committee composed of six regular members of the Society appointed by Council and elected representatives of the sections and groups shall be responsible for scientific programs of the Society. The term of each member shall be for three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairperson of the Committee, who shall be an ex officio member of the Council, without vote. The President Elect and Executive Director shall be ex officio members, without vote. ❖

APS Launches Stop-Gap Fellowship Program

Earlier this year, the APS Council launched a stopgap initiative in response to the diminishing success rate of candidates competing for NIH F32 Fellowship support. In order to assist our members contending with the reduction in available resources from NIH in support of postdoctoral fellowships, the Initiative targeted individuals who had narrowly missed NIH funding. This interim initiative was designed to provide our members with the ability to continue the training of future independent physiologists. The goal was to support postdoctoral fellowship candidates who were scheduled to work in the laboratories of members of the American Physiological Society. The Council committed funds to support up to 10 postdoctoral fellowships as part of this short-term initiative.

The Program's first deadline of August 1st resulted in the award of 3 Postdoctoral Fellowships. All of the applicants were APS members at the time of application and their postdoctoral mentors had been members in good standing for at least 3 years immediately prior to application. Each of the fellowship recipients had a non-funded NIH postdoctoral fellowship application with a priority score of 200 or better on which the applicant was the principal investigator.

The successful applicants received an award totaling $42,000 consisting of a stipend of $37,000 and $5,000 provided as the Fellow's institutional allowance for his/her use for health insurance, books, travel, etc. No indirect costs were allowed. The successful applicants were:

Chad C. Carroll, Ball State University: "***Analgesics, Exercise & Tendon Adaptations in the Elderly;***"

Sonnet Jonker, University of Iowa: "***Regulation of Fetal Cardiac Growth After Correction of Increased Hemodynamic Load;***"

Jonathan Wingo, Presbyterian Hospital of Dallas: "***Spinal Cord Injury and Heat Acclimation.***"

The next deadline for the APS Stop-Gap Postdoctoral Fellowship Program is January 2, 2008. Information about the Program can be found at http://www.the-aps.org/awards/student/postdocinitiative.htm. ❖

(continued from page 241)

tion, but the big challenge will be explaining how organisms respond as integrated systems.

Physiologists offer an important perspective on organismal function and performance because they apply knowledge about the physical sciences to biological systems while also using the life sciences to advance our comprehension of physical systems. They offer skills for revealing physical properties in biological contexts such as pressure, force, temperature, ion fluxes, oxygen fluxes, and enzyme kinetics. Conversely, recent research has shown, for example, that increasing atmospheric carbon dioxide is expected to alter plant physiology in ways that lead to increased continental runoff due to atmospheric changes.

The NAS report talks of melding the study of physiology with that of geochemistry, physics, genomics, and other sciences in "systems geobiology," a way of understanding the processes and feedback mechanisms influencing Earth's overall metabolism: "…global metabolic fluxes are the cumulative result of the specific capabilities of individual molecules, powering individual cells in different organisms, which themselves interact in many different communities."

Organismal biology links the dynamics of the geosphere, biosphere, and atmosphere.

Comparative and Evolutionary Physiology: Where We've Been

Understanding how organisms work within an environmental framework is a long-standing theme in the history of physiology. Claude Bernard's important conceptual contribution, *milieu interieur*, at the beginning of modern experimental physiology focused on the need to understand the physical-chemical properties of the aqueous environment of cells to uncover physiological principles.

Another milestone includes Walter Cannon's concept of homeostasis, a cornerstone in studies of organismal response to external environmental change—although not necessarily applicable to all organisms. A growing body of literature about mechanisms of response to environmental change, such as enantiostasis, is extending this fundamental concept.

Studying how organisms function in their natural environments fosters an appreciation of life's diversity and of the great variation in how organisms function. Increasingly well-resolved molecular phylogenies and the development of modern comparative evolutionary methods have been important factors in the progress of evolutionary physiology.

21st Century Integrative Biology: Where We're Going

Addressing the challenges of biology in the 21st century will require physiologists, like all biologists, to develop a wider view of our science. Today's integrative biology is directed toward advancing an understanding of interconnected, complex systems. Insights will come from the collective contributions of teams of investigators as well as those of individual researchers. In the process, the boundaries of what "counts as biology" will broaden to embrace even more of the theories and concepts of physics, chemistry, engineering, geological sciences, and the social and behavioral sciences.

Ecological and evolutionary concepts, so central to the maturation and practice of modern comparative studies in physiology, have resulted in a community trained to consider the environment as a larger framework essential to understanding the function of organisms—and understanding why organisms function as they do. The ability of physiologists to apply methods and principles from other disciplines, particularly the physical sciences and engineering, and to conduct integrative studies crossing multiple levels of biological organization, demonstrates a great breadth of scientific perspective and expertise.

Physiologists have a central role to play in understanding complex biological systems. Finding answers to 21st century questions in biology will require the critical cross-disciplinary perspectives and skills characteristic of integrative and comparative biology.

NSF Funding Opportunities for Physiologists

NSF's Biological Sciences Directorate (BIO) recently changed the organizational structure of one of its divisions to better reflect the challenges of 21st Century biology. The Integrative Organismal Biology Division is now Integrative Organismal Systems (IOS). The change emphasizes increasing support for studies that apply systems biology approaches to gain new conceptual and theoretical insights about organismal properties (http://www.nsf.gov/bio/ios/about.jsp).

IOS encourages systems approaches that combine experimentation, computation, and modeling that lead to a greater understanding of the emergent properties of organisms, such as resilience, robustness, and adaptability, and a greater capacity to predict organismal response to changing conditions. The new IOS emphases reflect a need to advance our understanding of complex biological systems, and a need to support teams of researchers who can apply multi-disciplinary insights and approaches.

In addition to opportunities within IOS, BIO supports physiologists through a number of additional programs and activities:

Research Coordination Networks (RCN) Program http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=11691&org=EF

National Evolutionary Synthesis Center (NESCent) http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=13584&org=EF

National Center for Ecological Analysis and Synthesis (NCEAS) http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=13450&org=EF

Advancing Theory in Biology (ATB) Program http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=501066&org=EF

National Ecological Observatory Network (NEON) http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=13440&org=DBI&from=home

NCEAS focuses on the "…development and testing of important ecological ideas and theories using existing data ..." The long history of ecophysiological and environmental physiology studies for advancing a mechanistic understanding of ecological patterns and ecological theory could be explored through NCEAS-supported working groups.

Similarly, NESCent focuses on synthetic approaches "…to foster a greater conceptual synthesis in biological evolution…." The wealth of published physiological data could be productively "mined" to advance a synthetic understanding of evolutionary physiology. Comparative and evolutionary physiologists, for example, can play a significant role in this context through their expertise in addressing the evolution of physiological systems.

The Research Coordination Networks program fosters "…interactions among scientists to create new research directions or advance a field." RCN supports

novel networking ideas, and communication and coordination of research, education, and training activities among groups of investigators "…across disciplinary, organizational, institutional, and geographical boundaries." Physiologists participating in integrative biology projects requiring the development of new teams of researchers would be a good match for RCN funding.

The Advancing Theory in Biology (ATB) Program is a new activity in BIO aimed at understanding "…emergence of complex biological phenomena from dynamic interactions among less complex elements…" through support of new conceptualizations and theoretical approaches. Physiologists might use ATB as a source of support for advancing an understanding of the rules by which emergent properties of organisms arise through the interactions of components.

On the horizon, the National Ecological Observatory Network (NEON) is being designed to provide a continental-scale research network of geographically distributed infrastructure at 20 core sites, connected via state-of-the-art cyberinfrastructure. Scientific teams will be able to conduct collaborative, comprehensive, and interdisciplinary measurements and experiments on ecological systems. NEON's synthesis, computation, and visualization infrastructure will create a virtual laboratory for the development of a predictive understanding of the direct effects and feedbacks among environmental changes and biological processes. Comparative and evolutionary physiologists can contribute significantly by providing unique perspectives and skills to this central scientific goal of NEON.

"The diverse living things of our world are endlessly fascinating," wrote the authors of the NAS report on the role of theory in biology. BIO offers a range of programs that support infrastructure and human resources, as well as research from molecules to ecosystems. The mission of the BIO Directorate is to enable the discoveries for understanding life. Central to realizing that mission is the basic research in physiology needed for understanding the organisms that are "endlessly fascinating." ❖

Membership

New Regular Members

***Transferred from Student Membership**

Nasreen Akhtar
Maulana Azad Med. Coll., New Delhi, India
Fahaid Hassan Al-Hashem
Kinf Khalid Univ., Saudi Arabia
John A. Babraj
Heriot-Watt Univ., Edinburgh, UK
Deborah Jean Baro
Georgia State Univ., Atlanta
Andreas M. Beyer*
Univ. of Iowa
Gunnar Blohm
Univ. Catholique De Louvain, Belgium
Patrice Brassard*
Copenhagen Muscle Res. Ctr., Denmark
Robert M. Brothers*
Presbyterian Hospital of Dallas, TX
Maurice J. Chacron
McGill Univ., Montreal, Canada
Lewis Longtang Chen
Univ. of Texas Med. Branch, Galveston
Sheldon Chen
Northwestern Univ., Chicago, IL
Yin Chen
Hamner Inst. for Health Sci.,
Res. Triangle Pk, NC
Jarrod Evan Church
Univ. of Melbourne, Australia
Kevin Currell
English Inst. of Sport, Marlow, UK
Yuanpu Peter Di
Univ. of Pittsburgh, PA
Paul Christian Dolber
Duke Univ. Med. Ctr., NC
Charles Lee Dumke
Appalachian State Univ., Boone, NC
Aurelie Edwards
Tufts Univ., Medford, MA
Tammi Sue Epp*
JBS United, Sheridan, IN
Diane Felsen
Weill Med. College, NY
Vincent Peter Ferrera
Columbia Univ., NY
Ila R. Fiete
California Inst. of Tech., Pasadena
Jonathan B. Fritz
Univ. of Maryland, College Park
Michael Ernest Fromm
Univ. of Nebraska
James F. Gillooly
Univ. of Florida, Gainesville
Michelle L. Gumz
Univ. of Florida, Gainesville
Tomoko Hayano
Kanmon National Med. Ctr., Japan
Lacy A. Holowatz*
Pennsylvania State Univ.
Seung M. Hong
Univ. of Delaware
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Cornell Univ., Ithaca, NY
Hiroshi Kitamura
RIKEN, Yokohama, Japan
Alan Kleinfeld
Torrey Pines Inst., CA
Joseph R. Koke
Texas State Univ., San Marcos, TX
Johanna A. Kolodziejski*
Keene State College, NH
Stephen C. Kolwicz*
Brigham and Women's Hosp., MA
Michelle C. LaPlaca
Georgia Inst. Tech./ Emory Univ., GA
Scott P. Levick
Univ. of South Carolina, Columbia
Richard Jonathan Levy
New York Med. Coll., Valhalla, NY
Fangming Lin
Univ. of Texas Southwestern Med. Ctr.
Andrew Thomas Lovering*
Univ. of Oregon, Eugene
Huifang Ma
Univ. of Pennsylvania
Lee Ann MacMillan-Crow
Univ. of Arkansas Med. Scis.
Clive N. May
Univ. of Melbourne, Victoria, Australia
Jenni Lockwood McCord*
Penn State Univ.
Thomas B. McFadden
Univ. of Vermont
Kathryn Medler
Univ. of Buffalo, NY
Donatella Mutolo
Univ. of Degli Studi Di Firenze, Italy
Takahiko Nakagawa
Univ. of Florida

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Univ. of Sao Paulo, Brazil
James T. Pearson
Monash Univ., Australia
Keith Paul Purpura
Weill Cornell Med. Coll., NY
Qining Qin
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Rafael Radi
Univ. De La Rep., Mentevideo, Uruguay
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Medical Coll. of Georgia
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Johana Vallejo-Elias*
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Chunbo Wang
Univ. of North Carolina, Chapel Hill
Xiao Qiu Bill Xiao
Oregon Univ., Beaverton
Kimiko Yamamoto
Univ. of Tokyo, Japan
Yi-Chun Zhu
Fudan Univ., China

New Student Members

Shaquria Adderley
St. Louis Univ., MO
Omar Ali
Univ. Sains, Malaysia
Megan Bardgett
Univ. of Kentucky
Allison Boardman
Simpson College, IA
Debra Conte
Univ. of California, Merced
Ashley Cudworth
Simpson College, IA
Urtis DeVetter
Simpson College, IA
Mandeep Dhindsa
Univ. of Texas, Austin
Elise Donovan
Colorado State Univ.
Christine Freeman
Univ. of Texas, Austin
Nicholas Greene
Texas A&M Univ.
Melissa Harrison
Univ. of Notre Dame, Western Australia
Muhammad Salman
Univ. Sains Malaysia
Pierre Megevand
Univ. of Geneve, Switzerland
Laura Miller
Simpson College, IA
Gilbert Moralez
Univ. of Texas, San Antonio
Ashley Nelson
Simpson College, IA
Nantinee Nualnim
Univ. of Texas, Austin
Jill Rahnert
Georgia Inst. of Technology
Hassaan Rathore
Univ. Sains Malaysia
Adam Stearns
Harvard Medical School, MA
Christopher Stembridge
Capital Univ., Columbus, OH
Brooke Stephenson
Univ. of Oklahoma HSC
Michael Stout
Ohio State Univ.
Arshani Wansapura
Univ. of Cincinnati, OH
Alia Winterbottom
Simpson College, IA
MacKenzie Worthington
Simpson College, IA
Carlos Xavier Custodio
Univ. Fed De Minas Gerais, Brazil

Recently Deceased Members

Victor P. Bond
Richland, WA
Jureta W. Horton
Dallas, TX
Alfred H. Lawton
Dowling Park, FL
Frederick E. Samson
Kansas City, KS
David A. Vaughan
Ellicott City, MD

The Physiologist
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2007 APS Conference
Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology
Austin, TX, August 9-12, 2007

The 2007 APS Conference: Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology, was held in the vibrant Texas capital of Austin. The conference took place over four days at the Hyatt Regency Austin on Town Lake hotel, which was ideally situated close to the heart of downtown Austin and the idyllic views of the Town Lake, which offered a spectacular vantage point for viewing the famous Congress Avenue bats. The Organizing Committee was chaired by Jane Reckelhoff, Univ. of Mississippi Medical Center, and included Vice-Chair, Joey Granger, also of the Univ. of Mississippi Medical Center, Kathryn Sandberg, Georgetown Univ., Carmen Hinojosa-Laborde, Univ. of Texas Health Science Center at San Antonio, J. Michael Wyss, Univ. of Alabama at Birmingham, John Stallone, Texas A&M Univ., College of Veterinary Medicine, and Ann Dominiczak, Univ. of Glasgow, UK. The Organizing Committee organized a program that included symposia, oral presentations for students and postdoctoral fellows, interactive poster sessions, and social networking opportunities to make this meeting a valuable experience for those who attended.

The conference was attended by 103 total registrants, of whom 29% of registrants were represented by young scientists, including nine postdoctoral and 21 students. Twenty-nine (28%) attendees identified themselves as APS members, and 15 (15%) registered as nonmembers, invited chairs and speakers made up the remaining 29 (28%) attendees. Table 1 (below) shows the breakdown of the different registration types. This conference also attracted a large group of registrants from outside the United States. Out of the 103 registrants, 20 (20%) represented registrants from Canada, Denmark, France, Germany, Iran, Italy, Japan, Nigeria, Switzerland, and Taiwan.

The meeting program consisted of seven symposia on a wide variety of topics. The audience was encouraged to share their ideas and thoughts with the speakers at the end of their talks. There were two oral presentation sessions that were dedicated to the postdoctoral fellows and students attending the meeting, giving them a valuable opportunity to present their work their peers. During the conference, special career workshops were hosted by the APS Career Opportunities in Physiology Committee to give the young scientists the opportunity to gain information and valuable career skills on presenting themselves at a meeting, presenting an abstract, and authorship of an abstract. The meeting also had several social activities including a Welcome and Opening Reception, which was designed to give attendees a chance to meet with long time colleagues, create new friendships, and enjoy some hot and cold hor d'oeuvres and beverages before the evening presentations. There was also two afternoon poster sessions where scientists presented their work, and discussed their finding with other attendees.

Meeting Organizer, Jane Reckelhoff at the Banquets and Awards Dinner.

A total of 85 abstracts were submitted for the meeting. Fifty-eight of these

Recipients of the Research Recognition Award for Outstanding Abstract by a Graduate or Postdoctoral Fellow at the Banquet and Awards Ceremony. L-R (Top): Abdolvahab Vahabzadeh, Maria Davila, Majid Nikpay, Jeffrey Gilbert, Maggie Keck, Rie Sasaki, Julio Sartori-Valinotti, Karl Pendergrass. L-R (Bottom): Birgitte Mahler, Connie Mark, Norma Ojeda, Babette LaMarca, and Sebastian Brokat.

Table 1. Registration Statistics

Registration Type	Number of Attendees (%)
APS Member	29 (28%)
Nonmember	15 (15%)
Postdoctoral	9 (9%)
Student	21 (20%)
Invited Chairs/Speakers	29 (28%)
Total	103 (100%)

abstracts were programmed as poster presentations. The remaining 27 abstracts were submitted by invited speakers. Of the volunteered abstracts submitted for the meeting, 38 (66%) were submitted by a female first author; 16 (28%) were submitted from institutions outside of the United States, including eight from Europe, four from Canada, two from Japan, one from Taiwan, and one from Iran.

On Saturday evening, Reckelhoff hosted the Banquet and Awards Presentation dinner. Attendees gathered at the hotel's ballroom for evening dinner, wine and conversation. During the dinner, eight postdoctoral fellows and 10 students were recognized as the recipients of the Research Recognition Award for Outstanding Abstract by a Graduate Student or Postdoctoral Fellow. The following individuals were presented with a certificate and cash prize: Sebastian Brokat, Charité Univ., Berlin, Germany, Norma Ojeda, Univ. of Mississippi Medical Center, Jennifer Rogers, Georgetown Univ., Babbette LaMarca, Univ. of Mississippi Medical Center, Maggie Keck, Univ. of Arizona, Connie Mark, Univ. of South Dakota, Birgitte Mahler, Aarhus Univ. Hospital, Denmark, Karl Pendergrass, Wake Forest Univ., Majid Nikpay, Univ. of Montreal, Canada, Rie Sasaki, Univ. of Mississippi Medical Center, Julio Sartori-Valinotti, Univ. of Mississippi Medical Center, Carie Reynolds, Univ. of Florida, Adam Mitchell, Georgetown Univ., Jeffrey Gilbert, Univ. of Mississippi Medical Center, Radu Illiescu, Univ. of Mississippi Medical Center, Maria Davila, Univ. of Texas Health Science Center at San Antonio, Abdolvahab Vahabzadeh, Iran Univ. of Medical Sciences, Iran, and Danny Quaglietta, Univ. of Toronto, Canada.

Attendees enjoy hor d' oerves while catching up with colleagues at the Opening Reception.

Attendees discuss their research during the poster sessions.

In addition Mariana Baserga, Univ. of Utah, Rayna Gonzales, Univ. of California, Irvine, TanYa Gwathmey, Wake Forest Univ., Brandiese Jacobs, Univ. of Maryland, Baltimore, and Karl Pendergrass, Wake Forest Univ., were the recipients of the Porter Physiology Development Committee's Minority Travel Fellowship Award, which is provided to encourage participation of under-represented minority students in the physiological sciences. With support from the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), the fellowship provides reimbursement of all expenses associated with travel and participation in the conference. The recipients of the award were matched with APS members: Virginia Miller, Mayo Clinic College of Medicine, David Pollock, Medical College of Georgia, Barbara Alexander, Univ. of Mississippi Medical Center, Martin Frank, APS Executive Director, and J. Michael Wyss, Univ. of Alabama at Birmingham respectively, who were attending the conference, offered guidance and made introductions to the other scientists.

Recipients of the Porter Physiology Development Committee's Minority Travel Fellowship Award. L-R: Tan Ya Gwathmey, Brandiese Jacobs, Karl Pendergrass, and Mariana Baserga.

The American Physiological Society and the Organizing Committee gratefully acknowledges the financial support provided though generous educational grants from NIH-NIDDK, NIH-NHLBI, Bristol-Meyers Squibb Company, and Transoma. ❖

APS Members Volunteer to Visit Classrooms for PhUn Week 2007

More than 100 APS members and trainees volunteered to work with teachers in coordinating K-12th grade classroom visits across the nation and Puerto Rico during the first week in November to celebrate Physiology Understanding Week (PhUn Week) 2007. In total, the volunteer efforts reached approximately 3,150 students at all grade levels.

As part of PhUn Week, physiologists visited the classrooms of local teachers to do hands-on physiology activities with the students. The program gives students a chance to meet and learn from research scientists, learn about physiology in their daily lives, and explore physiology as a possible career. It also builds local partnerships between science teachers and scientists to provide new materials for teachers and give researchers a chance to reach out to the next generation of scientists. Downloadable instructional resources and career presentations were obtained from the PhUn Week website: http://www.PhUnWeek.org. PhUn Week 2007 t-shirts for the presenters and memorabilia for the students were provided by the APS.

PhUn Week 2007 was highlighted by the Boston Children's Museum with an all-day event on Saturday, November 3. APS member Andrea Gwosdow partnered with the museum and coordinated a crew of more than 25 volunteers for the event. The PhUn Day featured the museum's Kid Power Exhibit on exercise and health. Classroom visits across the nation continued throughout the rest of the week and month. ADInstruments, a provider of computer-based data acquisition and analysis systems for the life sciences, generously loaned instruments for events in Missouri and South Dakota, coordinated by APS K-12 Minority Outreach Fellow Jessica Clark and APS Councillor Barbara Goodman, respectively. Watch the next issue of *The Physiologist* for highlights of PhUn Week 2007 events and for early preparations for next year's PhUn Week, November 3-7, 2008. ❖

David S. Bruce Awards for Excellence in Undergraduate Research

The annual David S. Bruce Awards for Excellence in Undergraduate Research (provides $500 award) will be granted to up to 20 currently enrolled undergraduate students who are presenting a poster at the Experimental Biology (EB) meeting.

Requirements:

To be considered for the award, the undergraduate student must be the first author of an abstract submitted to an APS session at EB and either the candidate or the abstract sponsor must be a member of APS.

The student must:

1) be enrolled as an undergraduate student at the time of the application and at the time of the EB meeting;

2) be the first author on a submitted abstract for the EB meeting (students may not submit more than one abstract for the award competition each year);

3) be working with an APS member who attests that the student is deserving of the first authorship;

4) submit a one-page letter that discusses his/her role in the research, the significance of the research, and his/her career plans; and

5) have not previously won the Bruce Award.

Application Instructions:

Application information can be obtained from the APS website (http://www.the-aps.org/awards/student.htm#Bruce).

All applications must be submitted online at http://www.the-aps.org/awardapps.

Deadlines:

January 11, 2008: Deadline for completion of application;

March 1, 2008: Notification of Finalists;

April 6, 2008: Poster judging of Finalists.

Applications will be reviewed by the APS Education Committee. The Committee will select finalists from among the applicants. Finalist will present their posters and be interviewed by the committee during the EB meeting. After the interviews, the Committee will select the awardees. All finalists will receive certificates.

Abstract Qualities:

Successful abstracts typically include: a clearly stated hypothesis or aim; a technical approach to the study; the pertinent results obtained with quantitative and statistical comparisons, when appropriate; and a clearly stated conclusion, including the significance of the results to the field.

Poster Qualities:

Posters will be judged on quality of the poster and oral presentation, quality of graphics used, organization of the poster, creativity used in displaying and describing the research, as well as in the development of the research project, novelty of the research project, and the student's display of his/her understanding of the work and its significance.

Special Poster Session:

At EB, all undergraduate students will be invited to present their research at a special poster session, in addition to their regularly scheduled scientific session. The session will be held on Sunday, April 6, from 4:30 – 6:00 pm. All undergraduate first authors will receive a special invitation to present their research at this session.

The David Bruce Awardees will be announced during the session. ❖

Special Sessions at EB

Refresher Course in Respiratory Physiology
(Sponsored by the APS Education Committee)
Saturday, April 5, 8:00 AM–12:00 noon
Organizers: L. Britt Wilson, Robert W. Brock
Speakers:
John B. West, Mechanics of Breathing
Steven E. DiCarlo, Alveolar Ventilation/Diffusion of Gases
Robb W. Glenny, Ventilation/Perfusion Matching
Michael G. Levitzky, Cardiopulmonary Integration

Trainee Symposium:
Marketing Yourself on Paper for Academic Positions
Sponsored by the APS Trainee Advisory Committee)
Sunday, April 6, 8:00–10:00 AM
Organizers: Lacy A. Holowatz, Eric Berglund
Speakers:
Ryan Wheeler, Academic Cover letters & the Art of Self-Presentation
James A. Pawelczyk, Crafting the Research Statement
Kevin Johnston, Creating a Teaching Philosophy You Can Use

Careers Symposium:
Mid-career Transitions: Choices and Challenges
(Sponsored by the APS Career Opportunities in Physiology Committee)
Organizers: Rolando E. Rumbaut, Nansie McHugh
Monday, April 7, 5:45–7:45 PM
Speakers:
Marian R. Walters, How to manage mid-career transitions: voluntary and involuntary
David M. Pollock, Transitions from industry to academia (and vice-versa)
Edward J. Zambraski, Scientific career opportunities in the government/military
D. Neil Granger Assuming administrative/leadership positions while maintaining an active research program

Mentoring Symposium: Gainfully Employed: From Launching a Job Search to Navigating Negotiations
(Jointly sponsored by the APS Women in Physiology and ASPET Women in Pharmacology Committees)
Tuesday, April 8, 8:00–10:00 AM
Organizers: Siribhinya Benyajati (APS), Colleen Cosgrove Hegg (APS), Jelveh Lameh (ASPET)
Speakers:
Colleen Cosgrove Hegg, Launching a Job Search
Susan C. McKarns, Delivering a Dynamic Job Talk
Lynn Wecker, The Art of Interviewing: Winning *the* Job
Kim E. Barrett, Navigating Negotiations

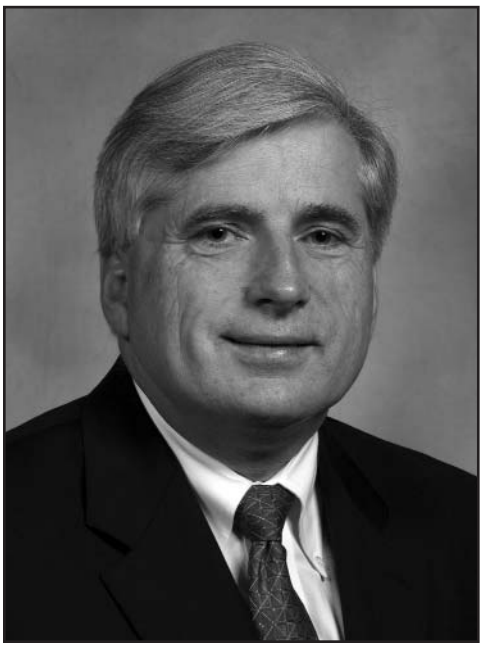
The Physiologist
Vol. 50, No. 6, 2007

Granger Receives 5th Schmidt-Nielsen Distinguished Mentor and Scientist Award

The APS Women in Physiology Committee is pleased to announce that Joey P. Granger, Billy S. Guyton Distinguished Professor, Professor of Physiology and Medicine, and Dean of the School of Graduate Studies in the Health Sciences at the University of Mississippi Medical Center, has been selected as the fifth recipient of the Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award. The Committee was extremely impressed with both his mentoring excellence and his outstanding contributions to physiological research.

Granger received his PhD at University of Mississippi Medical Center. He did his postdoctoral training at the Mayo Clinic and Foundation before being hired as an Instructor and then Assistant Professor in the Department of Physiology and Biophysics. He then moved to Eastern Virginia Medical School in Norfolk, VA where he served as an assistant professor and then was promoted to associate professor. In 1990 he moved to his current institution, University of Mississippi School of Medicine, where he was named Professor of Physiology and Biophysics. In 1996, he became the Associate Director of the Center for Excellence in Cardiovascular-Renal Research. He was named the Billy S. Guyton Distinguished Professor in the Department of Physiology and Biophysics in 2004. In 2006, he was named Interim Dean of the School of Graduate Studies in the Health Sciences and was appointed Dean in 2007.

Granger's research focuses on cardiovascular and renal physiology with respect to hypertension. He studies the physiological mechanisms whereby endothelial-derived factors alter renal function and lead to long-term alteration in the regulation of arterial pressure and hypertension, specifically pregnancy-induced hypertension. The excellence of his research has been recognized by not only the APS (including the 2008 E.H. Starling Distinguished Lectureship awarded by the Water and Electrolyte Homeostasis Section), but also the American Heart Association, the American Society of Hypertension, and the International Society of Hypertension, among others.



Joey P. Granger

Granger has successfully mentored five visiting scientists, 13 postdoctoral fellows, and 10 predoctoral students, many of whom are from outside the US. His mentees have gone on to successful and prominent positions (one departmental chair, one associate professor, and four assistant professors, among others) with national funding and numerous awards among themselves. In addition, Granger has had 16 medical and undergraduate student research fellows in his lab, which included two APS Undergraduate Summer Research Fellows. He is also active in K-12 education, sponsoring high school teachers from the APS Frontiers in Physiology Program in his lab, as well as high school students. It is noteworthy that Granger extends his mentoring far beyond his laboratory: he started a mentoring group for junior faculty in his department to help them obtain funding. To foster early interest in scientific research, Granger established a summer research internship program for undergraduate students in his department and served as an active judge for local science fairs, as well as a frequent speaker at local high schools. As a recent dean of Graduate Studies, Granger improved graduate education by providing better stipend and health insurance support for all graduate students at his institution.

Granger has received numerous teaching and research awards during his career. His innovative teaching methods and mentoring excellence have been recognized with the University of Mississippi Excellence in Teaching Award, the Sir William Osler Award for Outstanding Teaching in Basic Sciences, and the American Physiological Society-NIDDK Minority Fellowship Mentor Award (four times).

All of the people writing the supporting recommendation letters (high school teachers, medical, graduate, and undergraduate students, postdoctoral fellows, junior faculty and colleagues) spoke extremely highly of Granger. They all emphasized his hands-on science and personal mentoring and doing what is needed for each person in his lab to be successful at each stage of their career, be it first-author publications, co-authoring a prestigious review article, a chance to present and meet people at meetings, assistance on writing grants, or the opportunity for collaboration or learning a new technique. In addition, they all passionately attested to his warmth and caring about the person, their quality of life, their problems, their family, and his continual efforts to make sure he supports them in all aspects of their life.

There will be a reception in Dr. Granger's honor at which he will give a talk on mentoring during the 2008 Experimental Biology meeting in San Diego, CA. It will be held on Monday, April 7 at 12:00 PM at the San Diego Hotel. All trainees and mentors are invited to attend.

APS congratulates Dr. Granger on this well-deserved honor. ❖

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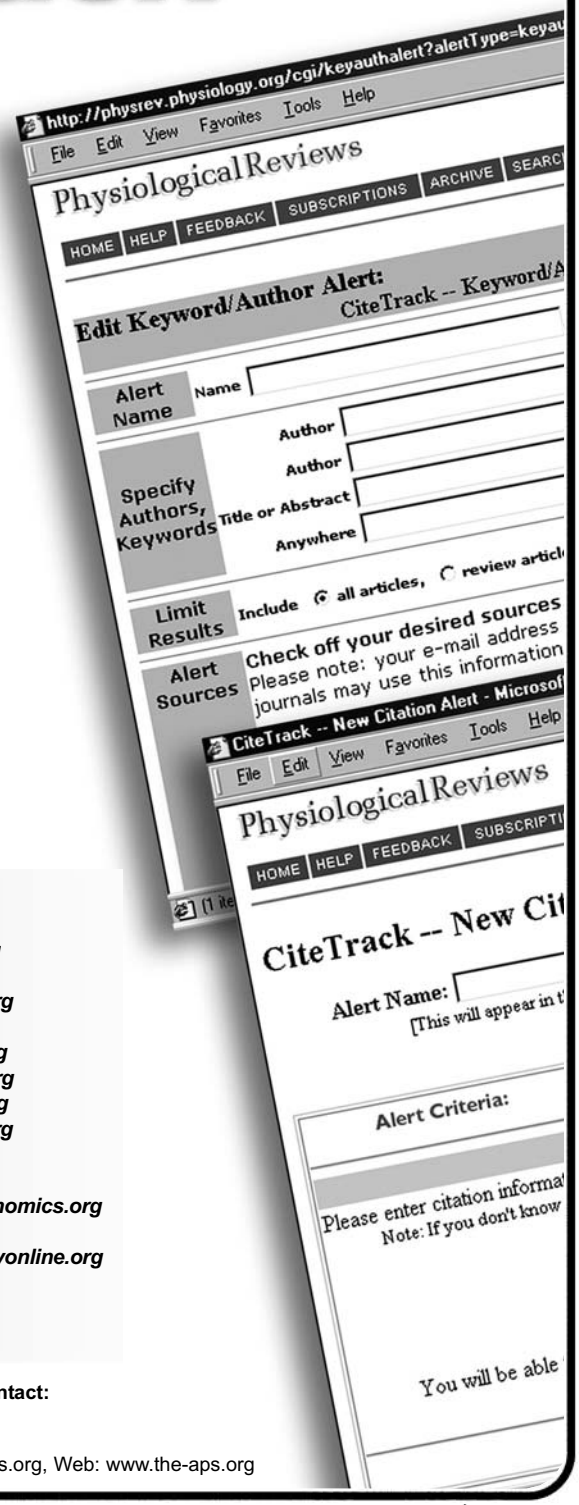

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APS Early Career Professional Service Award

Award: $1,000 and complimentary registration to Experimental Biology meeting

Deadline: January 25, 2008 Apply online at http://www.the-aps.org/awardapps.

The Early Career Professional Service Award honors an early career stage (graduate student, post-doctoral fellow, Assistant Professor or equivalent position) member of APS. The Award will honor someone who is judged to have made outstanding contributions to the physiology community and demonstrated dedication and commitment to furthering the broader goals of the physiology community. This can be by serving on professional committees, participating in K-12 education outreach, participating in scientific advocacy and outreach programs, or by otherwise strengthening and promoting the physiology community.

Applications should include: 1. A one-page letter written by the applicant stating the basis for the application with a synopsis of the applicant's specific contributions to the physiology community and evidence related to the criteria; 2. Two additional support letters written by individuals who are familiar with the substantive contributions of the applicant to professional service; 3. Applicant's current curriculum vitae.

Eligibility requirements: 1. APS member in good standing (either student or regular member); 2. Not above the rank of Assistant Professor or equivalent in government, industry or medicine; 3. Not a current member of the Trainee Advisory Committee; 4. Plan and have support to attend Experimental Biology meeting to receive the award (travel support is NOT provided). Graduate student and Postdoctoral applicants must provide confirmation from their research advisor or department chair that travel funds to the meeting will be available; 5. Be willing to write a brief article on professional service for *The Physiologist.*

The Trainee Advisory Committee will act as the selection committee for the award.

For more information, see http://www.the-aps.org/awards/society/earlycareer.htm. ❖

APS Partners with MentorNet to Offer Mentoring Program

Make a big difference in the life of a physiology trainee with as few as one to two emails per month or 15 minutes per week.

The American Physiological Society is now a proud partner with MentorNet, the Mentoring Network for Diversity in Physiology, an award-winning One-on-One mentoring program.

The APS Women in Physiology Committee would like to encourage you to sign up to be: an online mentor; a protégé (APS membership, either student or regular, required)

Mentors:

Physiology faculty are needed as mentors for graduate students, postdoctoral fellows, or new investigators. As part of MentorNet's One-on-One E-mentoring programs, trainees pursuing science careers are matched with mentors for 8-month mentoring relationships conducted via email.

MentorNet currently has many proteges seeking faculty mentors in physiology, neuroscience, the biological sciences, and biological/biomedical engineering. As APS trainees begin participating, we will need even more mentors.

Please consider volunteering as a mentor and publicizing the program to your colleagues by passing on this message. Even if you choose not to be a mentor, spreading the word about MentorNet to other faculty members can help us to provide mentors for those proteges waiting to be matched!

Benefits of E-Mentoring with MentorNet:

Convenience: Do it at times that suit your schedule. Only about 15 minutes/week.

Support: Access to MentorNet's online mentoring materials to guide your experience.

Outreach: Opportunities to connect with students, postdocs, and early career faculty outside of your university.

Satisfaction: Know that you have helped someone else by sharing your experiences, advice and support on issues such as work/life balance, research, tenure, and university life. Furthermore, mentoring has been demonstrated to help mentors gain perspective and clarity about their own career paths.

Trainees (Graduate Students, Postdoctoral Fellows, New Investigators):

Here is an opportunity for you to get additional information, encouragement, advice, and access to networks from someone in your field and, if you choose, from outside your current institution. You can search for and choose the mentor that best suits your needs and have a chance to discuss topics such as career options, networking, work/life balance, research issues, grant writing and tenure.

Don't miss out on this great opportunity to expand your network of contacts. Sign up now as a MentorNet protégé.

Mentoring relationships last 8 months. Because mentors and students communicate entirely by email, they can communicate wherever and whenever they choose. MentorNet's research-based programs have proven effective by providing "real world" information, encouragement, advice, and access to networks for students, and particularly for women. "My mentor always gives me the encouragement that I need," says one MentorNet student. "Sometimes those few words make a big difference to me."

For questions, please contact Melinda Lowy, APS Higher Education Programs Coordinator (mlowy@the-aps.org, 301-634-7787). ❖

The APS Undergraduate Summer Research Fellowship Program

The APS Undergraduate Summer Research Fellowships program funds up to 24 fellowships during the summer. These fellowships are to support full-time undergraduate students to work in the laboratory of an established investigator. The intent of this program is to excite and encourage students to pursue a career as a basic research scientist.

Applicants must have an over-all GPA of ≥3.0 (0-4.0 scale). Faculty sponsors/advisors must be active members of the APS in good standing.

Selection of participants is based on academic merit and the availability of appropriate faculty mentors. Special consideration is given to applicants whose socioeconomic background, access to educational opportunities, and other life experiences suggest that they would especially benefit from this type of program.

These fellowships provide: $3,000 summer stipend to the student (10 weeks support); $300 grant to the faculty sponsor/advisor; up to $1,000 travel award/reimbursement to the student so that he/she may attend and present their data at the APS annual meeting (Experimental Biology) or an APS fall Conference.

The deadline for the Application Instructions: application information can be obtained from the APS website (http://www.the-aps.org/education/ugsrf/index.htm). All applications must be submitted online at http://www.the-aps.org/awardapps.

Deadline: receipt of all application materials is **Friday, February 1, 2008.** (Applications received by the APS after February 1 will not be reviewed.)

Award recipients will be notified by April 1, 2008 for the funding of the Fellowships for the summer of 2008. All applications will be reviewed, evaluated, and ranked by the APS Career Opportunities in Physiology Committee. Decisions will be final. ❖

APS Supports Local and Regional Science Fairs

Did you know that APS supports local and regional Science Fairs? Each year the APS will sponsor an award at local and regional science fairs on a first come, first serve basis. This award was initiated by the APS Careers Committee. The outreach to science fairs will engage members in participating in their local and regional fairs. This effort could have very positive effects within the physiology field. Any APS member who participates as a judge in a local or regional science fair at an elementary, middle, or high school is eligible to apply to receive APS support. One student from each science fair will receive an APS t-shirt and a certificate for the best physiology project. The teacher of the winning students will receive a Women Life Scientist's Book and a teacher resource packet. To request an award package please visit The APS Science Fair web site at www.the-aps.org/education/sciencefair or contact Scarletta Whitsett (swhitsett@the-aps.org) at the APS Education Department. ❖

Science Policy

Bringing the NSF Message to the Hill

In September 2007, APS President Hannah Carey and Councilor James Hicks joined with scientists from other disciplines in Washington, DC to discuss with Members of Congress the importance of the National Science Foundation (NSF). The meetings were organized by the Coalition for National Science Funding (CNSF), a group of scientific societies and institutions that work together to advocate for increased NSF funding.

The annual event brought together more than 40 scientists from diverse disciplines including physics, ecology, mathematics, chemistry, microbiology and physiology. Participating scientists were grouped by state and went on a series of meetings with a society government affairs representatives. Participants also attended an orientation session the evening before the meetings to introduce themselves to their colleagues and familiarize themselves with the talking points for the meetings. Since Congress has proposed a generous increase in the NSF budget for the next fiscal year, the main purpose of the meetings was to introduce the scientists as constituents who rely on NSF funding to carry out their research, and thank the Members of Congress for their generous support of the NSF budget.

Scientists visited more than 75 offices from 15 states to discuss the importance of NSF. As Congress prepares to finalize research budgets for next year, the hope is that these visits reinforced the critical importance of federal support for science and the NSF.

If you are interested in participating in events like the CNSF Hill visits, get in touch with the APS Government Relations and Science Policy Office. http://www.the-aps.org/pa. ❖

The Physiologist
Vol. 50, No. 6, 2007

Finding Teaching Experiences During Your Postdoc

Siribhinya (Sinya) Benyajati
University of Oklahoma Health Sciences Center

Do Postdoctoral Fellows Need Teaching Experience?

Today graduates and postdoctoral fellows are presented with a range of career options: academic research scientists, scientists in industry, science teachers, science writers, science legal consultants, and science policy professionals. Yet, according to the 2001 National Science Foundation Survey of Doctoral Recipients, approximately 50% of biological and health sciences doctoral recipients are employed in academia. A more recent survey by *The Scientist* (vol. 21(3), 2007) found that 40% of the 2,555 surveyed postdoctoral fellows are planning on an academic position. Since the vast majority of academic careers require a person to be able to teach, whether in a formal classroom or in some other format, having teaching skills and experience will therefore help most postdoctoral fellows to obtain a job in academia, especially at four-year colleges and liberal arts institutions. In addition, many research universities now acknowledge the importance of university teaching and the value of faculty teaching skills. It was reported that recent graduates from the University of Colorado were offered higher base salaries for faculty jobs because they had specialized classroom training (http://www.nagps.org/files/tatraining.pdf?PHPSESSID=dcb7a205236ab775c3340406ddadb71f). A national survey of newly hired faculty and their chairpersons agreed that graduate programs did not adequately focus on preparation for college teaching (*Adams, 2002: What Colleges and Universities Want in New Faculty,* http://www.aacu.org/pff/PFFpublications/what_colleges_want/index.cfm), which makes the acquisition of teaching experiences during postdoctoral training even more desirable.

Sinya Benyajati

Furthermore, teaching skills (see below) are skills that everyone, regardless of career choice, can use in the workplace (eg, in seminars, coaching employees, developing audio-visual materials for presentations, and publications).

What Type of Teaching Skills Do Postdoctoral Fellows Need?

Quality teaching not only includes well-structured lectures but also the ability to utilize new instructional methods or pedagogies (e.g., use of technology, active learning, collaborative learning, field-based learning, simulations) and creative techniques that effectively engage diverse students and support learning. Trainees need more than just the experience of teaching classes; they should also develop skills in working with students that include problem solving and advising.

The American Physiological Society and the Association of Chairs of Department of Physiology (*APS/ACDP List of Professional Skills for Physiologists and Trainees, 2003*: http://www.the-aps.org/education/skills.htm) recommend that trainees should develop the following teaching skills: effective classroom teaching to varied audiences in terms of subject matter; effective classroom teaching in terms of pedagogy; ability to convey the competence in subject matter and confidence in one's ability to teach; ability to develop course curriculum and individual lessons; effective use of common instructional aids, including audiovisual techniques; ability to help students understand the general principles and concepts underlying a particular lesson; ability to explain both basic and difficult concepts clearly; ability to put a specific lesson into larger context (clinical relevance, prior material); ability to ask good questions (testing, study, case histories); ability to provide feedback to students; awareness of the strengths and limitations of various means for evaluating teaching performance; ability to adjust lesson plan based on information garnered from student questions; ability to foster an effective learning environment including showing respect for the student, encouraging their intellectual growth and providing a role model for scholarship and intellectual vigor

How Do Postdoctoral Fellows Find Teaching Experience?

Obtaining teaching experience while completing a postdoctoral appointment can sometimes be difficult. Even postdoctoral fellows who have a strong desire to teach may struggle to find time for both research and teaching activities. Postdoctoral fellows mainly receive teaching opportunities/trainings provided by their institutions, departments, and advisors. Most teaching opportunities are found at academic institutions. However, postdoctoral fellows in industry laboratories can still find teaching opportunities through networking and seeking out mentors at academic institutions in nearby locations.

Mentors as Resources. To obtain a teaching opportunity, the postdoctoral fellow must take a proactive approach, expressing interest and seeking advice from the mentor. Most importantly, the postdoctoral fellow needs to have a men-

Siribhinya (Sinya) Benyajati, is an Associate Professor in the Department of Physiology at the University of Oklahoma Health Science Center. She teaches Renal Physiology to medical, dental, pharmacy, physician assistant and graduate students. She shares her passion for teaching and mentoring with local high school seniors, advises biology students in community colleges and has served as Director of the Summer Undergraduate Research Experi-ence Program and Coordinator for the other three NIH-sponsored undergraduate research programs (INBRE, NARCH, UBEP) at the Oklahoma Health Sciences Center campus.

In 2007, Benyajati received the 24th annual Stanton L. Young Master Teacher Award, one of the largest awards in the nation for medical teaching excellence.

She is the current Chair of the APS Women in Physiology Committee.

tor/advisor that supports his/her career development and will allow more flexibility in incorporating training opportunities with research. With the approval of the mentor, the postdoctoral fellow can, as a start, arrange to observe a faculty-taught class session in the department and then meet with the instructor to talk about his/her approaches to teaching. The mentor/advisor could also arrange for a supervised teaching session within the department [leading a discussion session, teaching a lab, guest lecturing, teaching a small portion of a course on an adjunct basis (at your own or another institution)], after which the advisor or other faculty could provide constructive feedback about the fellow's teaching performance (what went well, what could be improved, what was gleaned from the experience). The advisor could also help set up other types of teaching arrangements for the postdoctoral fellow, such as individual tutoring or facilitating review or help sessions for students.

Institutional Resources. Many institutions now provide resources to improve teaching skills by establishing "centers for teaching and learning." These centers sponsor workshops, seminars, and brown-bag lunch events and provide a library of resources to help graduate students, professional students, postdoctoral fellows, and faculty members learn and improve their teaching techniques. Interested postdoctoral fellows should check out the resources at their institutions and take advantage of the help that such a resource center can provide.

A number of institutions offer courses related to education to trainees. These institutions are members of the national Preparing Future Faculty (PFF) Program that provide graduate students and postdoctoral fellows with opportunities to observe and experience faculty responsibilities that include teaching, research, and service (http://www.preparing-faculty.org). Although the exact curricula of the PFF Programs vary among institutions, the core features are the same. For example, at the University of Oklahoma Health Sciences Center, the PFF Program is a one-year interdisciplinary program offered to graduate students and postdoctoral fellows as a two-course sequence. The first two-credit hour course provides a didactic background in instructional methods. Upon completion of the course, fellows will have assembled individual teaching portfolios comprised of teaching philosophy, lesson plans, instructional objectives, instructional media, self-assessment tools, and structured peer evaluation tools. The second two- to three-credit hour course provides discipline-specific teaching experience in university classrooms under the supervision of assigned faculty mentor. Fellows who are interested in gaining skills in teaching and learning should check whether a similar PFF Program is available at their institution. Admission to such program usually requires a letter of permission from the mentor or supervisor.

Funding Resources. There are also government-sponsored, as well as institutional- and private foundation-sponsored, "Postdoctoral Teaching Fellowships" available to help overcome the difficulty postdoctoral fellows encounter with balancing time between research and teaching activities. However, these fellowships are generally available to postdoctoral fellows at specific institutions. With this type of fellowship, the fellow is required to spend a portion of training time learning how to be an educator of the future, similar to that described for the PFF program. Similar to the PFF Program, the commitment and contribution of the mentor is critical in the participation of the fellow in this type of fellowship. Some programs will recommend that a second independent mentor be appointed as the teaching mentor to the postdoctoral fellow. For the postdoctoral fellows who know early on that they want to teach, this type of fellowship is invaluable. Information on postdoctoral teaching fellowships can be found on several databases, such as PostdocJobs (http://www.postdocjobs.com/jobseekers/fellowships.shtml) and GrantsNet (http://www.grantsnet.com/search/srch_menu.cfm).

Other Resources. Other ways to develop and refine teaching skills during postdoctoral training are to utilize excellent teaching resources available both as hardcopies and online resources (see examples below) and attending training conferences.

American Physiological Society. Careers in Physiology Web Site: http://www.the-aps.org/careers/careers1/Postdoc/pteach.htm.

James Austin (2004) The Academic Scientists' Toolkit http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/0000/the_academic_scientists_toolkit.

Ken Bain (2004) *What the Best College Teachers Do*. Harvard University Press

Barbara Gross Davis (1993) *Tools for Teaching*. Jossey-Bass Publishers

Barbara Gross Davis (2008) *Tools for Teaching. Second edition*. John Wiley & Sons

Honolulu Community College. *Faculty Development:Teaching Tips Index:* http://honolulu.hawaii.edu/intranet/committees/FacDevCom/guidebk/teachtip/teachtip.htm.

Robin Wright (2001) The Art of Teaching http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/0910/art_of_teaching, and http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/0980/the_art_of_teaching_session_2_using_portfolios_to_improve_and_evaluate_teaching.

Tips for Getting Teaching Experience

Discuss your interest in getting teaching experience with your mentor early, ideally during your interview for the postdoctoral position, so that training opportunities can be accommodated during the postdoctoral training period.

If the research mentor cannot commit their time to the teaching development, with his/her permission, find an independent teaching mentor who can be involved in the training process.

Attend classes, workshops, or seminars on teaching that are offered at your institution, particularly courses that offer in-depth preparation for teaching and professional development as a future faculty (PFF Program).

Explore teaching publications and online resources to learn about teaching techniques and best practices.

Arrange to observe a faculty-taught class session in your department and discuss with the instructor about his/her approaches to teaching.

Arrange for a supervised teaching and feedback session with a faculty mentor.

Teach! Try a variety of teaching experiences (leading lab or discussion sessions, review sessions, lectures, individual tutoring, team teaching). ❖

Additional commentary and discussion on this topic can be found on the APS web site at http://www.the-aps.org/careers/careers1/mentor/postdocteach.htm.

Sounds of Science: Society Launches Podcast

The first episode of *Life Lines* went live on October 15, featuring interviews with John West and Chip Montrose and a study from the *Journal of Applied Physiology*. The podcast is in addition to the press release program, which issues releases to print, broadcast and online media outlets. The monthly podcast is part of the Society's commitment to share scientific knowledge with the general public. Life Lines aims to: provide greater public access to scientific information; promote public understanding of physiological research and its relevance to everyday life; and build recognition of the Society and its members.

If you haven't already, please check it out at http://www.lifelines.tv.

Media Roundup

Our journal studies have been highlighted in some of the leading newspapers and magazines in the country in recent months. Our clipping service noted APS studies in the Sacramento *Bee*, Toronto *Globe and Mail*, San Diego *Union Tribune, Newsday* and the New York *Post*, among other media outlets. In some cases, these mentions came from an "evergreen" release on water consumption.

Here are few examples of the stories that have appeared:

Low Lead Exposures Can Hurt Kidneys in US News and World Report (http://health.usnews.com/usnews/health/healthday/071010/low-lead-exposures-can-hurt-kidneys.htm)

The Washington Post (http://www.washingtonpost.com/wp-dyn/content/article/2007/10/10/AR2007101001497.html.)

Atlanta Journal Constitution (http://www.ajc.com/health/content/shared-auto/healthnews/envm/608975.html)

Austin American-Statesman (http://www.statesman.com/health/content/shared-uto/healthnews/envm/608975.html.)

CBC (Canada) News (http://www.cbc.ca/cp/HealthScout/071010/6101008AU.html.)

In addition, a study on the afternoon nap and blood pressure was picked up by:

The Los Angeles Times (http://www.latimes.com/features/health/la-he-nap22oct22,1,4614032.story?coll=la-headlines-health.)

*The Washington Post (*http://www.washingtonpost.com/wp-dyn/content/article/2007/10/23/AR2007102300734.html. (look under "Nap Time")

Innovations Report (Germany): (http://www.innovations-report.de/html/berichte/medizin_gesundheit/bericht-92985.html.)

If you know of a study that is in Articles in Press and might be of interest to the general public, please drop a line to Communications Director Donna Krupa at dkrupa@the-aps.org or call her at 301-634-7209.

APS-Sponsored Fellow Relocates to 'Fourth Estate'

AAAS Mass Media Fellow Katherine Leitzell successfully completed her 10-week assignment at US News & World Report *in Washington, D.C. this past summer. The Mass Media Fellowships are sponsored by various scientific societies and are meant to encourage communication of science to the general public. Leitzell, who was sponsored by APS, has a master's degree in neuroscience from the University of Southern California (USC) and is currently a freelance science writer. The following is a firsthand account of her experiences at* US News:

When I arrived at the offices of *US News & World Report* on a Thursday morning last summer, I didn't know what to expect. I had spent several days in a whirlwind orientation run by the AAAS, wandered around a bit in Washington D.C., and spent hours leafing through magazines. But all I'd heard from my editor was when to show up. I was on edge as I walked into the building, nervous about interviewing people, writing badly, or making a mistake.

I've always loved reading and writing. I found that in my graduate program at USC, this was something of an anomaly. While other students dreaded and complained about written qualifying exams, those weeks spent in the library were a paradise for me. I jumped at chances to write review articles, to author a book chapter, and to write for the USC magazine. So when I saw that the AAAS sponsors a program for graduate students to test their skills as science writers, I jumped at the chance.

By noon the first morning, I'd been assigned to report on three groundbreaking stem cell studies published simultaneously in *Nature* and *Cell*. My editor, Anne, asked me to work with one of the politics writers to put together a last-minute story for the next week's magazine. No time for nerves, I called up the study leaders, emailed a developmental biologist I knew at USC, and carefully read through the articles. I quickly found that my nervousness was unfounded—even though I stumbled over my words when I first got on the phone, I was relatively well versed in the research, and knew enough of the basics to speak intelligently with the scientists. I worked with Chris Wilson to piece together the science and politics, and we ended up with a one-page story in the next week's magazine.

After those first days under deadline, I struggled to develop pithy story ideas that would resonate with *US News* readers. I discovered that the process of science writing is a tug-of-war between scientific accuracy, a magazine's voice, and the readers' desire to see something new and exciting. My editor turned down many of my ideas because they were too esoteric for our readers. Others were nixed because the science was too new. I quickly discovered that it wasn't enough for a story to be interesting. It had to have a practical angle: Scientists discover a gene that could increase the risk of heart attack—so what? Here's how you can prevent a heart attack—perfect.

Over the course of the summer, I ended up writing on more topics than I could have imagined, given my perceived constraints. I wrote weekly for the website, and more occasionally for the print magazine. I researched diets, diseases, and genes. I began exploring the FDA, the EPA, and the Surgeon General's office. I discovered an interest

in women's reproductive health, and wrote on birth control, emergency contraceptives, and pregnancy. I even began exploring some of the clinical research behind alternative medicine. As I explored these topics, I began to understand why scientists so often complain about the quality of science writing. Only a few of my colleagues at *US News* had any background in science, yet they were asked every day to explain and interpret medical studies for the general public. Even when you understand something well, it's difficult to include all the nuances in less than 500 words. There's a reason that scientific prose is so jargon-filled, and that is because jargon is very exact.

One of the best things about working as a journalist this summer was the ability to get anyone on the phone. I had a license to ask both stupid and difficult questions, and whether I was talking to a busy doctor or a famous scientist, they were usually incredibly patient and very friendly. As a graduate student, I'd often been too nervous to pipe up with questions during lectures, fearing that I'd sound stupid. After talking with so many scientists in plain English, I no longer have that fear. They assume from the get-go that I know nothing, and if I prove them wrong, they're pleased.

By the end of the summer, I'd made the decision to plunge headfirst into science journalism. I'm now living in Colorado, writing part-time for a regional magazine while continuing to freelance on health and science for *US News & World Report*. I'm also taking advantage of my background to write about science for *Scientific American Mind* and *Backpacker Magazines*. It's a challenge to work as a freelancer, but unlike being a graduate student, the more work I do, the more I get paid. ❖

PHYSIOLOGY IN PERSPECTIVE: THE WALTER B. CANNON AWARD LECTURE (SUPPORTED BY THE GRASS FOUNDATION)

Barbara Block
Stanford Univ.

"Ecophysiology in the 21st Century: Probing Genomes, Oceans and Climate Change with Bluefin Tuna"

SATURDAY, APRIL 5, 5:45 PM

HENRY PICKERING BOWDITCH AWARD LECTURE

Stephanie W. Watts
Michigan State Univ.

"The Love of a Lifetime: 5-HT in the Cardiovascular System"

SUNDAY, APRIL 6, 5:45 PM

CLAUDE BERNARD DISTINGUISHED LECTURESHIP OF THE TEACHING OF PHYSIOLOGY SECTION

Randy Olson
Filmmaker, Prairie Starfish Productions

"Don't Be Such a Scientist: Talking Substance in an Age of Style"

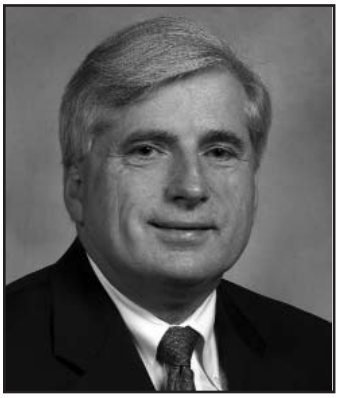
SUNDAY, APRIL 6, 10:30 AM

ROBERT M. BERNE DISTINGUISHED LECTURESHIP OF THE CARDIOVASCULAR SECTION

Michael Wolin
New York Medical College

"Reactive Oxygen Species and the Control of Vascular Function"

SUNDAY, APRIL 6, 2:00 PM



ERNEST H. STARLING DISTINGUISHED LECTURESHIP OF THE WATER AND ELECTROLYTE HOMEOSTASIS SECTION

Joey Granger
Univ. of Mississippi School of Medicine

"Hypertension During Preeclampsia: A Lesson in Integrative Physiology"

SUNDAY, APRIL 6, 3:15 PM

CARL LUDWIG DISTINGUISHED LECTURESHIP OF THE NEURAL CONTROL AND AUTONOMIC REGULATION SECTION

Patrice Guyenet
Univ. of Virginia Health System

"Is Hypertension a Neurological Disease?"

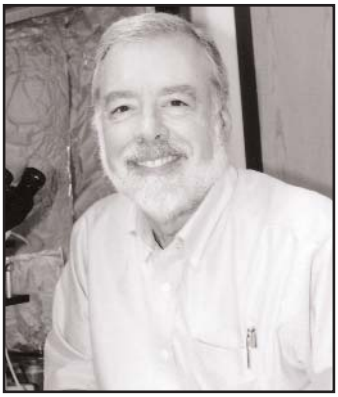
MONDAY, APRIL 7, 8:00 AM

SOLOMON A. BERSON DISTINGUISHED LECTURESHIP OF THE ENDOCRINOLOGY AND METABOLISM SECTION

David Wasserman
Vanderbilt Univ.

"Four Grams of Glucose"

MONDAY, APRIL 7, 10:30 AM

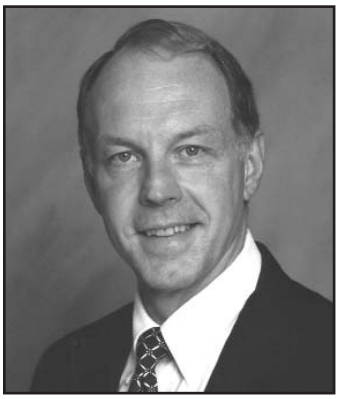


HUGH DAVSON DISTINGUISHED LECTURESHIP OF THE CELL AND MOLECULAR PHYSIOLOGY SECTION

Douglas Eaton
Emory Univ. School of Medicine

"The Salt of the Earth, Strike While the Ion is Hot"

MONDAY, APRIL 7, 2:00 PM



Edward F. Adolph Distinguished Lectureship of the Environmental and Exercise Physiology Section

Ron Terjung
Univ. of Missouri, Columbia

"Title"

Monday, April 7, 2:00 pm

August Krogh Distinguished Lectureship of the Comparative & Evolutionary Physiology Section

David Evans
Univ. of Florida

"Osmoregulation in Fishes: What Have We Learned Since August Krogh, Homer Smith and Ancel Keys?"

Monday, April 7, 3:15 pm

Julius H. Comroe, Jr. Distinguished Lectureship of the Respiration Section

Stella Kourembanas
Harvard Medical School

"Pulmonary Vascular Disease: New Insights on Mechanisms & Emerging Treatments"

Tuesday, April 8, 8:45 am

Joseph Erlanger Distinguished Lectureship of the Central Nervous System Section

Eve Marder
Brandeis Univ.

"Variability, Homeostasis and Compensation in Neuronal Networks"

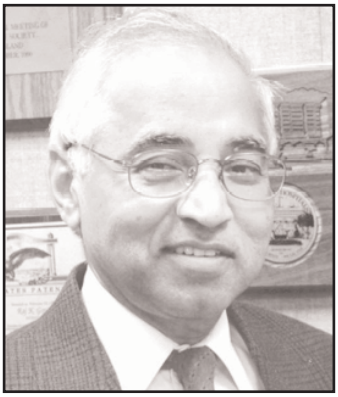
Tuesday, April 8, 10:30 am

Carl W. Gottschalk Distinguished Lectureship of the Renal Section

Peter Aronson
Yale Univ. School of Medicine

"Roles of Ion Exchangers in Renal NaCl Transport and Pathogenesis of Kidney Stones"

Tuesday, April 8, 2:00 pm



Horace W. Davenport Distinguished Lectureship of the Gastrointestinal & Liver Section

Raj Goyal
Harvard Medical School

"Nitrergic Nervous System: Its Role in the Gut"

Tuesday, April 8, 3:15 pm

Walter C. Randall Lecturer in Biomedical Ethics

Jerrold Tannenbaum
Univ. of California, Davis

"Bioethics and the Hamburger Principle: From Xenotransplantation to Chimeras and Back"

Tuesday, April 8, 2:00 pm

Saturday, April 5, 2008 8:00 AM-12:00 PM

Refresher Course
Refresher Course in Respiratory Physiology
Education Track
L. Britt Wilson and Robert W. Brock

Saturday, April 5, 2008 8:00 AM-5:30 PM

Symposium
Microcirculatory Society President's Symposium, Business Meeting and Social

Saturday, April 5, 2008 1:00 PM-3:00 PM

Workshop
Mining the Metabolome
Metabolism and Energy Track
Education Track
Willis K. Samson and Michael Hanley

Symposium
How to Communicate with the Public Directly
Career Development Track
TBA

Saturday, April 5, 2008 3:15 PM-5:15 PM

Workshop
Exercising the Metabolome
Metabolism and Energy Track
Education Track
David G. Parkes and Alastair V. Ferguson

Symposium
What Every Scientist Needs to Know About Ethical Issues in Biomedical Research
Career Development Track
Jane Reckelhoff

Award Session
APS Water and Electrolyte Homeostasis Section Trainee Finalist Awards Symposium

Saturday, April 5, 2008 4:00 PM-6:45 PM

Workshop
AFMR Translational Research Development Workshop

Saturday, April 5, 2008 5:45 PM-6:45 PM

Lecture
Physiology in Perspective—The Walter B. Cannon Memorial Award
Barbara A. Block

Sunday, April 6, 2008 8:00 AM-10:00 AM

Symposium
Recent Advances in the Renin-Angiotensin-Aldosterone System for the Investigation and Treatment of Hypertension
Translational Physiology Track
Christine G. Schnackenberg and Joey Granger

Symposium
Regulatory Mechanisms in Diseases of Epithelial Transport
Channels and Transporters Track
Jerrold Turner and Asma Nusrat

Symposium
Caveolae and Caveolins in Cardiovascular Physiology and Disease
Cell Physiology Track
Hemal H. Patel and Paul A. Insel

Symposium
Is Formative Assessment an Effective Way to Improve Learning?
Education Track
Jonathan Kibble and Penelope A. Hansen

Symposium
Marketing Yourself on Paper for Academic Positions
Career Development Track
Lacy A. Holowatz and Eric Berglund

Featured Topic
Out of the Shadows: Uncovering the Role of ACE2 and Ang-(1-7) in Cardiovascular Regulation
Eric Lazartigues

Featured Topic
Signaling and Control of Skeletal Muscle Remodeling
Cell Signaling Track
Ruud Schilder

Featured Topic
Renal and Circulatory Physiology and Pathophysiology in Metabolic Syndrome
Metabolism and Energy Track
Carolyn Ecelbarger

Featured Topic
Smarter Targeting of Genes for Cardiovascular Genomics
David Paterson and Julion Paton

Sunday, April 6, 2008 10:30 AM-12:30 PM

Physiology InFocus: One Physiology
Physiology and Global Health
Hannah V. Carey

Lecture
Claude Bernard Distinguished Lectureship of the APS Teaching of Physiology Section
Randy Olson

Tutorial
Publishing 101: Dos and Don'ts of Publishing in APS Journals
Career Development Track
Kim E. Barrett

Symposium
The Kidney: Aging, Apoptosis, Endocrine Sensitivity and the Kidney's Role in Hypertension
Translational Physiology Track
Michael Symonds

Symposium
Hepcidin Regulation of Iron Transport
Channels and Transporters Track
Marianne Wessling-Resnick, James Collins, and Mitch Knutson

Symposium
The Role of the Carotid Body in Oxygen Homeostasis
Oxidative Stress Track
Sukhamay Lahiri

Symposium
The Na^+ K^+ ATPase Pump: Regulation and Physiological Function in Cardiac and Skeletal Muscle
Channels and Transporters Track
Jean-Marc Renaud and Ole B. Nielsen

Symposium
Newly-Emerging Signaling Pathways in the Renal Microcirculation
Cell Signaling Track
Rodger Loutzenhiser and Pamela K. Carmines

Symposium
Macromolecular Complexes in Endothelial Force Transduction
John A. Frangos and Anthony G. Passerini

Featured Topic
Impact of Obesity on Cardiovascular Function: Role of Inflammation
Metabolism and Energy Track
David Stepp and Jonathan Tune

Featured Topic
Donald J. Reis Memorial Trainee Symposium
Javier Stern and Lara DeRuisseau

Sunday, April 6, 2008 2:00 PM-3:00 PM

Lecture
Robert M. Berne Distinguished Lectureship of the APS Cardiovascular Section
Michael Wolin

Sunday, April 6, 2008 3:15 PM-5:15 PM

Lecture
Ernest H. Starling Distinguished Lectureship of the APS Water & Electrolyte Homeostasis Section
Joey Granger

Lecture
Microcirculatory Society Landis Award Lecture
TBA

Symposium
Role of Endogenous Hydrogen Sulfide Signaling in Health and Disease
Cell Signaling Track
David W. Krause and Jeannette E. Doeller

Symposium
Skeletal Muscle Mitochondrial Function and Dysfunction with Age
Oxidative Stress Track
David Hood

Symposium
Novel Microscopy Techniques for Imaging Single Molecules in Living Cells and Tissues: RICS/STICS and TIRF Meet PALM while Driving OCT CARS
Cell Physiology Track
Education Track
Moshe Levi and Janos Peti-Peterdi

Symposium
Novel Therapeutic Targeting of the Autonomic Nervous System in Heart Failure and Hypertension
Translational Physiology Track
Robert Foreman and Helio Salgado

Symposium
Recent Advances in the Neurobiology of State-Dependent Control of Breathing
Leszek Kubin and Richard L. Horner

Symposium
Progress in Pharmacogenomics and Its Promise for Medicine
Translational Physiology Track
Burton E. Sobel and Charles A. Blake

Symposium
MicroRNA: Functional Significance in Mammalian Species
Mingyu Liang

Symposium
Novel Optical Methods for Studying the Living Circulatory System and Lung
Claudette St. Croix

Featured Topic
Regulation of ENaC by Membrane Lipids
Channels and Transporters Track
He-Ping Ma

Sunday, April 6, 2008 4:15 PM-5:15 PM

Lecture
WEH Young Investigator Award Lecture
TBA

Sunday, April 6, 2008 5:45 PM-6:45 PM

Lecture
Henry Pickering Bowditch Award
Stephanie W. Watts

Sunday, April 6, 2008 5:45 PM-7:45 PM

Poster Discussion
Trainee Highlights in Respiration Physiology
Judith Neubauer and Susan Margulies

Monday, April 7, 2008 8:00 AM-9:00 AM

Lecture
Carl Ludwig Distinguished Lectureship of the APS Neural Control & Autonomic Regulation Section
Patrice Guyenet

Monday, April 7, 2008 8:00 AM-10:00 AM

Symposium
Leukocyte-Dependent Arteriolar Vasoregulatory Dysfunction in Inflammatory Conditions
Oxidative Stress Track
Ronald J. Korthuis and Norman R. Harris

Symposium
The Controversy of Sarcolemmal and Mitocholdral KATP Channels and Cardioprotection
Channels and Transporters Track
Colin G. Nichols

Symposium
Role of Cholesterol in Cardiovascular and Renal Pathology
Translational Physiology Track
Douglas C. Eaton

Symposium
Extra-Nuclear Steroid Signaling, Roles in Modulating Disease and Physiology
Cell Signaling Track
Willis K. Samson and Ellis R. Levin

Featured Topic
Molecular Regulators of the Ins and Outs at the Apical Membrane of GI Epithelial Cells
Channels and Transporters Track
Curtis Okamoto and Catherine Chew

Featured Topic
Smoking Babies Don't Breathe
Translational Physiology Track
Ronald M. Harper and Estelle B. Gauda

Featured Topic
Regulation of Epithelial Transporters and Signaling Processes
Cell Signaling Track
Michael J. Caplan

Featured Topic
Metabolic Syndrome: Molecular Mechanisms, Omics, and Physiology
Metabolism and Energy Track
Jules Griffin

Featured Topic
Cell Phenotype and Function in Response to Lung Injury and Disease
Cell physiology Track
Michael Koval

Monday, April 7, 2008 10:30 AM-12:30 PM

Physiology InFocus: One Physiology
Physiological Basis of Ecosystem Health
Terrie Willliams

Monday, April 7, 2008 10:30 AM-11:30 AM

Lecture
Solomon A. Berson Distinguished Lectureship of the APS Endocrinology & Metabolism Section
David Wasserman

Symposium
Exercise Prescriptions for Prolonged Space Flight
Per A. Tesch

Symposium
Genomic and Proteomics in Colon Cancer
Translational Physiology Track
John Carethers

Symposium
Acute Lung Injury and the Acute Respiratory Distress Syndrome (ALI/ARDS): Therapeutics on the Horizon
Translational Physiology Track
Timothy M. Moore and Brian William Fouty

Featured Topic
Wiggers Award Featured Topic: Neural Control of the Circulation: Angiotensin and ROS in Heart Failure and Hypertension
Oxidative Stress Track
Irving H. Zucker

Featured Topic
CV Section Young Investigator Awardee Featured Topic: Intercellular Calcium Signaling in the Vasculature
Brant Isakson

Featured Topic
Energy Balance and Circulatory Control: Central Pathways and Mechanisms
Metabolism and Energy Track
Gregory D. Fink and Joseph R. Haywood

Featured Topic
Role of ROS and NO in Contraction-Stimulated Glucose Uptake in Skeletal Muscle
Oxidative Stress Track
Michael Reid

Featured Topic
Encouraging Unforgettable Learning
Education Track
Mary Pat Wenderoth

Monday, April 7, 2008 2:00 PM-3:00 PM

Lecture
Hugh Davson Distinguished Lectureship of the APS Cell & Molecular Physiology Section
Douglas Eaton

Lecture
Edward F. Adolph Distinguished Lectureship of the APS Environmental & Exercise Physiology Section
Ronald Terjung

Monday, April 7, 2008 3:15 PM-4:15 PM

Lecture
August Krogh Distinguished Lectureship of the APS Comparative & Evolutionary Physiology Section
Sponsored by Novo Nordisk Foundation
David Evans

Symposium
The Antiquity of Exercise, Exercise Physiology, and the Exercise Prescription for Health
Charles M. Tipton and Suzanne M. Schneider

Symposium
New Insights into the Urine Concentrating Mechanism
Channels and Transporters Track
Jeff M. Sands

Symposium
Focus on the Fibroblast: Therapeutic Target for the Failing Heart?
Translational Physiology Track
Carlin S. Long

Symposium
IBS and Chronic Constipation: Mechanisms and Novel Treatments
Translational Physiology Track
Shaila Basavappa

Symposium
Cell-Cell Communication in Lung Stress Responses
Cell Signaling Track
Jahar Bhattacharya and Michael Koval

Featured Topic
Hormones and Angiogenesis
Cell Signaling Track
Ellis R. Levin

Featured Topic
Gut Hormones in the Regulation of Body Weight and Metabolism: Are We Really What We Eat?
Metabolism and Energy Track
Helen E. Raybould

Featured Topic
NCAR Trainee Featured Topic
Jeff Potts and Weirong Zhang

Featured Topic
Hypertension: Integrated Mechanisms and Sequelae
Michael W. Brands

Featured Topic
Mechanotransduction Mediated by Primary Cilia
Cell Physiology Track
Carole M. Liedtke

Monday, April 7, 2008 5:45 PM-7:45 PM

Symposium
Mid-Career Transitions: Choices and Challenges
Career Development Track
Rolando E. Rumbaut and Nansie McHugh

Tuesday, April 8, 2008 8:00 PM-10:00 AM

Symposium
Temperature Sensing by TRP Channels
Channels and Transporters Track
Jie Zheng

Symposium
Microbial Infection, Inflammation and Intestinal Transport
Translational Physiology Track
Pradeep K. Dudeja and Didier Merlin

Symposium
Computational Physiology
Peter J. Hunter and Poul Nielsen

Symposium
Gainfully Employed: From Launching a Job Search to Navigating Negotiations
Career Development Track
Siribhinya Benyajati, Colleen Cosgrove Hegg, and Jelveh Lameh

Tuesday, April 8, 2008 8:00 AM-10:00 AM

Featured Topic
Arteriogenesis and Vascular Remodeling
Petra Rocic

Featured Topic
Cyclooxygenases and Cardiovascular Diseases
Paul M. Vanhoutte and Michel Feletou

Featured Topic
Satellite Cell Regulation with Aging and Exercise
Thomas Hawke

Featured Topic
Renal Section Young Investigator Award Featured Topic
Christine Maric

Featured Topic
Neurohypophyseal Hormones: Regulatory Control in Health and Disease
Thomas Cunningham and Catherine Uyehara

Tuesday, April 8, 2008 8:45 AM-9:45 AM

Lecture
Julius H. Comroe, Jr. Distinguished Lectureship of the APS Respiration Section
Stella Kourembanas

Tuesday, April 8, 2008 10:30 AM-11:30 AM

Lecture
Joseph Erlanger Distinguished Lectureship of the APS Central Nervous System Section
Eve Marder

Tuesday, April 8, 2008 10:30 AM-12:30 AM

Physiology InFocus: One Physiology
Global Physiological "Omics": Microbes to Medicine
Anne Kwitek

Symposium
Systems and Computational Biology: A Direction for Physiology in the 21st Century
Peipei Ping and William Chilian

Symposium
Chateau Resveratrol: Therapeutic Promise for Cardiovascular Disease
Translational Physiology Track
Dipak K. Das and Ronald J. Korthuis

Symposium
Ciliopathies: Common Themes in Diverse Genetic Disorders
Cell physiology Track
Lisa Satlin and Brad Yoder

Symposium
Plasticity in Airway Receptor Function: Sensors, Central Integration and Reflex Responses
Frank Powell and Lu-Yuan Lee

Featured Topic
Diving Physiology of Mammals and Birds
Andreas Fahlman

Featured Topic
Regulation of Epithelial Ion and Water Channels
Channels and Transporters Track
Mark A. Knepper

Featured Topic
Bacterial-Intestinal Interaction
Andrew Gewirtz

Featured Topic
Muscle Fatigue
Jean-Marc Renaud

Tuesday, April 8, 2008 2:00 PM-3:00 PM

Lecture
Walter C. Randall Lecture on Biomedical Ethics
Education Track
Jerrold Tannenbaum

Lecture
Carl W. Gottschalk Distinguished Lectureship of the APS Renal Section
Peter Aronson

Tuesday, April 8, 2008 3:15 PM-5:15 PM

Lecture
Horace W. Davenport Distinguished Lectureship of the APS Gastrointestinal & Liver Physiology Section
Raj Goyal

Symposium
Neuronal Plasticity in Health and Disease
Ida J. Llewellyn-Smith and Kaushik P. Patel

Symposium
Roles of Oxytocin and Vasopressin in Clinical Disorders
Translational Physiology Track
Sudar Alagarsamy and Catherine Uyehara

Symposium
Inhibiting Cyclooxygenase with Coxibs and NSAIDs: Efficacy vs. Cardiovascular Risk
Translational Physiology Track
Allison B. Reiss and Edwin S.L. Chan

Symposium
Mechano-Sensing at the Vessel Wall in Regulation of Atherogenesis
Cell physiology Track
Tzung K. Hsiai

Featured Topic
O2 Sensing in Pulmonary Vasculature in Health and Disease
Oxidative Stress Track
Stephen Archer

Featured Topic
Energy Balance, Cancer and Diabetes
Metabolism and Energy Track
Thomas M. Nosek

Featured Topic
Role of TRP Channels in Respiratory Function and Disease
Channels and Transporters Track
Mary I. Townsley and Wolfgang M. Kuebler

Tuesday, April 8, 2008 5:45 PM-7:45 PM

Business Meeting
APS Business Meeting

Wednesday, April 9, 2008 8:00 AM-10:00 AM

Physiology InFocus: One Physiology
Physiology and Lifestyle
Helen Raybould

Symposium
Using Nanotechnology to Answer Physiological Questions
Virginia M. Miller and John C. Lieske

Symposium
Myriad Mechanisms underlying the Pathophysiology of Diabetes
Metabolism and Energy Track
Cuihua Zhang and Ann Marie Schmidt

Symposium
Calponin and the Smooth Muscle Thin Filament
Cell physiology Track
Jian-Ping Jin

Symposium
Cardiac Intracellular Ca^{2+} Signaling in Health and Disease
Cell Signaling Track
Alicia Mattiazzi and Valeria Rettori

Symposium
The Role of GABA and Glutamate on Adult Neurogenesis
Stefano Vicini

Featured Topic
Cytokines, Inflammation and Autonomic Regulation
Oxidative Stress Track
Michael Kenney

Featured Topic
Androgens and the Aging Male and Female
Translational Physiology Track
Melinda Sheffield-Moore

Featured Topic
Comparative Immunology: Using Non-Model Systems to Understand the Evolution of Immunity
Kendra J. Greenlee

Wednesday, April 9, 2008 10:30 AM-12:30 PM

Symposium
Mechanisms of Metabolic Depression
Metabolism and Energy Track
Frank van Breukelen and Jason Podrabsky

Symposium
Cardiac Hormones: For the Treatment of Acute Myocardial Infarctions, Congestive Heart Failure, Acute Renal Failure and Cancer
Translational Physiology Track
David L. Vesely

Symposium
Reverse Engineering Towards the Goal of Vessel Regeneration
Kevin Healy and J. Kent Leach

Featured Topic
Exercise, Oxidative Stress, and Endothelial Function
Oxidative Stress Track
Shane A. Phillips

Featured Topic
Plasticity of Respiratory Motoneurons
Carlos B. Mantilla and Albert Berger

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Late-breaking abstracts will be accepted beginning the week of December 10, 2007. The abstracts will be accepted for poster presentations only and will be scheduled on Wednesday, April 9, 2008.

Late-breaking abstracts will be published online.

Late-breaking abstracts must be submitted online at www.eb2008.org with the $90 abstract fee by Wednesday, February 6, 2008.

Please visit www.eb2008.org for information about the meeting, including late-breaking abstract topic categories, the preliminary program, registration and hotel information. Please contact eb@faseb.org if you have questions.

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Register online by February 6, 2008 and complete your hotel reservations by March 3, 2008

Postdoctoral Positions

Carlos B. Mantilla and Albert BergerPostdoctoral Research Position: An NIH-funded postdoctoral position is immediately available to study autonomic control of circulation in health and cardiovascular diseases. Our laboratory uses multidisciplinary approaches to study cardiovascular responses to muscle afferent inputs and neural mechanisms of the response. Background in cardiovascular physiology or neurophysiology and experience with in vitro (brain slice or dissociated cell) or in vivo electrophysiological recording methods. Peripheral nerve recording technique in small animal is preferred but is not required. Required qualifications include a PhD or MD in Physiology or a related field. Salary will be commensurate with experience. Resumes accepted until position filled. Send curriculum vitae and names and addresses of three references to Dr. Li, (Email: jzl10@psu.edu). Heart & Vascular Institute H047, and Department of Medicine, The Penn State University College of Medicine, 500 University Dr., Hershey, PA 17033. Tel: 717-531-5051.

Postdoctoral fellowship: Kamal Rahmouni, PhD and Allyn Mark, MD in the Center on Functional Genomics of Hypertension in the Cardiovascular Research Center and Department of Medicine at the University of Iowa invite highly motivated applicants for postdoctoral positions for NIH funded (until 2012) research grants on neurobiology of energy homeostasis, autonomic regulation and blood pressure control relating to obesity and hypertension. Qualified candidates for these positions are expected to have a strong publication record and excellent references from their PhD research. A notable feature of this postdoctoral fellowship will be experience in combining state-of-the-art genetic and molecular methods with sophisticated neural and cardiovascular physiologic techniques to address fundamental mechanisms of the neurobiology of autonomic and blood pressure regulation and energy homeostasis in mouse and rat models of obesity and hypertension (*JCI* 2004, 114:652-8 and *Diabetes* 2005, 54:2012-18). Experience in genetics, molecular biology, neurophysiology and/or cardiovascular physiology is relevant. A distinctive feature of our laboratory is an exceptional record of career development for postdocs and excellent working environment. A recent survey of postdoctoral fellows by *The Scientist* magazine ranked the University of Iowa as the top research university for postdocs in North America and the fifth-best research institution overall. Send curriculum vitae and names of three references who can be contacted directly to: Dr. Kamal Rahmouni, 3135C MERF, University of Iowa Carver College of Medicine, Iowa City, IA 52242 or kamal-rahmouni@uiowa.edu.

NIH funded Postdoctoral Position: The Department of Psychiatry, University of Cincinnati, Cincinnati, OH has a postdoctoral position immediately available to study cellular/signaling mechanisms underlying neurovascular coupling in the brain. Our laboratory uses state-of-the-art techniques, including fast speed confocal calcium imaging, electrophysiology, immunohistochemistry, molecular biology and 3D cell reconstruction and others. A main focus of our work is the study of the signaling mechanisms governing bi-directional communication between neurons and their surrounding glial and vascular cells. Highly motivated applicants with a background in Neuroscience and experience in one of the listed techniques are encouraged to apply. A competitive salary and benefits will be commensurate with experience and in accordance with NIH guidelines. If interested please send a cover letter, curriculum vitae and contact information from three references to: Jessica A. Filosa, PhD, Department of Psychiatry (Rm 239A), University of Cincinnati, Cincinnati, OH 45237; Email: jessica.filosa@uc.edu; Tel.:513-558-2624.

Research Postdoctoral Fellow: A postdoctoral fellow position is available in the laboratory of Dr. Tom Curran at The Joseph Stokes, Jr. Research Institute of The Children's Hospital of Philadelphia, an interdisciplinary institution dedicated to conducting basic, clinical, and translational research on conditions and diseases that affect children. The postdoc will investigate the role of the Reelin pathway in brain development. Since the discovery of Reelin (D'Arcangelo et al., *Nature* 1995), several molecular components of a complex signaling pathway that controls cell positioning during brain development have been uncovered. We are using a combination of molecular, biochemical, cell biological and genetic approaches to unravel the mechanisms responsible for shaping the mammalian brain. Applicants must have a doctoral degree in biomedical sciences and a strong background in either molecular biology or neuroanatomy. Additional experience with mouse genetics is desirable. Postdoctoral fellows at The Children's Hospital of Philadelphia receive mentored training in a rich scientific and collaborative environment that includes the resources of the adjacent University of Pennsylvania. Additional experience with mouse genetics is desirable. Qualified individuals are requested to reply directly via Email to schaaf@email.chop.edu [EOE]

Postdoctoral positions: NIH-funded postdoctoral positions are immediately available, in the Renal Division at Brigham and Women's Hospital, Harvard Medical School, studying the molecular physiology of epithelial anion transporters. This research will be conducted under the auspices of an NIDDK Program Project Grant (PPG) on the pathobiology of nephrolithiasis. A variety of techniques will be employed, including heterologous expression of transporter cRNAs in Xenopus oocytes, generation and characterization of mutant and chimeric cDNAs, physiological characterization of anion transport mechanisms in epithelial cell lines, and phenotypic characterization of knockout mice. Interactions with other projects in the PPG will include the functional and biochemical characterization of genetic variants in human transporters and related genes, as identified in candidate gene analysis and/or whole genome association studies of patients with kidney stones. Interested applicants with experience in the molecular physiology of ion and/or solute transporters are encouraged to apply; at a minimum, a strong background in molecular biology is required. Applicants must be a US citizen or permanent resident and possess a PhD degree (or equivalent), should have excellent oral and written communication skills, and should display initiative, as well as independence. The candidate will be expected to present research findings at scientific conferences, assist in experimental design,

and apply for extramural postdoctoral funding during the first year of employment. Please send a statement of research interests, curriculum vitae, and the names and contact information of three references to: David Mount, MD, Renal Division, Brigham and Women's Hospital, Room 540 HIM Building, 4 Blackfan Circle, Boston, MA 02115, Email: dmount@rics.bwh.harvard.edu.

Postdoctoral Fellow: Department of Physiology, Otago School of Medical Sciences This is a fixed-term position for two years, and is part of a research project funded by the Neurological Foundation of New Zealand, focussing on "Metabotropic Glutamate Receptor Signalling in a Mouse Model of Cerebellar Ataxia." The Postdoctoral Fellow will carry out research aiming to establish how metabotropic glutamate receptor signalling is altered in a mouse model of cerebellar ataxia, the PMCA2 knockout mouse. Ataxia in the mouse is accompanied by defective cerebellar circuitry and disorganised expression of metabotropic glutamate receptors (mGluR1), the same type of receptors that are lost in a human form of ataxia. The Postdoctoral fellow will determine how mGluR1 signalling is disrupted in this ataxic mouse using whole cell recordings from cerebellar Purkinje neurones and will use in vivo manipulation of mGluR1 pharmacology with post hoc electrophysiological recordings as a way to rescue the defective cerebellar circuitry. This work will provide better understanding of how mGluR1 signalling influences the function of cerebellar circuits and may reveal future targets for the treatment of ataxia. The ideal candidate will have a strong interest in Neuroscience, particularly within the field of Ca2+ signalling at synapses. They will hold a PhD in a suitable discipline and be an experienced electrophysiologist (patch clamp within brain slices) and / or Ca2+ imager (living neurones) with a desire to expand their current knowledge and skills. The ideal candidate will also be fluent in spoken and written English. We offer a promising research project addressing important questions towards understanding the dynamics of cerebellar function using a combination of established and novel methods, excellent equipment and facilities, a stimulating environment, and a highly competitive salary. For expressions of interest or to request further information, please contact Dr. Ruth M. Empson, Department of Physiology, Tel 64 3 479 7464, Fax 64 3 479 7323, Email ruth.empson@stonebow.otago.ac.nz Reference Number: A07/153. Closing Date: Wednesday 31 October 2007. Application Information: with each application you must include an application form, an EEO Information Statement, a covering letter, contact details for three referees and one copy of your full curriculum vitae. For an application form, EEO Information Statement and a full job description go to: http://www.otago.ac.nz/jobs Alternatively, contact the Human Resources Division, Tel 64 3 479 8269, Fax 64 3 479 8279, Email job.applications@otago.ac.nz [EOE]

Postdoctoral Position: CNS Mechanisms of Obesity Hypertension. Applications are being considered for a postdoctoral position to study the central neural mechanisms that contribute to obesity-induced hypertension. Our laboratory uses a variety of approaches including telemetry, in vivo and in vitro electrophysiology, and functional neuroanatomy to identify the cellular mechanisms that contribute to elevated sympathetic outflow and arterial blood pressure in obesity. Previous experience with animal surgeries is preferred but not required. The applicant will have the opportunity to apply for individual extramural funding and have access to numerous faculty and research laboratories that are part of the Department of Physiology (http://www.mc.uky.edu/physiology/) and the Linda and Jack Gill Heart Institute (http://www.mc.uky.edu/cvrc/). Interested applicants should send a CV and contact information for 3 references to: Sean D. Stocker, PhD Department of Physiology, University of Kentucky, 800 Rose St. MS-508, Lexington, KY 40536, Email: sdstoc3@email.uky.edu

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Postdoctoral Positions: in the Department of Health and Human Services, National Institutes of Health, National Institute on Aging. The National Institute on Aging (NIA), a major research component of the National Institutes of Health (NIH) and the Department of Health and Human Services (HHS), is recruiting for several postdoctoral positions in the Neuroplasticity and Behavior Unit (NBU), Laboratory of Neurosciences (LNS) in the Intramural Research Program (IRP) at the NIA. The postdoctoral positions are available to study neural circuits important for learning and memory. Areas of investigation include the role of exercise, dietary supplementation and adult neurogenesis in memory function. The candidates for the multiple positions should have experience in one or more of the following fields of research: electrophysiology, immunohistochemistry, behavior, virology. The candidates must have a doctoral degree in a relevant field with five years or less of postdoctoral experience. Candidates with a strong work ethic and excellent written and presentation skills are encouraged to apply. The NIA IRP offers an outstanding training environment. Salary is commensurate with experience and accomplishments. Applicants should send curriculum vitae, bibliography, and 1,000 word overview of a proposed program along with three letters of recommendation to: Henriette van Praag, PhD, Section of Neuroplasticity and Behavior, Laboratory of Neurosciences, National Institute on Aging, 5600 Nathan Shock Drive, Baltimore, MD 21224 or by Email: vanpraagh@mail.nih.gov. Applications will be accepted until the positions are filled. [EOE]. HHS and NIH are equal opportunity employers.

Postdoctoral position: Penn State University seeks an individual with a PhD in a biomedically-related field and a strong interest in vascular aging to assist an NIH-funded project examining age- and sex-related alterations in blood flow to contracting skeletal muscles in humans. Current studies at our main campus (Noll Laboratory, University Park, PA) and in collaboration with the PPG-funded cardiovascular group at Penn State's College of Medicine (Hershey, PA) involve measurements of cardiac function, muscle blood flow and metabolism, neurovascular control and pharmacological manipulation of the peripheral circulation. The successful applicant will have exceptional resources to facilitate their research including access to a full-time study coordinator, Penn State's General Clinical Research Center, equipment fabrication shop, and biostatistical support. Some experience with human subjects is desirable. The salary and benefits associated with this position are

competitive. Review of applications will begin immediately and continue until the position is filled. Send letter of application indicating research interests, career goals and experience, a curriculum vitae, and the names and contact information of two to three professional references to: David N. Proctor, PhD, Penn State University, 105 Noll Laboratory, University Park, PA 16802-6900 (Tel.: 814-863-0724, Email: dnp3@psu.edu). [EOE]

Faculty Positions

Tenure-Track Assistant Professor Position, Skeletal Muscle Physiologist: The Department of Human Physiology, University of Oregon, invites applications for a tenure-track position at the level of Assistant Professor. The department has strengths in biomedical and rehabilitation research that span the fields of biomechanics, physiology, motor control, and athletic training. The ideal candidate will have a proven record of research investigating skeletal muscle function, preferably in human subjects, and a demonstrated ability or high potential to attract external funding. All areas of research related to muscle physiology will be considered, including cellular/molecular, metabolic, and integrative studies of normal and altered skeletal muscle function and processes, and their impact on human mobility, exercise, injury, rehabilitation, and health. A PhD or MD in a related field and two years of postdoctoral training or independent university research experience are required. Previous university-level teaching experience is highly desirable. The successful candidate is expected to establish a vigorous research program supported by extramural funding, contribute to the mission of the department in undergraduate and graduate teaching, and engage in departmental and university service. The successful candidate will have the ability to work effectively with faculty, staff and students from a variety of diverse backgrounds. Competitive salary support and start-up funds will be provided. Applicants should submit a curriculum vitae, a statement describing their research goals and teaching philosophy, representative recent publications, and three letters of reference to: Search Committee, Department of Human Physiology, 1240 University of Oregon, Eugene, OR 97403-1240. Application materials can be submitted electronically to: janb@uoregon.edu. Review of applications will begin November 15, 2007 and will continue until a suitable candidate is hired. The University of Oregon is an EO/AA/ADA institution committed to cultural diversity.

Assistant/Associate Professor: The Department of Physical Therapy and Rehabilitation Sciences at the University of Kansas Medical Center invites applications for a tenure track faculty member at the rank of Assistant/Associate Professor. Applicants must have a PhD; a background in physical therapy or exercise physiology is preferred. Applicants for the position should have well documented research agenda. The successful applicant will be expected to establish and maintain an active research program, obtain external funding, teach in the entry-level Doctor of Physical Therapy program, and mentor PhD students. The Department of Physical Therapy and Rehabilitation Sciences at the University of Kansas Medical Center is a well-established program offering an entry-level DPT degree, a post-professional DPT degree, a PhD in Rehabilitation Science, and a joint DPT-PhD degree. The program is ranked 10th in the nation among PT programs at public institutions by *US News and World Report*. The faculty has diverse research expertise in the areas of aging, wellness and fitness, diabetes, stroke, Parkinson's disease, peripheral joint injuries and scoliosis. Generous laboratory space and equipment are available. To learn more about the department, please visit our web site at http://www.ptrs.kumc.edu. Interested individuals should apply online at , position # J0010670. Applications will be accepted immediately. Questions can be directed to: Patricia S. Pohl, PhD, PT, Mail Stop 2002, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160; Tel.: 913-588-4564; Email: ppohl@kumc.edu.

Assistant/Associate Professor of Kinesiology: Physiology: Department of Kinesiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst. Appointment: Tenure-track, nine-month appointment, starting September 2008. Qualifications: Earned doctorate in Exercise Science, Kinesiology, Exercise Physiology or related field; record of scholarly research; evidence of success in or strong potential for obtaining extramural funding; demonstrated ability to teach in a higher education setting. Preference will be given to applicants with successful postdoctoral experience, a clear research agenda and strategy for seeking external funding; research experience in the cellular or molecular aspects of exercise physiology, muscle biology or a related area; an ability to work with faculty and staff in a broad range of Kinesiology academic programs; and a commitment to teaching and training a diverse student body. Responsibilities: the successful candidate is expected to establish an independent, externally-funded research program in an area of specialization within exercise physiology; teach undergraduate and graduate courses related to their specialty area; guide graduate student and postdoctoral fellow research; and actively participate in service to professional and University organizations. Interpersonal and communication skills that promote strong collaborations in research, teaching and program development with established faculty within the Department, School and University are essential. A research focus that complements existing faculty expertise is desirable. Salary: competitive and commensurate with qualifications. The University of Massachusetts Amherst is a vibrant and growing institution, committed to the enhancement of its stature as a leading public research university. The University is located in the Pioneer Valley region of western Massachusetts, which provides an excellent environment for cultural and recreational activities. Amherst, the flagship campus of the University system, is home to 19,400 undergraduate and 5,700 graduate students, and a world-class faculty that is committed to growth in scholarship, creative performance and production, opportunity, diversity and inclusion. The campus is a member of the Five College Consortium and collaborates with Amherst, Hampshire, Mount Holyoke and Smith Colleges on many initiatives and projects. The Amherst campus is in the second year of Amherst 250, an ambitious project to recruit an additional 250 new faculty members over a five-year period. Moreover, a $560 million, five-year capital improvement plan is being implemented, including

new construction, renovations and other infrastructure enhancements. Additional information about the campus and School of Public Health and Health Sciences is available online at http://www.umass.edu and http://www.umass.edu/sphhs. Department Description: The Department of Kinesiology (http://www.umass.edu/sphhs/kinesiology/) offers an interdisciplinary approach to the study of movement through investigation of its mechanical, neurological, biochemical, molecular, physiological and behavioral components. The Department currently serves ~ 400 undergraduate majors and 45 MS and PhD graduate students, with 11 tenure track faculty and several research faculty, postdoctoral fellows and lecturers. Departmental research funding currently comes from Government, Foundation and other sources including the National Institutes of Health, the National Science Foundation, the National Multiple Sclerosis Society and the American Diabetes Association. Application Process: applicants should mail a letter of application, curriculum vitae, statement of research plans and teaching philosophy, three reprints and three letters of recommendation to: Physiology Faculty Search, c/o Dr. Jane Kent-Braun, Department of Kinesiology, Totman 108, University of Massachusetts, 30 Eastman Lane, Amherst, MA 01003. Review of applications will begin November 12, 2007 and continue until the position is filled. [AA/EOE]

Tenure track positions: Available in all ranks in the Department of Physiology and Biophysics, School of Medicine and Biomedical Sciences, in the University at Buffalo, State University of New York. We are seeking candidates interested in using molecular, cellular, genetic and/or computational approaches to study signaling networks, molecular and cellular basis of human disease, single molecule interaction, cell differentiation and development. The ability to lead productive collaborative research will be considered in evaluation of applicants for senior positions. Additional information on the Department may be obtained by contacting Dr. Harold C. Strauss, Professor and Chair at hstrauss@buffalo.edu, or at http://www.smbs.buffalo.edu/phb. Applications in a single PDF file that includes CV, brief statement of research interests, and the names and email addresses of three references should be submitted at http://www.ubjobs.buffalo.edu, (posting #0601624). [AA/EOE]

Assistant Professor: The Section of Neurobiology, Physiology and Behavior, in the College of Biological Sciences, at the University of California, Davis, invites applications for a faculty position in Physiology at the assistant professor level. The section is continuing its initiative to build a program emphasis in Muscle Biology and encourages applicants specializing in skeletal, cardiac or smooth muscle physiology to apply. Areas of significant interest include, but are not limited to, exercise physiology and adaptation, muscle growth and atrophy, motor control, metabolic signaling and control, calcium signaling, and muscle mechanics. Successful applicants will be expected to establish a vigorous research program supported by extramural funding, and contribute to the teaching mission of the Section, including the Exercise Biology major. The successful applicant will be part of a growing group of muscle biologists that include two recent hires with interests in thick filament regulation of muscle contraction (Samantha Harris, PhD; University of Washington) and the role of the proteosome in muscle disease (Aldrin Gomes, PhD; UCLA). The Section has grown steadily since its inception in 1993 to include 32 ladder rank faculty who conduct research encompassing a general theme of integrative biology, ranging from muscle physiology and biomechanics, molecular endocrinology, environmental physiology, cell physiology, aging, molecular, cellular, and developmental neurobiology, systems neuroscience, and animal behavior. Candidates must possess a PhD or MD degree with significant postdoctoral experience. Applicants should send a letter describing their research plan and teaching interests, a curriculum vitae, copies of representative publications, and the names of at least five persons from whom references can be obtained to: Sue Bodine, Chair, Muscle Physiology Search Committee, Section of Neurobiology, Physiology, and Behavior, One Shields Avenue, University of California, Davis, CA, 95616-8519. All materials must be received by January 4, 2008 to be assured full consideration. For more information on the position and UC Davis in general, please visit the following web site: http://www.npb.ucdavis.edu/facultypositions/. [AA/EOE]

Assistant Professor - Exercise Physiology: The University of Maryland, Department of Kinesiology seeks a Tenure Track Assistant Professor to develop a research program in animal or human exercise physiology that extends and complements the research of the current Exercise Physiology faculty, to supervise graduate students, and to assist with graduate/undergraduate teaching. Qualifications: candidates must have a PhD degree in exercise physiology or a closely related life science field and must have postdoctoral training. The candidate's research must emphasize mechanistic endpoints related to the impact of physical activity on diabetes, other metabolic conditions, aging, cardiovascular disease or its risk factors. Candidates must provide evidence of productive publication history; previous external grants and teaching experience preferred. Women and minorities are strongly encouraged to apply. Salary is competitive and commensurate with qualifications. The appointment will begin in August 2008, with an earlier start possible. For further information on the position and the Department see http://www.hhp.umd.edu/KNES/. Contact James Hagberg PhD, Department of Kinesiology, University of Maryland, College Park, MD 20742-2611; Email: hagberg@umd.edu. College Park is the flagship campus of the University of Maryland System with over 2,500 faculty and 25,000 undergraduate and 10,000 graduate students. The University is located 8 miles from Washington DC and serves a diverse constituency. [AA/EOE]

Assistant Professor of Biology: Tenure track position with full benefits to start September 1, 2008. Qualifications: strong commitment to undergraduate education, with a broad background in Animal Physiology. All subdisciplines and animal model systems will be considered. PhD required; postdoctoral experience preferred. Previous teaching experience is desirable. Salary: competitive. Responsibilities: teaching six course-equivalents per three-quarter

year which may include some combination of: introductory biology for non-majors; co-teaching one quarter of introductory biology for majors; vertebrate physiology; and graduate/advanced undergraduate course in candidate's area of expertise. Active and productive research program in animal physiology, involving undergraduates, is required. Start-up funds are provided from the College; research grants are available from the College and University on a competitive basis; modest departmental support for continuous research activity will also be provided. The candidate will be encouraged to seek external funding to further support research activities. After the first year, colleagues participate in student academic advising and develop a program of service to the Department, College, and University. Program: the Department of Biological Sciences serves approximately 400 undergraduate majors, sponsors MS (thesis research) and MA (non-thesis) graduate programs, participates in an allied interdisciplinary major in Environmental Sciences, and provides instruction for the General Education Program. We are a research-active faculty with a strong commitment to teaching. The Department of Biological Sciences is housed in a spacious and well-equipped teaching, research and support facility, including a 2,000 square foot state-of-the-art staffed animal care facility. Location: the College of Liberal Arts and Sciences, including the Department of Biological Sciences, is located at the Lincoln Park Campus, approximately three miles north of Downtown Chicago and eight blocks from Lake Michigan. The Lincoln Park area is considered to be among the most desirable residential districts in Chicago. Public transportation and freeway access are excellent. Application: review of applications begins November 1 and will continue until the position is filled. Please send: *1*) vita; *2*) three letters of reference; *3*) statement of research interests; *4*) statement of educational philosophy and teaching interests; and *5*) general list of equipment and supply needs with cost estimates to: Animal Physiology Search Committee, Department of Biological Sciences, DePaul University, 2325 N. Clifton Avenue, Chicago, IL 60614. Additional inquiries to above address, or fax: 773-325-7596; Email: jdean@depaul.edu. The Department of Biological Sciences seeks diversity in its faculty. We encourage applications from women, people of color, and the members of other historically underrepresented groups. [AA/EOE]

Assistant Professor. Comparative Physiologist: The Department of Zoology and Physiology at the University of Wyoming invites applications for a full-time, nine-month, tenure-track Faculty Position, starting August 2008 at the rank of Assistant Professor. Exceptional candidates may be considered at a higher level. We seek an individual interested in comparative, ecological, evolutionary and/or integrative aspects of physiology who uses molecular approaches to address physiological questions at the organismal level in natural systems, but encourage applicants with other backgrounds. The candidate must have a PhD and a strong research record. The successful candidate will teach in our Department's physiology program. Departmental research strengths include ecology, wildlife/fisheries, neuroscience, and physiology. Interested applicants should send a curriculum vitae, a statement of research and teaching interests, three publications, and three letters of recommendation to: Physiology Search Committee, Department of Zoology and Physiology, Dept 3166, 1000 E University Avenue, Laramie, WY 82071. Fax: 307-766-5625. Website: http://uwyo.edu/Zoology; Email: zprequest@uwyo.edu. Review of applications will begin in December 2007. [AA/EEO]

Assistant Professor, Faculty: The Department of Physiology at the University of Arizona (http://www.physiology.arizona.edu) invites applications for a tenure track faculty position at the Assistant Professor level in the area of Cardiovascular Physiology with an anticipated start date of July 1, 2008. The successful candidate will be expected to establish a nationally recognized research program. Candidates with approaches directed at the molecular, cellular, or systems levels are encouraged to apply. Qualifications include a PhD (or equivalent doctoral degree) and a strong publication record. The successful candidate will contribute to the educational mission of the department, which includes teaching medical, graduate and undergraduate students. A competitive start-up package is available. The Department of Physiology has a strong tradition of research collaboration with other academic units at the University of Arizona. Opportunities exist for a shared appointment with the Cardiovascular or Diabetes Research Themes. To apply, please go to http://www.uacareertrack.com and search Job # 39077. Review of material begins on October 8, 2007.

Assistant or Associate Professor, Tenure-track: The Department of Physiology and Pharmacology in the Schulich School of Medicine & Dentistry at The University of Western Ontario invites applications from outstanding early career investigators to fill three probationary (tenure-track) faculty positions in the broad areas of Drug Metabolism-Pharmacokinetics, Organogenesis-Developmental Biology, and Reproductive Biology. Successful candidates will be appointed at the level of Assistant or Associate Professor, with exceptional candidates considered for appointment in a tenured position at the level of Associate Professor. Qualified applicants must have a PhD or MD degree (or equivalent) with training relevant to the disciplines of Physiology and/or Pharmacology, and would have an outstanding record of achievement in research and publication. The selected appointees will be expected to: *1*) establish and maintain a vigorous externally-funded research program; *2*) have a commitment to and demonstrated aptitude for teaching at the undergraduate and graduate levels; and *3*) provide graduate student supervision. Western is one of Canada's leading research-intensive universities, and the Schulich School of Medicine & Dentistry has a long history of excellence in basic biomedical, applied and clinical research. Western has a full range of academic and professional programs for over 32,000 undergraduate and graduate students. The university campus is in London, a thriving city of over 350,000, located midway between Toronto and Detroit. London boasts an international airport, galleries, theater, music and sporting events (see http://www.goodmovelondon.ca). The Department of Physiology and Pharmacology is the largest research-based medical science department in the Schulich School with over 85 associated faculty members, 100 graduate students, 25 postdoctoral fellows, and 40 departmental and research staff. The Department has a strong commitment

to graduate, undergraduate and professional education. Areas of research excellence include the physiology and pharmacology of the cardiovascular, neural, reproductive, endocrine and musculoskeletal systems, and developmental biology related to these systems. Many faculty members in the Department are leaders in nationally-funded collaborative research programs. Funding of several large infrastructure grants has provided state-of-the-art research laboratories and core facilities. New recruits will also have access to the London Regional Genomics Centre, a city-wide genomics core research facility that supports high-throughput genome analysis; London Regional Proteomics Centre, providing state-of-the-art structural biology and mass spectrometry analyses; the London Regional Innovarium, a network of state-of-the-art animal facilities; and London Regional In Vitro Molecular Imaging Centre, a network of advanced microscopy and molecular imaging facility. Further information about the Department is at: http://www.physpharm.fmd.uwo.ca. Please send detailed Curriculum Vitae, a brief statement of research accomplishments and future plans, copies of representative publications, and the names of three referees to: Dr. R. Jane Rylett, Professor and Chair, Department of Physiology and Pharmacology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada N6A 5C1. Applications will be accepted until the positions are filled. Western's Recruitment and Retention Office is available to assist in the transition of successful applicants and their families. Positions are subject to budget approval. Applicants should have fluent written and oral communication skills in English. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Western is committed to employment equity and welcomes applications from all qualified women and men, including visible minorities, aboriginal people, and persons with disabilities.

Assistant Professor: The Department of Military and Emergency Medicine at the Uniformed Services University in Bethesda, MD, invites candidates to apply for the position of Assistant Professor. Qualifications include a PhD in Applied Physiology, expertise in exercise physiology and a background in molecular biology. We seek an enthusiastic researcher and educator with a strong interest in conducting laboratory and field research related to mechanisms of sustained exercise, fatigue, and environmental extremes. Must be able to work as part of a team and have demonstrated leadership skills. Submit CV and names of three references by December 3, 2007 to: Dr. Patricia A. Deuster, Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814. [AA/EOE]

Assistant Professor: The Department of Health Sciences at Gettysburg College invites applications for a full-time tenure-track position in human anatomy and physiology at the Assistant Professor level beginning August 2008. A doctoral degree is required. The successful candidate will be expected to teach in our rigorous health science-based undergraduate program, to supervise undergraduate research, and to maintain an active personal research program. Teaching responsibilities may include courses in the following areas: human anatomy and physiology, research methods, and an upper level course in area of expertise. Gettysburg College is a highly selective liberal arts college located within 90 minutes of the Baltimore/Washington metropolitan area. Established in 1832, the College has a rich history and is situated on a 220-acre campus with an enrollment of over 2,600 students. Gettysburg College celebrates diversity and welcomes applications from members of any group that has been historically underrepresented in the American academy. The College assures equal employment opportunity and prohibits discrimination on the basis of race, color, national origin, gender, religion, sexual orientation, age, and disability. Send letter of application describing teaching and research interests, curriculum vitae, and three letters of recommendation, at least one of which addresses the candidate's teaching ability, to: Dan Drury, Co-Chairperson, Department of Health Sciences, Box 432, Gettysburg College, Gettysburg, PA 17325. Review of applications will begin on January 1, 2008 and will continue until the position is filled. (For more information about the College, see our web page: http://www.gettysburg.edu).

Assistant Professor of Biology, Animal Physiology: The Department of Biology at San Francisco State University invites applications for a tenure-track physiologist position at the Assistant Professor level. We seek applicants working in all areas of vertebrate or invertebrate physiology. Preference will be given to candidates whose research interests complement existing strengths in the Department, which include endocrinology, neurobiology and ecological physiology. Applicants must be committed to teaching both graduate and undergraduate courses and to developing a vigorous, externally funded research program. The successful candidate should have strong communication skills and the ability to work effectively with faculty, staff and students from diverse ethnic, cultural, and socioeconomic backgrounds. Qualifications for this position are a PhD degree, postdoctoral training, and a strong research record. Teaching experience is desirable. Applicants should send their curriculum vitae, separate statements of research and teaching interests, copies of significant publications and reference letters to: Chair, Animal Physiology Search Committee, Dept. of Biology, San Francisco State University, 1600 Holloway Ave., San Francisco, CA 94132-1722. We encourage electronic submission of applications as a single PDF file (excluding reference letters; publications may be sent as separate PDF files) with "Animal Physiology Search Committee" in the subject line to animalph@sfsu.edu. Review of applications begins 15 November 2007 and continues until a suitable candidate is chosen. San Francisco State University, a member of the California State University system, serves a diverse student body of 29,000 undergraduate and graduate (master's level) students. The mission of the University is to promote scholarship, freedom, human diversity, excellence in instruction, and intellectual accomplishment. SFSU faculty members are expected to be effective teachers and demonstrate professional achievement and growth through continued research, publications, and/or creative activities. SFSU and the Department of Biology are strongly committed to a diverse professoriate that includes women and individuals from underrepresented minority groups. More information about this position and the Department of Biology can be found through the website: http://www.sfsu.edu/~biology. The anticipated start for this position is August 2008 (fall semester). [EOE/AA]

Assistant/Associate/Full Professor, Neuromuscular physiologist: The Department of Orthopaedic Surgery at the University of California, San Diego is seeking a highly qualified and energetic neuromuscular physiologist with strong interest in applications to orthopaedic surgery. The applicant should have a strong background in experimental neurophysiology in the context of movement and function. This is a new, tenure track position created to complement the Department's highly regarded research program in muscle physiology and biomechanics. Appointment will be at the Assistant, Associate or Full Professor or In Residence Professor level, commensurate with qualifications and experience. Salary will be based on the UC pay scale. Candidates should possess a doctoral degree, have a strong record of academic research, including peer-reviewed publications. Applicants will be expected to secure extramural funding to support research, and should have demonstrated teaching excellence. It is highly desirable for the applicants to have demonstrated interest in and commitment to translational research. Responsibilities will include research and teaching at UCSD and the VA. Filing deadline: 01/31/2008. Applications received by, or thereafter until position is filled, will receive thorough consideration. Send a detailed CV, copies of selected recent publications, and three letters of recommendation to: Richard L. Lieber, PhD, Professor and Vice-Chair, University of California, San Diego, Department of Orthopaedic Surgery, 9500 Gilman Drive, M/C 9151, La Jolla, CA 92093-9151, email: , http://medicine.ucsd.edu/ortho. [EOE/AA]

Assistant/Associate Professor: Washington State University Program in Health Sciences (Exercise Physiology and Metabolism) invites applications for a nine-month, full-time, permanent, tenure-track appointment at the level of Assistant or Associate Professor (depending on qualifications) located at the WSU Spokane campus. Position is available August 2008. Position Description: the successful candidate will be expected to teach, maintain a focused line of research with significant extramural funding, and participate in the service missions of the university. Required qualifications include a doctoral degree in a relevant area before first date of employment and evidence of scholarly productivity with potential for extramural funding. Preferred qualifications include postdoctoral experience in an area relevant to exercise biology with research emphasis in, but not limited to, cellular signaling, molecular, genomic, and/or proteomic approaches to address the role of exercise in chronic disease prevention or management, and excellent communication skills. Salary will be commensurate with qualifications and experience. Applicant screening begins November 1, 2007. To apply, send the following items to the Search Committee Clerical Manager (see below): Letter of application addressing qualifications and responsibilities, Curriculum vitae, names of three references with mail and email addresses and phone numbers (references will not be contacted until candidate approval is secured), narrative of research plan, including information on grant applications recently submitted (abstract, agency to which it was submitted, amount requested, status of funding) and planned (title, brief summary), statement of teaching philosophy. Send information to: Saren Kennedy, Search Committee Clerical Manager, Attn: E. Carolyn Johnson, PhD, FACSM, College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495 Tel.: 509-358-7630; Fax 509-358-7627; Email: saren@wsu.edu (PDF format preferred) For more information contact: E. Carolyn Johnson, PhD, FACSM, Search Committee Chair, Associate Professor, Program in Health Sciences (Exercise Physiology and Metabolism), College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495 Tel.: 509-368-6733 Email: ecarolj@mail.wsu.edu The complete job description is available at http://www.phs.spokane.wsu.edu and http://www.chr.wsu.edu. [EEO/AA]

Full Professor of Physiology, Medical School Faculty: The University of Medicine and Health Sciences, St. Kitts, will be opening our doors to our first MD Program in January 2008. Established by the founder and former owner of the Ross University School of Medicine, this beautiful, 10-acre oceanfront campus on the Caribbean Island of St. Kitts houses a state-of-the-art-facility that compares with the best medical schools in the world. In order for UMHS-SK to provide a medical education second to none, we seek only the finest faculty members under the direction of the Provost/Dean of Medicine and invite applications for Professor of Physiology. Minimum qualification for these positions is an earned master's degree in subject area. A Doctoral degree is preferred. Recent experience teaching in an accredited MD program in the US is highly desirable. A full description of the positions listed above can be found on our website http://www.umhs-sk.org/hr We offer a TAX-FREE annual salary, an idyllic environment, and the opportunity to become involved in the growth and success of the institution. Please submit a letter of interest, CV and references to: The University of Medicine and Health Sciences, St. Kitts, North American Administrative Offices, 460 West 34th Street, NY, NY 10001, Fax: 212 279-8640 or Email: MBruce@ross-central.com, UMHS-SK Educating the next generation of physicians.

Tenure-Track Vertebrate Physiologist: The Department of Biology, Earlham College, seeks an individual that is first and foremost excited about teaching physiology—-in lecture, laboratory and research venues—-to bright and motivated undergraduates in a nationally-ranked department, at a small liberal arts college. Teaching responsibilities include a human physiology course(s), an upper level specialty course, and contributions to team-taught introductory courses in cell physiology and genetics. A commitment to collaborative student-faculty research, and an ability to bridge our departmental strengths between cellular/molecular and whole organism biology are essential. Applicants who have an interest in one or more of the following are especially attractive: comparative physiology, anatomy, systems biology, use of 'omics' tools. PhD or equivalent required; teaching or postdoctoral experience desirable. Review of applications begins November 1, 2007. Send curriculum vitae, three letters of reference, and statements describing research interests and teaching philosophy to Dr. Peter Blair, Dept. of Biology, Earlham College, Richmond, IN 47374. (http://www.earlham.edu/~biol/) We particularly encourage applications from women, racial minorities, and Quakers. [AA/EOE]

Assistant Professor: Faculty Position in Integrative Animal Physiology. The Department of Biological Sciences at Clemson University invites applications for a tenure-track faculty position in integrative animal physiology at the Assistant Professor level, to begin August 2008. Postdoctoral experience is required. We are seeking a broadly-trained biologist whose research utilizes multidisciplinary approaches to improve understanding of organismal function and adaptation. Specific areas of research are open but should emphasize comparative, experimental, or evolutionary approaches; preference will be given to candidates with expertise in vertebrate systems. The successful candidate will be expected to interact with faculty having diverse interests ranging from organismal biology, ecology, and evolution to cell, developmental, and molecular biology, thereby supporting University emphasis areas in Sustainable Environment and Biomedicine and Biotechnology. The successful candidate will also be expected to establish innovative, externally-funded research programs of national distinction, and to be an excellent teacher. Teaching responsibilities include one upper level undergraduate course in comparative physiology or vertebrate biology and graduate course(s) in one's specialty. Applications should include a curriculum vitae, no more than three reprints, a statement of current and planned research, a statement of teaching philosophy and interests, and names and contact information for three references. Review of applications will begin November 9, 2007 and will continue until the position is filled. Please send application materials by Email as .doc or .pdf files to: sallyb@clemson.edu. Further information about this position, departmental resources, programs, and faculty research interests are available at: http://www.clemson.edu/biosci. [AA/EOE]

Assistant Professor: Exercise Science (with interests in Physical Activity, Nutrition and Obesity), Assistant Professor, (Two positions). The University of Nebraska at Kearney invites applications to fill two tenure-track faculty positions to build a program with research and public health promotion emphasis in nutrition, physical activity and obesity prevention. This recruitment is part of UNK's Program of Excellence Initiative to expand research and community program opportunities in these areas. Both appointments will include teaching responsibilities in the Exercise Science program within the Department of Health, Physical Education, Recreation and Leisure Studies within the College of Education. The successful applicants will work with the faculty of the Human Performance Laboratory to build an active team to apply for extramural funding, and to develop and implement research programs and community outreach interventions in the areas of physical activity, nutrition and/or obesity prevention. Required: earned doctoral degree in exercise science or related field (ABD considered) and evidence of ability to conduct research and garner external funding. Preferred: experience in obesity prevention, physical activity or nutrition assessment or community intervention programming. Excellence in teaching and the ability to communicate effectively with students and community groups is essential. Willingness to work with existing and new faculty to develop an active team is critical. Start Date: August 2008. Competitive salary and benefits. Application review begins December 1, 2007 and continues until positions are filled. To apply, follow directions to complete the online Faculty Profile at http://employment.unk.edu. Also attach a letter of application, vita and names and telephone numbers of five references to the online profile. For questions about the positions: Kate Heelan, Director, Human Performance Lab, Department of HPERLS; 308-865-8180; Fax: 308-865-8073 or Email: heelanka@unk.edu. For questions about the application: 308-865-8655 or Email employment@unk.edu [AA/EO/ADA]. http://www.unk.edu.

Exercise Science (with interests in Physical Activity, Nutrition and Obesity), Assistant Professor, (Two Tenure-track positions): University of Nebraska at Kearney. To apply and for position requirements and application information visit http://employment.unk.edu For questions about the positions: Kate Heelan, Director, Human Performance Lab, Department of HPERLS; 308-865-8180; Fax 308-865-8073 or Email: heelanka@unk.edu For questions about the application: 308-865-8655 or Email employment@unk.edu AA/EO/ADA. http://www.unk.edu.

Assistant Professor: Doane College seeks Assistant Professor of Biology, full-time, tenure-track, beginning August 2008. Responsible for teaching human physiology, cadaver-based human anatomy, introductory cell biology, and mentoring undergraduate student research. Prefer research expertise in physiology, cell biology, developmental biology, or other biomedically related fields. PhD Experience in a liberal arts college. Prior teaching experience preferred. Doane seeks candidates who thrive in a collaborative, creative teaching environment. Send letter of application, resume, statement of teaching philosophy and research interests, and contact information for three references electronically to: Maureen Franklin, VPAA, AcademicAffairs@doane.edu. Positions posted on college website at http://www.doane.edu/About_Doane/Listings/Faculty/. Review of applications will begin immediately and will continue until the position is filled. [EOE]

Assistant Professor, (Anatomy/Biology): The Department of Natural, Information and Mathematical Sciences invites applications for a full time, tenure-track, 10-month, biology position at the assistant professor level beginning August 2008. Responsibilities include teaching, when offered, an introductory course in biology for majors, basic human anatomy for nursing and allied health, developmental anatomy (combined vertebrate anatomy and embryology), and an upper-level biology course, as well as maintaining a productive research program. Research with undergraduates is encouraged and supported. Publication is expected. Appropriate university/professional/community service is also required including contributing to academic and pre-professional program advising, assessment of the major; and engaging in campus initiatives to increase retention and enrollment. More information about the department and our state-of –art facilities can be found at: http://www.iuk.edu/~konims/ Requirements include an earned doctorate in biology (ABDs near completion of dissertation will be considered and if hired will have two years to earn the doctorate which is required for tenure), experience in teaching at the undergraduate level in human/vertebrate anatomy and introductory biology, and

research potential in the field. Postdoctoral experience, experience in using teaching technologies and in working with undergraduate research is desired. Salary is competitive and includes an excellent fringe benefits package. Although the review process will commence November 30, applications will be accepted until the position is filled. Send a cover letter and resume outlining appropriate education and work experience, a one-page teaching statement outlining teaching philosophy, a one-page research statement outlining research objectives, official copies of undergraduate and graduate transcripts, and the names, addresses and telephone numbers of at least three references to Chairperson, Biology Search Committee, Department of Natural, Information & Mathematical Sciences, Indiana University Kokomo, PO Box 9003, Kokomo, IN 46904-9003. You may also Email the above materials to LuAnn Name (lname@iuk.edu). One of eight Indiana University campuses, Indiana University Kokomo is a comprehensive non-residential campus located 50 miles north of Indianapolis in Kokomo, IN, a city with a population of about 48,000. Committed to student success, the campus serves approximately 2,800 students from an 11 county area in north central Indiana. An additional 220 students pursue degrees in technology in cooperation with Purdue University. IU Kokomo has approximately 240 faculty and staff and 125 part-time employees. Associate, baccalaureate, and master's degrees are offered. Additional information about Indiana University Kokomo can be accessed at http://www.iuk.edu. Persons with disabilities that need modifications or adjustments to participate in the application process should contact the Affirmative Action Office at 765-455-9529. [AA/EOE]

Assistant Professor Integrative Animal Physiology: The Department of Biological Sciences at the University of Alabama invites applications for a tenure-track position at the rank of Assistant Professor in integrative animal physiology to begin August 2008. Applicants must have a PhD and postdoctoral research experience. Candidates who study signaling mechanisms that underlie physiological responses in either invertebrate or vertebrate systems are particularly encouraged to apply. The successful candidate will be expected to establish an active, externally-funded research program that includes undergraduate and graduate student mentoring. The successful applicant will contribute to the teaching mission of the department in the areas of physiology, anatomy, and their area of specialization such as endocrinology. To apply, mail hardcopies of curriculum vitae, a letter of application that includes your research interests and goals, a statement of teaching philosophy, a list of courses in your area of expertise, and have three letters of reference sent to: Search Committee-Integrative Animal Physiology, Department of Biological Sciences, Box 870344, The University of Alabama, Tuscaloosa, AL 35487. Questions about the position may be addressed to Dr. Stephen Secor, Chair of the Search Committee at ssecor@biology.as.ua.edu or 205-348-1809. Review of applications will begin December 3, 2007, and continue until the position is filled. For more information visit our website at http://www.as.ua.edu/biology. [AA/EOE]

Assistant Professor: Tenure-Track Appointments, Faculty of Health, The School of Kinesiology and Health Science, York University, Toronto, Ontario, is seeking three (3) tenure-track appointments at the Assistant Professor level in the following areas: Musculoskeletal Biomechanics: expertise in muscle and/or bone mechanics, with an emphasis on mechanisms of injury or disease. The successful applicant will be required to teach anatomy at the undergraduate level. Cardiovascular Physiology: expertise in either vascular or cardiac physiology with an emphasis at the cellular or molecular levels. Neuroscience /Rehabilitation/Athletic Therapy: expertise in cellular/molecular approaches to neurological aspects of exercise with a focus on rehabilitation and injury. Preference would be to an individual who works at both the basic science and patient population levels, and candidates with Athletic Therapy Certification. Starting date is July 1, 2008. A PhD (or equivalent) is required. Duties will include: undergraduate and graduate teaching, supervision in the graduate program in Kinesiology and Health Science (MA, MSc and PhD), conducting a major program of research, and academic service responsibilities. Candidates must demonstrate competence in undergraduate teaching. The present Master's and Doctoral programs cover health-related aspects of exercise physiology, motor control, biomechanics, psychology and fitness. A previous and promising publication record in refereed journals is essential. High priority will be given to candidates with the ability to develop a productive research program supported by external funding. The successful candidates must be eligible for prompt appointment to the Faculty of Graduate Studies. Applicants should send a curriculum vitae, a covering letter stating future research goals, three relevant reprints and have three letters of reference sent by December 1, 2007 to: Dr. Ira Jacobs, Chair, School of Kinesiology and Health Science, York University, 4700 Keele Street, Toronto, Ontario, M3J 1P3, Email: kinchair@yorku.ca All positions at York University are subject to budgetary approval. Further information about the School can be obtained at http://www.kinesiology.yorku.ca and http://www.yorku.ca/kahs York University is an Affirmative Action Employer. The Affirmative Action Program can be found on York's website http://www.yorku.ca/acadjobs or a copy can be obtained by calling the affirmative action office at 416-736-5713. All qualified candidates are encouraged to apply; however, Canadian citizens and Permanent Residents will be given priority.

Assistant Professor of Physiology: The Department of Physiology at Midwestern University invites applications for a full-time, tenure-track faculty position at the rank of Assistant professor to start July 1, 2008. Applicants must have a PhD, at least two years of postdoctoral training and excellent oral communication skills. The successful candidate will be expected to teach in physiology courses for medical, pharmacy, dental, and allied health students and to develop and maintain an externally funded research program. Current areas of research in the Department include metabolic and signal transduction mechanisms in the diabetic myocardium, diabetes and exercise, the mechanisms of genistein action on intestinal and vascular function, caveolin function in vascular smooth muscle, and insect respiratory physiology. Review of applicants will begin November 1, 2007 and will continue until the position has been filled. Interested persons should

submit (electronically or conventional mail) a curriculum vitae that includes a brief summary of research interest, future research plans, teaching philosophy and the manes and addresses of four references to: Dr. Fred Romano, Department of Physiology, Midwestern University, Arizona college of Osteopathic Medicine, 19555 N. 59th Avenue, Glendale, AZ 85308. froman@midwester.edu Tel.: 623-572-3721

Assistant/Associate Professor Metabolic Biology–SoLS: The Translational Genomics Research Institute (TGen) and the Center for Metabolic Biology at Arizona State University seek highly motivated scientists for one or two faculty positions at the level of Assistant or Associate Professor. Research areas can include a broad range of interests in the areas of insulin resistance, type 2 diabetes mellitus and related complications, lipid metabolism, cardiovascular disease. Candidates who are working at the interfaces among genomic, proteomic, and functional studies of proteins are especially encouraged to apply, and experimental approaches seeking links between genes that are candidates for disease processes and the function and abundance of the proteins encoded by these genes would be highly desirable. Two years of postdoctoral research experience and evidence of college level teaching experience desired. The Diabetes, Cardiovascular and Metabolic Diseases Division at TGen, whose mission is to utilize genomic approaches to develop novel or improved diagnostic and treatment strategies for metabolic disorders, including diabetes and related complications, and the Center for Metabolic Biology, whose mission is to define the molecular mechanisms of insulin resistance are jointly recruiting these positions. The successful candidates will have appointments in the School of Life Sciences and the Center for Metabolic Biology at Arizona State University as well as TGen. Modern laboratory space, clinical research center, proteomics and genomics instrumentation are available to the faculty. Generous startup packages will be provided. To apply, send letter of application highlighting your academic expertise and accomplishments, statement of research focus and accomplishments, statement of teaching philosophy and experience, a current CV, three representative publications. Those applying for Assistant level should have three letters of recommendation sent to the Chair, SoLS Metabolic Biology Search Committee on letterhead and signed; those applying for Associate level should supply contact information (name, institution, address, Email address and phone number) for three (3) references. Electronic applications are preferred (to Elaine.Finke@asu.edu), but hard copies will be accepted if mailed to Chair, SoLS Metabolic Biology Search Committee, School of Life Sciences, Box 874501, Arizona State University, Tempe, AZ 85287-4501. Application Deadline**:** December 1, 2007; if not filled, weekly thereafter until search is closed. A background check is required for employment. [AA/EOE]

Assistant Professor of Physiology: The Department of Physiology, Chicago College of Osteopathic Medicine at Midwestern University (Downers Grove IL; http://www.midwestern.edu) invites applications for a tenure-track faculty position at the rank of Assistant Professor. Applicants must have a PhD, at least two years of postdoctoral training, excellent oral and written communication skills and a commitment to the education of future health-care professionals. The 12-month faculty position based in the Chicago College of Osteopathic Medicine (CCOM) is supported by a competitive salary and benefit package that is funded fully by the institution. Physiology instruction to health profession students is integral to the mission of the Physiology department. The successful candidate will participate in team-taught physiology courses for Osteopathic Medical, Pharmacy and Health Sciences students and in the research training of Masters level graduate students. Development of a well-focused, externally funded research program is expected. Startup funds and dedicated lab space are provided. The research area is open. Current strengths in the department include cardiac electrophysiology and central and peripheral neural control of the cardiovascular, respiratory and gastrointestinal systems. MWU is a NIH R15 (AREA) eligible institution. Additional sources of funding at MWU currently or have included R01, R03 and R21 mechanisms, AHA, ADA, other private foundations and industry. Downers Grove is a prosperous western suburb of Chicago and there is easy train and expressway access to the academic, cultural and recreational amenities of the city and greater Chicagoland area. Review of applicants will begin in November 2007 and will continue until the position has been filled. Interested persons should submit electronically (pdf file to kohaga@midwestern.edu) a curriculum vita that includes teaching experience, a brief summary of research interests and future research plans, and the contact information for three references to: Kathleen O'Hagan, PhD, (kohaga@midwestern.edu), Department of Physiology, Chicago College of Osteopathic Medicine, Midwestern University, 55 31st Street, Downers Grove, IL 60515.

Assistant Professor, Metabolic Physiology: The Department of Kinesiology and the Center for Metabolic Biology at Arizona State University invites applications for a tenure-track position at the Assistant Professor level in the Department of Kinesiology beginning in the spring of 2008. The Center for Metabolic Biology is a multidisciplinary group of basic scientists comprised of members of the School of Life Sciences, Department of Kinesiology and Department of Chemistry and Biochemistry. The mission of the Center is to unravel the basic mechanisms underlying the insulin resistance syndrome. A faculty member is sought who studies metabolic physiology using human, animal or *in vitro* models. Research areas could include the role of inflammatory response, lipids, or mitochondrial dysfunction in insulin resistance, and/or the role of muscle contraction in improving insulin action. The candidate will be expected to carry out an active, externally-funded research program, teach undergraduate and graduate courses and train graduate students and/or postdoctoral research fellows and participate in professional and university service. Required Qualifications: *1*) earned doctorate in appropriate discipline; *2*) evidence of a publication record consistent with rank in appropriate journals; *3*) experience of teaching undergraduate or graduate courses in an appropriate discipline; *4*) evidence of funded research or the potential to develop a funded research program; and *5*) evidence of a desire to work within a multidisciplinary environment. Desired Qualifications: *1*) at least two years of postdoctor-

al research experience; *2*) demonstrated evidence of college/university teaching experience; and *3*) evidence of a research focus compatible with research of current ASU faculty in metabolic physiology. Application Requirements: To apply, please submit the following: *1*) letter of application highlighting your academic expertise and professional accomplishments; *2*) a statement of research focus and accomplishments; *3*) a statement of teaching experience and philosophy; *4*) a current curriculum vitae; *5*) three representative publications; and *6*) three letters of recommendation. Send applications by Email to Nicole.barr@asu.edu. Electronic applications are preferred but hard copies will also be accepted and must be sent to: Chair, Metabolic Physiology Search Committee, Center for Metabolic Biology, Arizona State University, Box 873704, Tempe, AZ 85287-3704. Application Deadline: November 15, 2007; if not filled, weekly thereafter until search is closed.
[AA/EOE]

Assistant Professor Tenure track: The new Department of Cell and Systems Biology at the University of Toronto invites applications for a tenure track faculty position to be appointed at the Assistant Professor level in the field of Systems Biology - Neurobiology to begin July 1, 2008. We particularly encourage candidates to apply who have demonstrated excellence in addressing fundamental questions in neurobiology using high-throughput approaches or gene/protein network analyses with bioinformatics, genomic, proteomic, electrophysiological, or imaging tools. Our vision is to advance Systems-wide analyses in Neurobiology which complement existing strengths in the department (http://www.csb.utoronto.ca). Candidates should have at least two years of research experience beyond their doctoral degree. In addition to pursuing a vigorous, internationally recognized research program, the successful candidate will contribute to undergraduate and graduate teaching in the molecular life sciences. She or he would also be expected to network with researchers across campus to take advantage of the extensive resources in Systems Biology at the University of Toronto and its affiliated institutions. A generous start-up package will be provided. Salary commensurate with qualification and experience. Applicants should arrange to have at least three letters of recommendation sent directly to the address below. In addition, applicants should forward their curriculum vitae, copies of significant publications, and statements of research and teaching interests to the Chair, Systems Biology Search Committee, Department of Cell and Systems Biology, University of Toronto, 25 Harbord Street, Toronto, Ontario M5S 3G5, Canada by January 31, 2008. Inquiries should be directed to Les Buck at buckl@zoo.utoronto.ca. The University of Toronto offers the opportunity to teach, conduct research and live in one of the most diverse cities in the world, and is responsive to the needs of dual career couples. The University of Toronto is strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, persons with disabilities, members of sexual minority groups, and others who may contribute to the further diversification of ideas. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

Instructor or Assistant Professor: Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA. Appointment: Twelve-month, full-time; starting date: July 2008 (Negotiable). Qualifications: Completed Doctorate in Physiology, Kinesiology, Biology, Health and Exercise Science or related field; research interest in muscle physiology and rehabilitation; quality publication record; potential for and/or record of external grant funding. Preferred: minimum of two years postdoctoral training, experience performing single muscle fiber contractile studies. Priority Research Area: applicants are sought who utilize basic or applied/integrative methodologies to address health issues related to muscle pathology. The candidate will collaborate with established investigators in the Muscle Cell Physiology Laboratory at Spaulding Rehabilitation Hospital. Current research in the laboratory involves the study of muscle pathophysiology in aging, neuromuscular disease, and spinal cord injury involving human subjects and animal models using the chemically skinned single muscle fiber preparation. Responsibilities: conduct independent and collaborative research; aggressively seek and maintain extramural funding; publish in high impact journals; direct resident, doctoral and postdoctoral research; participate in resident research course and didactics. Expectations: the successful candidate is expected to establish and maintain a nationally recognized externally funded research program, and to integrate their research with that of current members of the department. The successful candidate will have outstanding departmental support, strong research infrastructure, excellent departmental colleagues, and potential for collaborative opportunities within the department and with other investigators at Harvard Medical School. Application process: submit: *1*) a letter of application addressing this position and a curriculum vita; *2*) official transcripts for all degrees; and *3*) three references specific to this position to: Lisa S. Krivickas, MD, Associate Professor, Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, 125 Nashua St., Boston, MA 02114; 617-573-2761; lkrivickas@partners.org. Applications must be postmarked by January 1, 2008 for full consideration. The search will remain open until suitable candidates are identified.

Research Positions

Senior Research Pharmacologist: Abbott Laboratories, Chicago, IL. Follow your aspirations to Abbott for diverse opportunities, competitive salaries, great benefits, a 401(k) retirement savings plan, a company paid pension plan and profit sharing, all with a company providing the growth and strength to build your future. Description: Senior Research Pharmacologist/Associate Research Investigator, (Grade 17-18) full-time position available. Will perform and oversee in vivo safety pharmacology studies (cardiovascular and renal) to define the pharmacologic profiles of novel discovery compounds. Will be expected to develop new cardio-renal models in support of drug discovery efforts. Excellent communication skills are critical since this person will collaborate extensively with multiple project teams. The ability to provide clear direction to discovery projects based on interpretation of complex physiological data is essential. Will

be expected to supervise at least one direct report. Qualifications: Ph.D or equivalent required. Established expertise in in vivo cardio-renal pharmacology based on graduate and/or postdoctoral training. Must be able to design and interpret results from studies that provide definitive conclusions. Good verbal, written and presentation skills are required. Must also have excellent organizational abilities (record keeping, collaborative and time management skills). Must be capable of regularly publishing in high-impact, peer-reviewed journals. Education: PhD required or equivalent. Abbott welcomes and encourages diversity in our workforce. To apply for this position, please visit us at: http://appclix.postmasterlx.com/track.html?pid=402881bd15b2ab890115b569bc020f97&source=the-aps [EOE/AA]

Endowed Chair in Nephrology and Hypertension: Dartmouth Medical School and Dartmouth-Hitchcock Medical Center invite applications for the position of Constantine and Joyce Hampers Endowed Chair and Research Director of Nephrology. A physician-scientist active in patient care, graduate medical education and research will hold a joint appointment in the Department of Medicine, a basic science department and, if appropriate, the VA Medical Center. This individual will be responsible for directing, promoting, and developing research programs in Nephrology in collaboration with innovative and nationally recognized programs in basic, translational and clinical research. Substantial resources, including an NIH funded Training Program, are available to support the development of the Nephrology Research Program. Dartmouth-Hitchcock Medical Center is a 369-bed tertiary care hospital in New Hampshire, with 500 medical and graduate students, and, along with its affiliate VA Medical Center, is a major teaching hospital for Dartmouth Medical School. The successful candidate will be board certified in Internal Medicine and Nephrology, have an outstanding record of scholarly achievement and sustained extramural research funding, possess excellent interpersonal and mentoring skills, and possess organizational and administrative ability. Applicants must qualify for a senior academic appointment as Associate Professor or Professor of Medicine at Dartmouth Medical School. The committee will begin reviewing applications on February 15th, 2008. A curriculum vitae, description of current and future research plans, and names of three references should be submitted electronically to: Bruce A. Stanton, PhD, Chair, Nephrology Search Committee, Professor of Physiology, Dartmouth Medical School, Hanover, NH 03755 bas@Dartmouth.edu [AA/EOE]

Director Positions

Director, Center for Integrated Research in Cognitive and Neural Sciences:, Southern Illinois University Carbondale (SIUC)) and the School of Medicine invites applications for the Director of the a newly established Center for Integrated Research in Cognitive and Neural Sciences (CIR-CNS). CIR-CNS is an interdisciplinary initiative that will build on existing researchers on the Southern Illinois University Carbondale and SIU School of Medicine Springfield campuses, and new recruits. The Director will have a unique opportunity to establish and promote multidisciplinary research groups in a center focused on fundamental, integrative, rehabilitative, and behavioral neural science. The Director of CIR-CNS will be offered a tenure-track appointment at the associate or full Professor or Associate Professor rank level in the Department/College most appropriate to the candidate's expertise, with a 12-month state-funded sponsored salary, generous start-up funds, and spacious research facilities. Departmental affiliates may include the Departments of Anatomy, Physiology, or Biochemistry and Molecular Biology in the SIU School of Medicine-Carbondale, or the Department of Psychology or Rehabilitation Institute at Southern Illinois University Carbondale. The candidate must have a PhD and/or MD degree, a strong publication record, and experience working with multidisciplinary research groups. The ideal candidate should have an internationally recognized and funded research program in an area of basic and/or clinical neuroscience, and leadership qualities to promote collaboration and ensure vigorous growth of the Center in the full range of cognitive and neural sciences. Evidence of successful training of graduate and/or postdoctoral students is also required. Applications will be reviewed beginning November 30, 2007, and continue until the position is filled. Applicants should submit a cover letter highlighting their interests and qualifications, curriculum vitae, research summary, and contact information for four persons qualified and willing to discuss the applicant's abilities to fill this position. Applications may be submitted electronically in PDF or RTF format to: lsmartin@siu.edu, or submit by regular mail to: CIR-CNS Director Search Committee, Office of the Vice Chancellor for Research and Graduate Dean, c/o Linda Martin, Anthony Hall Room 220 (mail code 4344), Southern Illinois University Carbondale, 1265 Lincoln Drive, Carbondale, IL 62901-6512. Applications will be reviewed beginning November 1, 2007 and continue until the position is filled. Information on the position, the departments, and participants affiliated with the Center can be found on the website: http://www.siu.edu/~ovcr/circns.html. https://www.siu.edu/%7Eovcr/. This is a security-sensitive position. Before any offer of employment is made, the University will conduct a pre-employment background investigation, which includes a criminal background check. Women and minority applicants are encouraged to apply. SIUC is an affirmative action/equal opportunity employer that strives to enhance its ability to develop a diverse faculty and staff to increase its potential to serve a diverse student population. All applications are welcomed and encouraged and will receive consideration. [AA/EOE].

Scientific Director: The Children's Hospital of Philadelphia, one of the leading pediatric hospitals and research facilities in the world, ranks among the top two pediatric hospitals nationwide in National Institutes of Health funding, and is home to one of the nation's largest pediatric research programs, spanning virtually every area of pediatric medicine. Groundbreaking clinical and laboratory research activities are conducted through the hospital's new Joseph Stokes Jr. Research Institute, under whose auspices more than 150 investigators and their staffs are pursuing hundreds of active research projects at any given time. To that end, we are seeking a Scientific Director, who will enable us continue to pioneer new therapies,

integrate novel technologies, and tackle the toughest healthcare issues that face our patients and their families. And we maintain our role as a leader in harnessing the data derived from patient care to guide and drive laboratory and clinical investigation, an approach that has served as the foundation of the "bench to bedside" nature of our research program. Research is, and will continue to be, a cornerstone of the Hospital's mission and perhaps the key element in our overall goal of improving pediatric health worldwide. At Stokes Institute at Children's Hospital, we are embarking upon a new era of research that will change the direction and intensity of our efforts while enhancing the care for our patients and families. [EOE]

Scientific Director: The Scientific Director of the Biostatistics and Data Management reports to the Director of the Office for Clinical and Translational Research within the Joseph Stokes, Jr. Research Institute. The Scientific Director oversees two direct reports and a staff of 23 Masters and PhD level biostatisticians, data management and information systems personnel to support investigators throughout The Children's Hospital of Philadelphia. This support includes oversight of the preparation of grants and proposals, design and management of databases, computer systems support, statistical data analysis and interpretation, and dissemination of written reports. The Director works closely with the Chief of the Division of Biostatistics and Epidemiology, who serves as the Faculty Advisor to the staff, in providing the necessary biostatistical expertise required by investigators. Two managers support the Director in the day-to-day department operations. The Director is responsible for allocating resources within the department, communicating with researchers throughout the hospital, and overseeing all revenues and expenses associated with the department. Qualifications: Education & Experience: doctoral degree in a quantitative field, or demonstrated equivalent experience in a research environment; minimum of six years experience in statistical analysis, data management or information systems related to medical data; minimum of six years participation in either government-funded research projects or industry-sponsored drug-development or pre-clinical research, or equivalent; minimum of six years prior experience programming in any combination of PL/SQL, database design software, statistical software, or programming languages such as Visual Basic, C++ or Java; experience in report writing as demonstrated by either co-authorship in publications, or co-authorship in industry documents reporting clinical research results for regulatory purposes, or other evidence of writing skills; supervisory experience of at least two years and at least three subordinate staff. Knowledge, skills, & abilities: excellent leadership, problem solving and decision making skills; ability to work independently and take initiative when necessary; ability to work efficiently on multiple projects; ability to work under stress and meet deadlines; strong ethical conduct and ability to work with confidential and highly sensitive information. Good interpersonal skills; ability to work with faculty, medical researchers and staff. Good oral and written communication skills; ability to supervise and delegate tasks; ability to evaluate others' performance and provide support when deemed necessary; thorough understanding of the clinical research process; thorough understanding of how each facet of the group effects the clinical research process; thorough understanding of security standards in a clinical research environment; thorough understanding of the GCP, HIPAA and FDA guidelines and practices for clinical studies. Hope Lives Here. Our organization offers total compensation packages befitting a world class institution. Apply via e-mail to schaaf@email.chop.edu To apply online: http://www.chop.edu/careers [EOE]

Program Director – Undergraduate Science Education: The Howard Hughes Medical Institute (HHMI), a leading philanthropy devoted to biomedical research and science education, is seeking a Program Director to join our headquarters in Chevy Chase, MD. The Program Director, with an annual budget of over $40 million, oversees HHMI's Undergraduate Science Education activities, including institutional grants to colleges and research universities, and individual grants to professors. The successful candidate will have an advanced degree in science, a national reputation in science undergraduate education, demonstrated skill in managing people and programs, and a commitment to building innovative programs to strengthen biomedical science education. Responses should include research and undergraduate science education accomplishments, a description of administrative and management experience, and a statement of vision of science education challenges and opportunities. Visit http://www.hhmi.org for a complete position description. Send CV and cover letter to: Program Director, Howard Hughes Medical Institute, c/o PRM Consulting, Inc., Attention: Gregory Davis, Managing Director, 1814 13th Street, NW Washington, DC 20009. [AA/EOE]

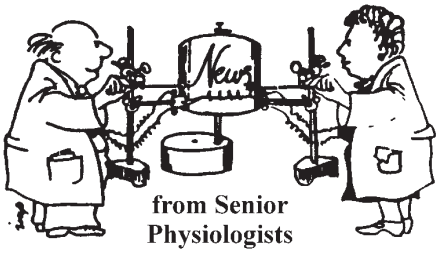
PhD Training Program in Space Life Sciences: The National Space Biomedical Research Institute (NSBRI)-sponsored PhD Training Program in Space Life Sciences at Texas A&M University (TAMU) is currently accepting applications. Students participating in this program work toward a PhD in Nutrition, Kinesiology, or Nuclear Engineering (Health Physics), and focus their research on space environment-induced bone loss, muscle wasting and/or cosmic radiation damage. The Space Life Sciences graduate program at TAMU is designed with immersive components including: fundamental courses in space life sciences, individual research and an experiential component with work at Johnson Space Center, Brookhaven National Laboratory and/or University of Texas Medical Branch. All trainees participate in outreach by teaching elements of space life sciences in a K-12 setting. To learn more about the program, please visit http://www.nsbri.org/GraduateEd. For more information and to request an application, please contact: Lindsey R. Briggs, Texas A&M University Program Coordinator, PhD Training Program in Space Life Sciences, 210 Kleberg Center, 2253 TAMU, College Station, TX 77843; Tel.: 979-862-7752; Fax: 979-862-1862; Email: lrbriggs@tamu.edu; Web site: http://www.nsbri.org/GraduateEd.

Letter to Ronald Freeman

Richard L. Malvin writes: "Thank you for your interest in what a physiologist is doing on entering the ninth decade of his life. In some respects I am doing what I did for the past many decades. Although I am an Emeritus Professor since turning 65 I still teach a bit but have removed myself from research. I leave that to the younger generation who have more difficulty in getting grants than my generation ever did.

"Why am I still engaged? While teaching medical students I found that many are hardly skeptical of unverified claims. Our med students even began an Alternative Medicine club in which they blindly accepted the assertions of a wide variety of practitioners of alternative treatments. This seemed to me to be the opposite of the scientific method, and what is more, dangerous for their patients. As it is difficult to change the thinking of adults in their mid twenties I elected to conduct a seminar course for sophomore undergraduates in our Honors College. The title is The History of Medicine and the Art of Humbug. It has been a rewarding experience for me and, I believe, for the students, as it is the most popular of the seminars. We discuss how early medicine turned into experimental and evidence based medicine from a beginning of anecdotal and non-evidenced based medicine. I must admit that meeting with young bright interested students once a week for two hours keeps my spirits high. My only regret is that our Medical School and probably many others pay no critical attention to fostering the skeptical approach to medical claims. Therapeutic touch is part of many hospital treatments. Why???

"What else am I doing? Enjoying life! I still play tennis regularly for about 4 to 6 hours per week. Unfortunately, I find that the balls made today dont fly off my racket as fast as the older balls, but the game is just as much fun. My lovely wife of 58 years is also a tennis nut. We travel quite a bit and in between we enjoy the cultural events of Ann Arbor: magnificent concerts, plays, dance, and opera.



from Senior Physiologists

"You asked if I had any words of wisdom to pass along to my younger colleagues. I am not sure that one can make such a broad statement. I can only reflect back on my life and tell what worked for me. The first thing is to select a mate who is truly a partner, who you sincerely love and respect. That makes the unavoidable ups and downs of life acceptable. Next, be true to yourself. If you are you will go through life with far fewer regrets than otherwise. Respect all people with whom you interact. You will be respected in turn. As for science do not be afraid to enter the unknown regions. They are the most interesting and usually will result in you being rewarded for your effort. And finally, be a skeptic. By that I do not mean you should believe in nothing. I mean that when a strange claim is made, such as therapeutic touch, or aura therapy, or whatever you should say, Show me the evidence.

"I eagerly await your next letter to me when I turn ninety. You see, I am an optimist."

Letter to Julio Cruz

Joseph C Ross writes: "Thank you for your letter. I enjoyed hearing from you. I was somewhat surprised the APS office knew about my 80th birthday. I did receive the birthday card. I was reasonably active in the APS in the earlier part of my career when I was very active in research and continued with some co-workers after I moved into administration. I am enclosing a copy of my curriculum vitae which will tell you more about my career, which included research, practice of medicine (pulmonary) and administration, all of which I enjoyed.

"I retired about eight years ago which gives me more time with my family (four daughters, one son, and twelve grandchildren and two great-grandchildren). My health has been good so we travel quite often. When I was President of the American College of Physicians, three other members of the A.C.P., the Executive Secretary of the organization and our wives gave lectures in Mexico City, Lima, Buenos Aires and Rio de Janeiro. That was a wonderful experience for us."

"Thank you for your letter." ❖

The Physiologist
Vol. 50, No. 6, 2007

Schultz Wins Seeds of Hope Award for Pioneering Research

Stanley G. Schultz

APS Member Stanley G. Schultz, University of Texas School of Medicine, Houston, was honored on September 28 for research that led to improved health conditions for people living in poverty. The Houston chapter of RESULTS presented Schultz with a Seeds of Hope Award during Building Champions to End Poverty, its annual dinner and program.

"I was privileged to direct some of the pioneering research that led to the breakthrough discovery that a simple solution of table salt, sugar and baking soda could prevent death from dehydration in those suffering from diarrhea," said Schultz, the honorary chair of this year's RESULTS benefit.

"In 1984, RESULTS achieved its first major victory by creating a Child Survival Account within our nation's foreign aid budget. This account made our discovery and other lifesaving services available to millions of children in the developing world," said Schultz, the H. Wayne Hightower Distinguished Professor of the Medical Sciences and the Fondren Family Chair in Cellular Signaling. "Oral rehydration therapy has saved more than 40 million lives over the past 30 years."

The local award is one of numerous honors Schultz has received for his lifelong work on the mechanisms of sodium and glucose-coupled absorption in the small intestine. Most recently, Schultz, a professor and former dean of the UT Medical School, received the prestigious Prince Mahidol Award in Medicine for his basic research that led to the development of oral rehydration therapy. King Bhumibol Adulyadej of Thailand presented the award to Schultz Jan. 31, 2007 at the Grand Palace in Bangkok.

APS Members Elected to Institute of Medicine

The Institute of Medicine (IOM) announced the names of 65 new members, raising its total active membership to 1,501. In addition, the Institute honored five individuals by election to foreign associate membership, bringing the total members in that category to 82. With another 68 members holding emeritus status, the total IOM membership is now 1,651. Included among the new members are three APS Members.

Newly elected APS members are: Robert J. Alpern, Dean, Yale University School of Medicine, New Haven CT; Emery N. Brown, Massachusetts General Hospital Professor of Anesthesia, Massachusetts General Hospital and Harvard Medical School; and professor of computational neuroscience, health science, and technology, Massachusetts Institute of Technology, Boston; and Alan H. Jobe, Professor of Pediatrics, University of Cincinnati School of Medicine; and Director of Prenatal Biology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Above are the recipients of the following Endocrinology & Metabolism Section Awards: New Investigator Award; Virendra B. Mahesh Award for Excellence in Endocrinology; Mead Johnson Research Award in Endocrinology and Metabolism Young Investigator; Research Recognition Award.

Linda Toth Honored with CRL Excellence in Refinement Award

APS Member Linda Toth, Southern Illinois University (SIU) School of Medicine, received the 2007 Charles River Laboratories' Excellence in Refinement Award last month at the 6th World Congress on Alternatives and Animal Use in the Life Sciences in Tokyo. Sponsored by Charles River Laboratories, in cooperation with the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), the award honors an individual who has made an outstanding contribution to the development, promotion and/or implementation of refinement alternatives. "Refinement," one of the "3Rs of alternatives," refers to methods aimed at minimizing pain and distress for laboratory animals. Toth was chosen to receive this award for "a body of research that improves both the understanding and practice of refinement alternatives." Trained in pharmacology and in veterinary medicine, she is Professor in the Department of Pharmacology and Associate Dean of Research and Faculty Affairs at Southern Illinois University School of Medicine. Her exceptional ability to integrate scientific goals and animal care serves to enhance both the quality of research and the quality of life for laboratory animals.

Benos Named University of Alabama Distinguished Faculty Lecturer

APS Past President Dale J. Benos will receive the University of Alabama (UAB) Academic Health Center's most prestigious faculty award: the 2007 Distinguished Faculty Lecturer. He is the chairman of the Department of Physiology & Biophysics at UAB. The award "acknowledges Benos' many

achievements and the high regard in which he is held by his peers," according to a statement from the university.

Schneider Appointed Interim Dean at University of Tennessee

Edward Schneider was appointed interim dean for the College of Graduate Health Sciences at the University of Tennessee Health Science Center in Memphis. He joined UTHSC in 1973 and has been associate dean for the College of Graduate Health Sciences since 1997. He also serves as a professor of physiology and biophysics.

Body Notes Composer Performs in California

Hector Rasgado-Flores and cellist Joyce Geeting performed *Body Notes: A Musical Interpretation of Human Physiology* on Sept. 9 at California Lutheran University in Thousand Oaks, CA. The music, written by Rasgado-Flores and commissioned by the APS, was first performed at the International Congress of Physiological Sciences in 2005. He teaches at Rosalind Franklin University of Medicine and Science in Chicago. He is also a pianist and composer who trained at the Royal School of Music in London and the National School of Music in Mexico City.

Goldberg Receives Knobil Award

APS member Alfred Goldberg of Harvard Medical School has been chosen to receive the 2007 Ernst Knobil Award from the University of Texas Medical Center in Houston. This annual award includes a $10,000 prize and prize lectureship and is given in honor of their former Dean, Ernst Knobil, a distinguished endocrinologist. This award is in recognition of Goldberg's many fundamental contributions to our understanding of the mechanisms and regulation of intracellular protein degradation. This prize has been previously award to Eric Kandel, Joseph Goldstein, Stan Prusiner, and Jeffrey Friedman.

Yassine Amrani is currently Research Assistant Professor, Department of Infection/Immunity and Inflammation, at the University of Leicester, Leicester,UK. Prior to this position Amrani was Research Assistant Professor, Translational Research laboratories, University of Pennsylvania, Philadelphia, PA.

Stephane Baudry is currently a Researcher, Department of Neurophysiology of Movement Lab, University of Colorado, Boulder. Formerly, Baudry was affiliated with Applied Physiology Lab, University Libre De Bruxelles, Brussels, Belgium.

Timothy A. Butterfield, an Assistant Professor, recently affiliated with University of Kentucky, Lexington. Butterfield had been associated with Ohio State University of Columbus, Sports Medicine Center.

Kendra Greenlee is currently Assistant Professor, Department of Biological Science, North Dakota State University, Fargo. Prior to this position Greenlee was a Postdoctoral Fellow, Department of Pulmonary/Critical Care Medicine, Baylor College of Medicine, Houston, TX.

Alastair Hutchison is currently Professor of Pediatrics, Department of Pediatrics/Division of Neonatology, University of South Florida, Tampa. Prior to this position, Hutchison was Professor of Pediatrics, Women's & Children's Hospital of Buffalo, State University of New York, Buffalo.

Akimichi Kaneko is currently Dean Professor, Department of Physiology, Kio University School Health Science, Kita-Katsurgi-gun, Japan. Prior to this position, Kaneko was Professor and Chairman, Seijjoh Univ School Rehabilition, Koryo-cho City, Japan.

Hiu Yee Kwan is currently Postdoctoral Fellow, Department of Nutritional Science and Toxicity, Berkeley, CA. Prior to this position Kwan was Research Coordinator, Department of Physiology, The Chinese University of Hong Kong.

Susumu Minamisawa is currently Professor, Science and Engineering, Waseda University, Tokyo, Japan. Prior to this position, Minamisawa was Associate Professor, Department of Physiology, Yokohama City University Graduate School of Medicine, Shinjuku-ku, Japan.

Erik M. Schwiebert is currently Chief Scientific Officer and Director, DiscoveryBioMed, LLC, Birmingham, AL. Prior to this position, Schwiebert was Associate Professor of Physiology and Biophysics, University of Alabama, Birmingham.

Colin Selman is currently Lecturer, Integrative Physiology/Dept Zoology, University of Aberdeen, UK. Prior to this position, Selman was PDRA, Center for Diabetes and Endocrinology, University College of London, UK.

Ira James Smith, has affiliated with the Harvard University, Brighton, MA. Smith had been associated with the Department of Medicine, Duke University, Durham, NC.

John A. White is currently Professor, Department of Bioengineering, University of Utah, Salt Lake City. Prior to this position White was Associate Professor, Department of Biomedical Engineering, Boston University, Boston, MA.

Donna A. Williams is currently the Associate Dean for Research & Graduate Education in the College of Nursing at Montana State University in Bozeman, MT. Previously, Williams was at the Sinclair School of Nursing at the University of Missouri in Columbia, MO.

Richard J. Traystman is currently Professor/Vice Chancellor for Research, University of Colorado Health Science Center, Denver, CO. Prior to his new position, Traystman was Associate Vice President, Oregon Health and Science University, Portland, OR.

Matthew C. Kostek is currently Assistant Professor, Department of Exercise Science/Public Health Research Center, University of South Carolina, Columbia, SC. Prior to this position, Kostek was a Postdoctoral Fellow, Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC.

Uwe M. Fischer is currently Postdoctoral Fellow, Department of Pediatric Surgery, University of Texas Medical School, Houston,TX. Prior to this position, Fischer was Researcher, Clinic for Cardiothoracic Surgery, University of Cologne, Germany.

Yifan Yang is currently a Postdoctoral Fellow, in the Department of Kinesiology at McMaster University, Hamilton, ON, Canada. Previously, Yang was a Postdoctoral Fellow in the Department of Orthopedic Surgery at the University of California, Irvine, CA. ❖

Wine Wizard

Some good stuff is showing up this month. Mostly reds, but a couple of whites. Not just good value, but also, actually, good.

2006 McManis Viognier, California. $9. Go after this one. McManis is making a name for itself and here is another reason why. Unmistakable nose of Viognier—peach, apricot and even some spice and fig. The palate has both elegance and richness with good viscosity. The flavors are again peach/apricot with very good acidity and no oak noted. The finish is where I find many Viogniers break down —not this one that has good length with decent, lingering fruit flavors.

2006 Kali-Hart Chardonnay, Monterey $10. There is a clear trend back from heavy oaky buttery Chardonnay starting in California, and here is another example of that trend. This has a touch of rubbery sulfur on the nose but it blows off, and does not appear on the palate. The nose and palate both reflect crisp apple/lime notes, and the oak is very light. There is excellent acid and little buttery feel. Lighter style, slightly tart, but good with seafood, for sure.

2006 Domaine des Cassagnoles "Gros Manseng" $8. May be hard to find, don't try too hard, but a pleasant, clean, if generic, white wine from France that has surprising strength of tropical/citric fruit and good mouthfeel. Not complex, but nice with appetizers or cheese.

2006 Woop Woop Shiraz, South Australia $9. Here is another great value.

Peter Wagner

Very approachable if simple rich viscous deeply flavored shiraz with soft tannin, light oak, adequate acid and lots of jammy ripe fruit. Should be widely available, a great party wine, good enough for dinner mid-week as well.

2004 Bogle Phantom red wine $13. This is an odd mix of Petite Sirah, Zinfandel and a splash of Mourvedre. It is serious stuff and well worth trying. A big wine with lots of dark berries and American oak (dill, coconut) on the nose. On the palate it is extracted, big, with loads of dark berry fruit and firm tannins. Rich, viscous, balanced, with good acid and decent length. Great with grilled red meats, that's for sure. Very good value.

NV Grove Street Meritage Napa Valley, $8. This is an oddball - Napa fruit, a true Bordeaux blend (aka, Meritage), a remarkable price and "NV" non-vintage. That is, a blend across more than one year's harvest. It is really very good. Fresh dark berry nose and palate. It is a lighter style wine, not heavy, not overripe, with some elegance and structure. At first it is a bit closed and comes over as hard and lean and tannic, but give it some air time and swirling in the glass, have it with food and it really shines with smooth deep dark fruit and nice acid/tannin backbone. All for $8. 2005 Kilikanoon "Parable" Shiraz McLaren Vale (South Australia). $33. Not cheap, likely hard to find, but this is wonderful, special occasion wine that compares with the best Australia has to offer (at much higher prices). Beautiful stuff, wow. Like Elderton Command for those that know Elderton, but half the price. Forward nose of ripe but not pruny dark berries and coconut/dill (from the American oak). Palate is intense, forward dark berry fruit that is very fresh and lively with excellent acid and medium, silky tannins to lend structure. Mouthfeel is velvety, smooth, deep, lush, but not overdone and structured with some eucalyptus/mint and great depth of flavor. Perfect balance and great length. You will thank me if you can find it, you will hate me if you can't. I bought three. ❖

Physiology in Perspective

Walter B. Cannon Memorial Lecture

The Cannon Memorial Lecture, sponsored by the Grass Foundation, honors Walter B. Cannon, President of the Society from 1913-1916, and is presented annually at the spring meeting to an outstanding physiological scientist, domestic or foreign, as selected by the President-Elect with the consent of Council. The recipient presents a lecture on "Physiology in Perspective," addressing Cannon's concepts of "The Wisdom of the Body." The lecture is considered for publication in the Society journal of their choosing. The recipient receives an honorarium of $4,000, a plaque, and reimbursement of expenses incurred in association with delivery of the lecture. The membership is invited to submit nominations for this lecture. A nomination shall be accompanied by a candidate's curriculum vitae and one letter detailing the individual's status and contributions.

More information on the award and nomination procedures are available at http://www.the-aps.org. Nominations should be sent to: The APS Cannon Lecture Award, c/o Linda Jean Dresser, 9650 Rockville Pike, Bethesda, MD 20814-3991; or submitted online at http://www.the-aps.org/cgi-bin/Election/Lecture_form.htm.

2008

January 30–February 3

Developmental Vascular Biology Workshop III, Monterey, CA. *Information:* Bernadette Englert, Tel: (301) 760-7745; Email: mailto:bernadette@navbo.org; Internet: http://www.navbo.org/dvb08Workshop.htm.

February 2-6

Joint Meeting of the Biophysical Society 52nd Annual Meeting and 16th International Biophysics Congress, Long Beach, CA. *Information:* Yvonne Butters, Biophysical Society, 9650 Rockville Pike, Bethesda, MD, 20814. Tel.: 301-634-7226; Fax: 301-634-7114; Email: ybutters@biophysics.org; Internet: http://www.biophysics.org/meetings/2008.

February 5-7

RACMEM 2008 - Recent Advances and Controversies in Measuring Energy Metabolism, Denver, CO. *Information:* Internet: http://www.uchsc.edu/racmem/.

February 17-21

9th International Symposium on Resistance Arteries 2008, Hamilton Island, Australia. *Information:* Internet: http://medicalsciences.med.unsw.edu.au/somsweb.nsf/page/9thISRA2008.

March 2-7

Molecular Mechanisms in Lymphatic Function and Disease, Ventura, CA. *Information:* Geert Schmid-Schonbein, University Of California, San Diego, Department Of Bioengineering, 9500 Gilman Drive, 0412, La Jolla, CA 92093-0412. Email: gwss@bioeng.ucsd.edu; Internet: http://grc.org/programs.aspx?year=2008&program=molecmech.

May 16-21

2008 American Thoracic Society International Conference (ATS), Toronto, Canada. *Information:* American Thoracic Society, 61 Broadway · New York, NY 10006-2755. Tel.: 212-315-8600; Fax: 212-315-6498; Email: ats2008@thoracic.org; Internet: http://www.thoracic.org/index.cfm.

June 4-6

Second Annual Scientific Meeting of The Organization for the Study of Sex Differences, New Orleans, LA *Information:* Viviana Simon, PhD, Tel: 202-496-5002; Email: viviana@ossdweb.org; Internet: http://www.ossdweb.org/meeting_2008.html.

June 8-14

IWPCPS®-10—Tenth International Workshop on Physical Characterization of Pharmaceutical Solids, Bamberg, Germany. *Information:* Internet: http://www.assainternational.com/workshops/IWPCPS_10/IWPCPS_10.cfm.

June 28-July 3

33rd FEBS Congress and 11th IUBMB Conference, Biochemistry of Cell Regulation, Athens, Greece. *Information:* Georgina Alexopoulou, Promotion and Communication. Tel.: +30 210 6889100; Fax: +30 210 6844777; Email: febs-iubmb2008@cnc.gr; Internet: http://www.febs-iubmb-2008.org/.

August 17-22

IASP 12th World Congress on Pain, Glasgow, Scotland, UK. *Information:* Fiona McGillvray or Vicki Grant, Congress Secretariat, Meeting Makers, Jordanhill Campus, 76 Southbrae Drive, Glasgow G13 1PP, United Kingdom. Tel.: +44 (0) 141 434 1500; Fax: +44 (0) 141 434 1519; Email: jasp2008@meetingmakers.co.uk; Internet: http://www.iasp-pain.org/AM/Template.cfm?Section=World_Congress_on_Pain&Template=/CM/HTMLDisplay.cfm&ContentID=3928.

September 8-15

Cardiovascular & Respiratory Systems Modeling: From Cell to Organ, Seattle, WA. *Information:* Kay Sterner, The NSR Physiome Project, Box 355061, University of Washington, Seattle, WA 98915-5061; Tel.: 206-685-2005; Email: sterner@u.washington.edu; Internet: http://www.physiome.org/Course/sept07.html.

September 11-14

Workshop on the Biology of Signaling in the Cardiovascular System, Cape Cod, MA. *Information:* Bernadette Englert, Tel: (301) 760-7745; Email: mailto:bernadette@navbo.org; Internet: http://www.navbo.org/BSCS08Workshop.html.

September 28-October 2

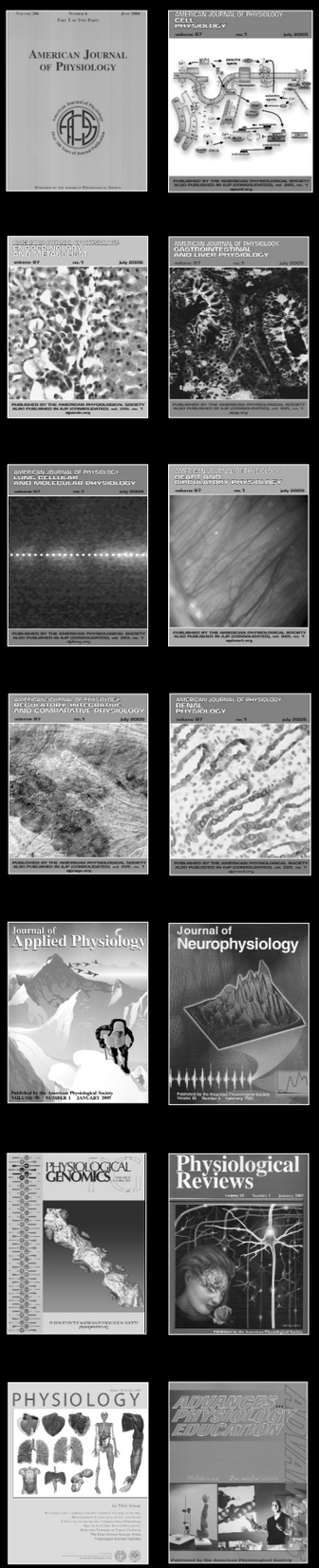
XXII International complement Workshop, Basel, Switzerland. *Information:* Administrative Secretariat, ICW, C/O AKM Congress Service, Clarastrasse 57, PO Box 4005, Basel, Switzerland. Tel.: +41 61 686 77 11; Fax: +41 61 686 77 88; Email: info@akm.ch; Internet: http://www.akm.ch/ICW2008/.

October 30-November 2

The 2nd World Congress on Controversies in Diabetes, Obesity and Hypertension (CODHy), Barcelona, Spain. *Information:* Comtec Headquarters & Administration, 53 Sderot Rothschild, PO Box 68, Tel Aviv, 61000, Israel. Tel.: 972-3-5666 166; Fax: 972-3-5666 177; Email: cony@comtecmed.com; Internet: http://www.codhy.com/.

December 7-11

American Society for Matrix Biology (ASMB) 2008 National Meeting, San Diego, CA. Information: Program Chair: Bill Parks. Tel.: 206-897-1303; Email: parksw@u.washington.edu; Internet: http://www.asmb.net/.



Physiology

Journals of the American Physiological Society

The Journal Publishing Program of the American Physiological Society (APS) covers the entire spectrum of physiology—examining major physiological systems, from the cellular and molecular to the organ and system level. These prestigious peer-reviewed journals are available in print and online. An online subscription to the APS journals provides you with immediate access to the latest issue of the journal as well as with continued access to all content published previously online. Subscribers to the online journals also get access to the fastest possible publication of original research articles through our **A**rticles in **P**res**S** feature—articles published in manuscript form within a few days of acceptance. The APS journal titles are

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9.10.07

2007 AMERICAN PHYSIOLOGICAL SOCIETY CONFERENCE

Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology

August 9-12, 2007, Austin, Texas

CONFERENCE PROGRAM AND ABSTRACTS

The American Physiological Society
9650 Rockville Pike, Bethesda, Maryland 20814 (USA)
Tel: 301-634-7967 • Fax: 301-634-7264
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2007 APS Conference

Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology

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John Stallone
Texas A&M Univ. Col. of Vet. Med

Acknowledgements

The Conference Organizers and The American Physiological Society gratefully recognize the generous financial support provided through unrestricted educational grants from:

NIH, National Heart, Lung, and Blood Institute
Bristol-Myers Squibb Company
Transoma

2007 APS Conference

Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology

August 9-12, 2007, Hyatt Regency Austin on Town Lake

Thursday, August 9	Friday, August 10	Saturday, August 11	Sunday, August 12
3:00 PM **Registration** 6:00 - 8:00 PM **Opening Reception** 8:00 - 9:00 PM Symposium I: **Sex Steroids in Clinical and Epidemiological Studies** Participants : **Jane Reckelhoff**, (Chair) Univ. of Mississippi Med. Ctr. **Pamela Ouyang,** Johns Hopkins Bayview Med. Ctr. **Sharon Silbiger,** Montefiore Hosp.	7:00 AM **Registration** 8:00 - 9:40 AM Symposium II: **Update on Sex Steroid Receptors and Cardiovascular Diseases** Participants: **Pascale Lane**, (Chair) Univ. of Nebraska Med. Ctr. **Matthias Barton**, Univ. Hosp. of Zurich, Switzerland **Chawnshang Chang**, Univ. of Rochester **Theo Pelzer**, Univ. of Wuerzburg, Germany **John Cidlowski,** NIEHS, NIH 9:40 - 10:00 AM Break 10:00 – 11:00 AM Symposium III: **Sex Steroids and Vascular Function** Participants: **John Stallone,** (Chair) Texas A&M Univ. Col. of Vet. Med., College Station **Sue Duckles,** Univ. of California, Irvine **Raouf Khalil,** Harvard Univ. 11:00 AM – 1:00 PM **Selected Oral Presentations** **J. Michael Wyss,** (Chair) Univ. of Alabama at Birmingham 1:00 - 4:00 PM FREE TIME 2:00 – 4:00 PM **Career Workshop** 4:00 - 6:00 PM **Poster Session** 6:00 - 8:00 PM FREE TIME 8:00 - 9:00 PM Symposium IV: **Sex Steroids and Metabolic Syndrome** Participants: **Carmen Hinojosa-Laborde,** (Chair) Univ. of Texas Hlth. Sci. Ctr., San Antonio **Domenic Sica,** VA Commonwealth Univ. **Carolyn Bondy,** NICHD, NIH	7:00 AM **Registration** 8:00 - 9:45 AM Symposium V: **Sex Steroids, the Renin-Angiotensin System and Hypertension** Participants: **Kathryn Sandberg,** (Chair) Georgetown Univ. **Mark Chappell,** Wake Forest Univ. **Judith Miller,** Univ. of Toronto **Edwin Jackson,** Univ. of Pittsburgh **J. Michael Wyss,** Univ. of Alabama at Birmingham 9:45 - 10:00 AM Break 10:00 AM - 12:00 PM Symposium VI: **Sex Steroids and Target Organ Injury** Participants: **David Pollock,** (Chair) Med. Col. of Georgia **Douglas Bowles,** Univ. of Missouri, Columbia **Christine Maric,** Georgetown Univ. **Chris Baylis,** Univ. of Florida, Gainesville **Virginia Miller,** Mayo Clinic & Foundation **Raymond Quigley,** Univ. of Texas Southwestern 12:05 PM – 1:00 PM **Selected Oral Presentations** **Virginia Miller,** (Chair) Mayo Clinic & Foundation 1:00 - 4:00 PM FREE TIME 2:00 – 4:00 PM **Career Workshop** 4:00 - 6:00 PM **Poster Session** 7:00 PM **Conference Banquet and Awards Presentations**	8:00 AM **Registration** 9:00 - 10:30 AM Symposium VII: **Sex Steroids, Pregnancy, Pre-eclampsia, and Fetal Programming** Participants: **Barbara Alexander,** (Chair) Univ. of Mississippi Med. Ctr. **Bridget Brosnihan,** Wake Forest Univ. **Joey Granger,** Univ. of Mississippi Med. Ctr. **S. Ananth Karumanchi,** Harvard Univ. Med. Sch.

Location:

The 2007 APS Conference, Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology will be held August 9-12, 2007 at the Hyatt Regency Austin, 208 Barton Springs Road, Austin, TX 78704, telephone (512) 477-1234, FAX: (512) 480-2069.

Onsite Registration Hours:

Thursday, August 9 …….....3:00—9:00 PM
Friday, August 10 ……..... 7:00 AM—1:00 PM
Friday, August 10 ……..... 4:00 PM— 8:30 PM
Saturday, August 11 …… 7:00 AM—1:00 PM
Saturday, August 11 …… 4:00 PM— 6:00 PM
Sunday, August 12 ……....8:00—10:00 AM

On-Site Registration Fees:

APS Member..... $350
Retired Member $235
Nonmember..... $400
Postdoctoral..... $290
Student $235

The registration fee includes entry into all scientific sessions, opening reception and banquet.

Payment Information:

Registrants may pay by institutional or personal check, traveler's check, MasterCard, VISA or American Express. Checks must be payable to *"The American Physiological Society"* and drawn on a United States bank payable in US dollars.

Student Registration:

Any student member or regularly matriculated student working toward a degree in one of the biomedical sciences is eligible to register at the student fee. Nonmember postdoctoral fellows, hospital residents and interns, and laboratory technicians do not qualify as students. Nonmember Students who register onsite must provide a valid university student ID card. APS Student members should present their current APS membership card indicating their student category status.

Postdoctoral Registration:

Any person who has received a Ph.D. degree in physiology or related field, within four years of this meeting, as attested to by the department head is eligible to register at the postdoctoral fee.

A statement signed by the department head must accompany the registration form and remittance when registering.

Press:

Press badges will be issued at the APS registration desk, only to members of the working press and freelance writers bearing a letter of assignment from an editor. Representatives of allied fields (public relations, public affairs, etc.) must register as nonmembers.

Continuing Medical Education (CME):

The Federation of American Societies for Experimental Biology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Category I Continuing Medical Education (CME) credits will be offered at this meeting. All CME applications must be completed online after the meeting has concluded. Please visit the APS website in August for more details on submitting your CME application at: www.the-aps.org/austin. For the purposes of Continuing Medical Education credits toward the American Medical Association Physician's Recognition Award, the 2007 APS Conference: Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology is jointly sponsored by the Federation of American Societies for Experimental Biology. There is a $45 application fee, payable upon submission of the form. Please include your payment with the completed CME form. For more information, contact the FASEB Office of Scientific Meetings and Conferences at 301-634-7010.

Program Objective:

Upon completing the program, participants should gain more knowledge in the field of sex steroids and how they affect genders in the physiology of the cardiovascular-renal systems. The goal of the conference is to accumulate together a critical mass of scientists who have interests in sex steroids in physiology of the cardiovascular and renal systems to promote the exchange of ideas and potential collaborations in the future.

Target Audience:

The intended audience for this meeting includes all levels of researchers working in the field of sex steroids, particularly as it pertains to the cardiovascular and renal systems.

This meeting has been made possible through the generous support from:

NIH, National Heart, Lung, and Blood Institute
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DAILY SCHEDULE

THURSDAY, AUGUST 9, 2007

Symposium I

1.0 **SEX STEROIDS IN CLINICAL AND EPIDEMIOLOGICAL STUDIES**
Thur., 8:00 - 9:00 PM, Texas Ballroom II/III.

Chair: **Jane Reckelhoff**, *Univ. of Mississippi Med. Ctr.*

8:00 PM **1.1** Introduction. **Jane Reckelhoff.** *Univ. of Mississippi Med. Ctr.*

8:05 PM **1.2** The Latest on the Cardiovascular Effects of Hormone Therapy in Postmenopausal Women. **Pamela Ouyang.** *Johns Hopkins Bayview Med. Ctr.*

8:30 PM **1.3** Sex Steroids and Renal Disease in Humans. **Sharon Silbiger.** *Montefiore Hosp., Bronx.*

FRIDAY, AUGUST 10, 2007

Symposium II

2.0 **UPDATE ON SEX STEROID RECEPTORS AND CARDIOVASCULAR DISEASES**
Fri., 8:00 - 9:40 AM, Texas Ballroom II/III.

Chair: **Pascale Lane**, *Univ. of Nebraska Med. Ctr.*

8:00 AM **2.1** Introduction. **Pascale Lane.** *Univ. of Nebraska Med. Ctr.*

8:05 AM **2.2** Sex Steroid Receptors and Atherosclerosis. **Matthias Barton.** *Univ. Hosp. of Zurich, Switzerland.*

8:25 AM **2.3** Increased Hepatic Steatosis and Insulin Resistance in Mice Lacking Hepatic Androgen Receptor via Modulation of PTP1β/PPARα Involved in Lipid and Glucose Homeostasis. **Chawnshang Chang.** *Univ. of Rochester.*

8:45 AM **2.4** Estrogen Receptor Studies Using Transgenic Animals. **Pascale Lane.** *Univ. of Nebraska Med. Ctr.*

9:05 AM **2.5** Redundant, Divergent or Opposing Functions of Estrogen Receptor Subtypes ERα and ERβ in Hypertension, Cardiac Hypertrophy and Heart Failure? **Theo Pelzer.** *Univ. of Wuerzburg, Germany.*

9:25 AM **2.6** The Glucocorticoid Receptor: One Gene, Many Proteins - New Machanisms for Tissue Specific Anti-Inflammatory Actions of Gluco-corticoids in Health and Disease. **John Cidlowski.** *NIEHS, NIH.*

Plan to Attend the Welcome and Opening Reception

Thursday, August 9
6:00 – 8:00 PM

Foothills II Ballroom

Symposium III

3.0 **SEX STEROIDS AND VASCULAR FUNCTION**
Fri., 10:00 - 11:00 AM, Texas Ballroom II/III.

Chair: **John Stallone**, *Texas A&M Univ. Col. of Vet. Med., College Station.*

10:00 AM **3.1** Introduction. **John Stallone.** *Texas A&M Univ. Col. of Vet. Med., College Station.*

10:05 AM **3.2** Estrogen and Mitochondria: A New Paradigm for Vascular Protection? **Sue Duckles.** *Univ. of California, Irvine.*

10:25 AM **3.3** Sex Steroids and Vascular Responses in Aging. **Raouf Khalil.** *Harvard Univ.*

10:45 AM **3.4** Rapid Nongenomic Effects of Androgens on the Vascular Wall. **John Stallone.** *Texas A&M Univ. Col. of Vet. Med., College Station.*

Oral Presentations I

4.0 **SELECTED ORAL PRESENTATIONS**
Fri., 11:00 AM - 1:00 PM, Texas Ballroom II/III.

Chair: **J. Michael Wyss**, *Univ. of Alabama at Birmingham.*

11:05 AM **4.1** Dihydrotestosterone Modulates Cerebral Vascular Tone in Part by Enhancing COX-2. **Rayna Gonzales.** *Univ. of California, Irvine.* **(5.13).**

11:12 AM **4.2** Early Diabetic Kidney Damage in the Mouse VCD Model of Menopause. **Maggie Keck.** *Univ. of Arizona.* **(10.11).**

11:19 AM **4.3** Sex Differences in the Response to Vasoactive Substances in Early Uncontrolled Diabetes. **Adam Mitchell.** *Georgetown Univ.* **(10.12).**

11:26 AM **4.4** Does Gender Influence Cardiovascular and Renal Responses to Water Immersion? **Donald Watenpaugh.** *Univ. of North Texas Hlth. Sci. Ctr.* **(5.24).**

11:34 AM **4.5** Sex Differences in Diabetic Renal Remodeling: Effects of Growth Hormone. **Jennifer Rogers.** *Georgetown Univ.* **(10.13).**

11:41 AM **4.6** Female Gender Protects Obese Rats from Nephropathy of the Metabolic Syndrome. **Jesus Dominguez.** *Vet. Affairs Med. Ctr. and Indiana Univ. Med. Ctr.* **(10.15).**

11:48 AM **4.7** Developmental Changes of Autonomic Control of Heart Rate in the Conscious Behaving Rat: State and Sex Influences. **Carie Reynolds.** *Univ. of Florida.* **(5.7).**

11:55 AM **4.8** Differential Expression of Neprilysin and Angiotensin Converting Enzyme 2 may Contribute to Decreased Organ Damage in the Female Hypertensive mRen2.Lewis Rat. **Karl Pendergrass.** *Wake Forest Univ.* **(10.3).**

12:02 PM **4.9** Testosterone Modulates Heart Rate Variability in Swine. **April Durtschi.** *Univ. of Missouri, Columbia.* **(5.9).**

12:09 PM **4.10** Effect of Estrogens and Selective Estrogen Receptor Modulators on Vascular Reactivity in the Perfused Mesenteric Vascular Bed. **Connie Mark.** *Univ. of South Dakota.* **(5.20).**

12:16 PM **4.11** Testosterone Supplements Promote Renal Injury and Exacerbate Hypertension in Aging SHR. **Radu Iliescu.** *Univ. of Mississippi Med. Ctr.* **(10.4).**

12:23 PM **4.12** Sex Differences in the Relationship Between Rat Mesenteric Venular Protein Leakage and Tissue Protein Clearance. **Rie Sasaki.** *Univ. of Missouri, Columbia.* **(5.21).**

12:30 PM **4.13** Testosterone Mediates Hypertension and Renal Injury in Dahl Rats Despite High Sodium Diet-mediated Decrease in Testosterone Levels. **Licy Yanes.** *Univ. of Mississippi Med. Ctr.* **(10.6).**

12:38 PM **4.14** Population Extremes-based Approach Defines Gender Differences in Adrenergic and Renal Genes Contributing to Blood Pressure. **Brinda Rana.** *Univ. of California, San Diego.* **(10.7).**

12:45 PM **4.15** Effect of Age and Estrogen Loss on Estrogen Receptor Alpha and Beta in Kidney of Dahl Salt Sensitive Rats. **Ma Eugenia Davila.** *Univ. of Texas Hlth. Sci. Ctr. at San Anotnio.* **(10.8).**

Don't forget…..
Pick up your Banquet Ticket by 10:00 AM on FRIDAY

This banquet is free but you MUST have a ticket for entry

Career Workshop

MAKING A GREAT IMPRESSION AT A SCIENTIFIC MEETING: PRESENTING YOUR POSTER, PRESENTING YOURSELF

Fri., 2:00 - 4:00 PM, Texas Ballroom II/III.

A special workshop presented by the APS Career Opportunities in Physiology Committee.

Poster Session

5.0 SEX STEROIDS IN HEART AND VASCULAR FUNCTION

Fri., 4:00 - 6:00 PM, Texas Ballroom I.

Board #

1 **5.1** Sex-based Differences in the Architecture of the Hypertrophied Heart in Salt Stressed Borderline Hypertensive Rats. **J. Krontiris-Litowitz, and R. Fulton.** *Youngstown State Univ., and Belmont Tech. Col., Clairsville.*

2 **5.2** Estrogen Receptor Alpha Interacts with 17β-hydroxysteroid Dehydrogenase Type 10 and Regulates its Enzymatic Activity in the Heart. **T. Pelzer, and V. Jazbutyte.** *Univ. of Wuerzburg, Germany.*

DAILY SCHEDULE

Board #

3 **5.3** Characterization and Functional Analysis of the 5'-flanking Region of the ERa Gene in the Human Heart. **S. Fritschka, S. Mahmoodzadeh, and V. Regitz-Zagrosek.** *Charité Univ., Berlin, Germany.*

4 **5.4** Voluntary Exercise Induces Sex-Specific Physiological Cardiac Remodeling. **S. Brokat, K. Cantow, N. Ehrenberg, A. Kühne, J. Thomas, and V. Regitz-Zagrosek.** *Charité Univ., Berlin, Germany.*

5 **5.5** Comparison of the Second Derivative Photoplethysmography a-a Interval Method and Electrocardiogram R-R Interval Method. **T. Kikuchi, Y. Sano, S. Urushidani, and J. Abo.** *Tokyo Univ. of Marine Sci., and Tech., Japan.*

6 **5.6** Cardiac Size and Plasma Volume: Potential Mechanisms for POTS? **Q. Fu, J. Hastings, S. Shibata, T. Van Gundy, R. Shook, and B. Levine.** *Presbyterian Hosp. of Dallas and Univ. of Texas Southwestern Med. Ctr.*

7 **5.7** Developmental Changes of Autonomic Control of Heart Rate in the Conscious Behaving Rat: State and Sex Influences. **C. Reynolds, C. Ward, N. Doperalski, D. Fuller, and L. Hayward.** *Univ. of Florida.*

8 **5.8** Testosterone Modulates Heart Rate and QT Interval in Swine. **A. Durtschi, and L. Rubin.** *Univ. of Missouri, Columbia.*

9 **5.9** Testosterone Modulates Heart Rate Variability in Swine. **A. Durtschi, L. Rubin, and J. Dodam.** *Univ. of Missouri, Columbia.*

10 **5.10** Role of Oxidative Stress in Parity-Induced Coronary Dysfunction. **S. Kaufman, and H. Tawfik.** *Univ. of Alberta, Canada.*

11 **5.11** Analysis of the Effect of E2 on the Human MMP2 Expression in HT1080 Cells: A Promoter Based Analysis. **E. Dworatzek, S. Mahmoodzadeh, and V. Regitz-Zagrosek.** *Charité Univ., Berlin, Germany.*

Board #

12 **5.12** Cutaneous Venoarteriolar Response is not Impaired in Postural Orthostatic Tachycardia Syndrome. **T. Van Gundy, S. Shibata, R. Shook, M. Sandgarten, J. Hastings, B. Levine, and Q. Fu.** *The Inst. for Exercise and Environ. Med., Dallas.*

13 **5.13** Dihydrotestosterone Modulates Cerebral Vascular Tone in Part by Enhancing COX-2. **R. Gonzales, D. Krause, and S. Duckles.** *Univ. of California, Irvine.*

14 **5.14** Gender and Circulating Endothelial Progenitor Cell Number and Apoptosis. **B. Stauffer, O. MacInearney, G. Hoetzer, E. Kushner, J. Cech, C. Westby, and C. DeSouza.** *Univ. of Colorado, Denver, and Univ. of Colorado, Boulder.*

15 **5.15** Gender Differences in Endothelial Functions, Vascular Estrogen Receptors, eNOS and Triglycerides. **S. Chou, Y. Wang, S. Tsau, and Y. Lau.** *Chang Gung Univ., Taiwan.*

16 **5.16** Estradiol Inhibits Apoptotic Signaling and Microvascular Endothelial Cell Hyperpermeability. **E. Childs, B. Tharakan, and F. Hunter.** *Texas A&M Univ. Hlth. Sci. Ctr. Col. of Med. /Scott and White Hosp.*

17 **5.17** Gender Modulation of Venous Function in Spontaneously Hypertensive Rats. **D. Martin, R. Redetzke, E. Vogel, C. Mark, and K. Eyster.** *Univ. of South Dakota.*

18 **5.18** Sex Differences in the Response to Vasoconstrictor and Vasodilator Substances in Chronically Stressed Male and Female Rats. **A. Mitchell, J. Rogers, A. Myers, Z. Zukowska, and S. Mulroney.** *Georgetown Univ.*

19 **5.19** Estrogen Decreases Mitochondrial Oxidative Stress in Human Brain Microvascular Endothelial Cells. **A. Razmara, S.P. Duckles, L. Sunday, C. Stirone, X. Wang, D.N. Krause, and V. Procaccio.** *Univ. of California, Irvine.*

Board #

20 **5.20** Effect of Estrogens and Selective Estrogen Receptor Modulators on Vascular Reactivity in the Perfused Mesenteric Vascular Bed. **C. Mark, R. Tatchum-Talom, D. Martin, and K. Eyster.** *Univ. of South Dakota.*

21 **5.21** Sex Differences in the Relationship Between Rat Mesenteric Venular Protein Leakage and Tissue Protein Clearance. **R. Sasaki, S. Bingaman, and V. Huxley.** *Univ. of Missouri, Columbia.*

22 **5.22** Sex Difference in the Regulation of Muscle Blood Flow During Static Handgrip Exercise. **M. Kawamoto, K. Morimoto, and A. Takamata.** *Nara Women's Univ., Japan.*

23 **5.23** Skeletal Muscle Arterioles Demonstrate Sexual Dimorphism with Respect to Macromolecule Transvascular Exchange Pathways. **V. Huxley.** *Univ. of Missouri, Columbia.*

24 **5.24** Does Gender Influence Cardiovascular and Renal Responses to Water Immersion? **D. Watenpaugh, B. Pump, P. Bie, and P. Norsk.** *Univ. of North Texas Hlth. Sci. Ctr., Danish Aerospace Med. Ctr. of Res.,Copenhagen, Denmark.*

25 **5.25** Effect of Estrogen Replacement on Osmoregulatory and Central Angioteisin II-induced Fluid Regulation in Ovariectomized Rats. **K. Torii, K. Morimoto, and A. Takamata.** *Nara Women's Univ., Nara, Japan.*

26 **5.26** Aldosterone Excretion During Chronic Intermittent Hypoxia in Male and Female Rats. **C. Hinojosa-Laborde, T. Craig, C. Mehring, T. Cunningham, and S. Mifflin.** *Univ. of Texas Hlth. Sci. Ctr. at San Anotnio.*

27 **5.27** Genome-Wide Scan for Genomic Determinants of Alcohol and Tobacco Use in French Canadian Families. **M. Nikpay, O. Seda, J. Tremblay, E. Merlo, D. Gaudet, T. Kotchen, A. Cowley, and P. Hamet.** *Univ. of Montreal, Canada, and Med. Col. of Wisconsin.*

Symposium IV

6.0 **SEX STEROIDS AND METABOLIC SYNDROME**

Fri., 8:00 - 9:00 PM, Texas Ballroom II/III.

Chair: **Carmen Hinojosa-Laborde**, *Univ. of Texas Hlth. Sci. Ctr., San Antonio.*

8:00 PM **6.1** Sex Differences in Sleep Apnea. **Carmen Hinojosa-Laborde.** *Univ. of Texas Hlth. Sci. Ctr. at San Antonio.*

8:20 PM **6.2** Sex Differences in Metabolic Syndrome and Cardiovascular Disease. **Domenic Sica.** *Virginia Commonwealth Univ.*

8:40 PM **6.3** The Parental Origin of the X Chromosome and Metabolic Risk Factors. **Carolyn Bondy.** *NICHD, NIH.*

SATURDAY, AUGUST 11, 2007

Symposium V

7.0 **SEX STEROIDS, THE RENIN-ANGIOTENSIN SYSTEM AND HYPERTENSION**

Sat., 8:00 - 9:45 AM, Texas Ballroom II/III.

Chair: **Kathryn Sandberg**, *Georgetown Univ.*

8:00 AM **7.1** Introduction. **Kathryn Sandberg.** *Georgetown Univ.*

8:05 AM **7.2** Sex Differences in Angiotensin II, Angiotensin Converting Enzyme 2 and Angiotensin-(1-7). **Mark Chappell.** *Wake Forest Univ.*

8:25 AM **7.3** Gonadal Hormone-independent Sex Chromosome Effects in Angiotensin II-induced Hyper-tension. **Kathryn Sandberg.** *Georgetown Univ.*

8:45 AM **7.4** Role of the RAS in Sex Differences in Hypertension. **Judith Miller.** *Univ. of Toronto, Canada.*

9:05 AM **7.5** 2-Methoxyestradiol: A Safe and Effective Cardiorenal Protective Hormone Therapy for Women and Men. **Edwin Jackson.** *Univ. of Pittsburgh.*

9:25 AM **7.6** The Role of Estrogens and Polyphenols in Hypertension and Diabetes. **J. Michael Wyss.** *Univ. of Alabama at Birmingham.*

Symposium VI

8.0 **SEX STEROIDS AND TARGET ORGAN INJURY**

Sat., 10:00 AM - 12:00 Noon, Texas Ballroom II/III.

Chair: **David Pollock**, *Med. Col. of Georgia.*

10:00 AM **8.1** Introduction. **David Pollock.** *Med. Col. of Georgia.*

10:05 AM **8.2** Sex Steroids, Coronary Smooth Muscle, Atheroclerosis and Restenosis. **Douglas Bowles.** *Univ. of Missouri, Columbia.*

10:25 AM **8.3** Critical Role for ET_B Receptors in Attenuating the Response to Environmental Stress in Female, but not Male Rats. **David Pollock.** *Med. Col. of Georgia.*

10:45 AM **8.4** Sex, Diabetes and Renal Injury. **Christine Maric.** *Georgetown Univ.*

11:05 AM **8.5** Sex, NO and Aging. **Chris Baylis.** *Univ. of Florida.*

11:25 AM **8.6** Sex Steroids, Platelet Aggregation and Inflammation. **Virginia Miller.** *Mayo Clinic & Fdn.*

11:45 AM **8.7** Androgens Stimulate Proximal Tubule Transport. **Raymond Quigley.** *Univ. of Texas Southwestern Med. Ctr.*

Oral Presentations II

9.0 **SELECTED ORAL PRESENTATIONS**

Sat., 12:05 - 1:00 PM, Texas Ballroom II/III.

Chair: **Virginia Miller**, *Mayo Clinic & Fdn.*

12:05 PM **9.1** Reduced Uterine Perfusion Pressure Increases Soluble Flt-1 Expression in Pregnant Rats. **Jeffrey Gilbert.** *Univ. of Mississippi Med. Ctr.* **(10.23).**

12:12 PM **9.2** Sleep Deprivation and Nocturnal Urine Output-Gender Dif-ference in the Effect. **B. Mahler.** *Aarhus Univ. Hosp., Denmark.* **(10.18).**

12:19 PM **9.3** Analysis of the Effect of E2 on the Human MMP2 Expression in HT1080 Cells: A Promoter Based Analysis. **Elke Dworatzek.** *Charité Univ., Berlin, Germany.* **(5.11).**

12:26 PM **9.4** Elevated Agonistic Autoantibodies to the Angiotensin Type 1 Receptor in Response to Placental Ischemia and TNF Alpha in Pregnant Rats. **Babbette LaMarca.** *Univ. of Mississippi Med. Ctr.* **(10.24).**

12:34 PM **9.5** Characterization and Functional Analysis of the 5'-flanking Region of the ERa Gene in the Human Heart. **Stephen Fritschka.** *Charité Univ., Berlin, Germany.* **(5.3).**

12:41 PM **9.6** Vasomotor Sympathetic Neural Control is Enhanced in Early Pregnant Women. **Qi Fu.** *Presbyterian Hosp. of Dallas.* **(10.26).**

Career Workshop

WRITING YOUR FIRST PAPERS: THE "INS" AND "OUTS" OF AUTHORSHIP

Sat., 2:00 - 4:00 PM, Texas Ballroom II/III.

A special workshop presented by the APS Career Opportunities in Physiology Committee.

Poster Session

10.0 **SEX STEROIDS IN HYPERTENSION, DIABETES, AND PREGNANCY**

Sat., 4:00 - 6:00 PM, Texas Ballroom I.

Board #

28 **10.1** Aldosterone/NaCl-induced Hypertension: The Role of Gender, Sex Hormones and Central Reactive Oxygen Species. **B. Xue, A. K. Johnson, and M. Hay.** *Univ. of Iowa.*

29 **10.2** MPA but not Drospirenone Aggravates Renal Injury in Aldosterone-salt Treated Rats. **T. Pelzer, and P. A. A. Loza.** *Univ. of Wuerzburg, Germany.*

30 **10.3** Differential Expression of Neprilysin and Angiotensin Converting Enzyme 2 May Contribute to Decreased Organ Damage in the Female Hypertensive mRen2.Lewis Rat. **K.Pendergrass, B. Westwood, and M. Chappell.** *Wake Forest Univ.*

31 **10.4** Testosterone Supplements Promote Renal Injury and Exacerbate Hypertension in Aging SHR. **R. Iliescu, L. L. Yanes, J. C. Sartori-Valinotti, and J. F. Reckelhoff.** *Univ. of Mississippi Med. Ctr.*

Board #

32 **10.5** Sex Differences in Renal 11β - Hydroxysteroid Dehydrogenase Type 2 Immunoreactivity in Rat Kidneys. **D. Roesch, M. Shi, C. Ecelbarger, and K. Sandberg.** *Georgetown Univ.*

33 **10.6** Testosterone Mediates Hypertension and Renal Injury in Dahl Rats Despite High Sodium Diet-mediated Decrease in Testosterone Levels. **L. L. Yanes, R. Iliescu, J. C. Sartori-Valinotti, H. Zhang, D. Romero, and J. F. Reckelhoff.** *Univ. of Mississippi Med. Ctr.*

34 **10.7** Population Extremes-based Approach Defines Gender Differences in Adrenergic and Renal Genes Contributing to Blood Pressure. **B. Rana, P. Insel, N. Schork, and D. O'Connor.** *Univ. of California, San Diego.*

35 **10.8** Effect of Age and Estrogen Loss on Estrogen Receptor Alpha and Beta in Kidney of Dahl Salt Sensitive Rats. **M. E. Davila, T. Craig, and C. Hinojosa-Laborde.** *Univ. of Texas Hlth. Sci. Ctr. at San Antonio.*

36 **10.9** Sexual Dimorphic Regulation of AQP2 in DOCA-Salt Hypertension. **S. Masilamani, C. Berry, T. Musselman, and Z. Zhang.** *Virginia Commonwealth Univ.*

37 **10.10** Role of Hydrogen Peroxide in Mediating Hypertension and Proteinuria in Female SHR. **J. C. Sartori-Valinotti, W. Dorsett-Martin, R. Iliescu, L. L. Yanes, and J. F. Reckelhoff.** *Univ. of Mississippi Med. Ctr.*

38 **10.11** Early Diabetic Kidney Damage in the Mouse VCD Model of Menopause. **M. Keck, M. J. Romero-Aleshire, Q. Cai, P. B. Hoyer, and H. L. Brooks.** *Univ. of Arizona.*

39 **10.12** Sex Differences in the Response to Vasoactive Substances in Early Uncontrolled Diabetes. **A. Mitchell, A. Myers, and S. Mulroney.** *Georgetown Univ.*

40 **10.13** Sex Differences in Diabetic Renal Remodeling: Effects of Growth Hormone. **J. Rogers, C. Maric, K. Sandberg, and S. Mulroney.** *Georgetown Univ.*

Board #

41 **10.14** Role of Estrogens in Postmenopausal Obesity and Hypertension. **L. Fortepiani, and H. Zhang.** *Univ. of Texas Hlth. Sci. Ctr. at San Antonio, and Univ. of Mississippi Med. Ctr.*

42 **10.15** Female Gender Protects Obese Rats from Nephropathy of the Metabolic Syndrome. **J. Dominguez, and K. Kelly.** *Vet. Affairs Med. Ctr. and Indiana Univ. Med. Ctr.*

43 **10.16** Gender-Dependent Metabolic and Renal Effects of 2-Hydroxyestradiol in Obese Diabetic ZSF_1 Rats. **S. Tofovic, S. Bastacky, and E. Jackson.** *Univ. of Pittsburgh Sch. of Med.*

44 **10.17** Dysregulated Estradiol Metabolism in Pre-eclampsia. **S. Tofovic, E. Jackson, and G. Tofovic.** *Univ. of Pittsburgh Sch. of Med., Univ. St. Cyril and Methodius Sch. of Med., Skopje, Macedonia.*

45 **10.18** Sleep Deprivation and Nocturnal Urine Output-Gender Dif-ference in the Effect. **B. Mahler, K. Kamperis, S. Hagstroem, E. Radvanska, S. Rittig, and J.C. Djurhuus.** *Aarhus Univ. Hosp., Denmark.*

46 **10.19** Gender Bias Toward a Functional Subclass of Myelinated Visceral Afferent. **B. Li, and J. Schild.** *Indiana Univ. Perdue Univ. Indianapolis.*

47 **10.20** Estrogen Alters Myosin Heavy Chain Isoform Expression of Rat Vaginal Smooth Muscle. **M. Basha, T. Wang, J. Lassman, R. Moreland, A. J. Wein, and S. Chacko.** *Drexel Univ. Col. of Med. and Univ. of Pennsylvania.*

48 **10.21** Sex Hormones Contribute to Gender Differences in Programmed Hypertension Induced by Placental Insufficiency in the Rat. **N. Ojeda, D. Grigore, E. Robertson, and B. Alexander.** *Univ. of Mississippi Med. Ctr.*

49 **10.22** Sex Differences in Renal Function of Betamethasone-Treated Sheep: A Model of Fetal Programming. **T. Y. Gwathmey, L. Tang, J. Figueroa, M. Chappell, and J. Rose.** *Wake Forest Univ.*

Board #

50 **10.23** Reduced Uterine Perfusion Pressure Increases Soluble Flt-1 Expression in Pregnant Rats. **J. Gilbert, B. LaMarca, S. Babcock, K. Cockrell, and J. Granger.** *Univ. of Mississippi Med. Ctr.*

51 **10.24** Elevated Agonistic Autoantibodies to the Angiotensin Type 1 Receptor in Response to Placental Ischemia and TNF Alpha in Pregnant Rats. **B. LaMarca, R. Dechend, G. Wallukat, and M. Llinas.** *Univ. of Mississippi Med. Ctr., and Oberarzt HELIOS Clinic, Berlin, Germany.*

52 **10.25** Altered Cerebral Vascular Function in Response to Reductions in Uterine Perfusion in Pregnant Rats. **M. Ryan, G. McLemore Jr., J. Granger, and B. LaMarca.** *Univ. of Mississippi Med. Ctr.*

53 **10.26** Vasomotor Sympathetic Neural Control is Enhanced in Early Pregnant Women. **Q. Fu, S. Shibata, T. Van Gundy, J. Hastings, and B. Levine.** *Presbyterian Hosp. of Dallas, and Univ. of Texas Southwestern Med. Ctr.*

54 **10.27** Ability to Buffer Changes in pH During Ischemia – Are There Sex Differences in the Newborn Heart? **D. Quaglietta, M. P. Belanger, and C. Wittnich.** *Univ. of Toronto, Canada.*

55 **10.28** Orthotopic Liver Transplantation in Newborns–Lower Success Rates from Female Donors and Why Ischemic Metabolism May Play a Role. **D. Quaglietta, M. P. Belanger, and C. Wittnich.** *Univ. of Toronto, Canada.*

56 **10.29** The Role of Sexual Process in the Regulation of Stress-induced Cardiovascular Responses in Rat. **Z. Ghodarzi, N. Hydarieh, A. Khorami, S. Charkh-kar, M. Behnava, and A. Vahabzadeh.** *Iran Univ. of Med. Sci., Tehran, Iran.*

57 **10.30** Aortic Coartation-induced Hypertension During Pregnancy: A Model of Pre-eclampsia in Rats. **A. Adeagbo, N. L. Alsip, J. J. D. Lucca.** *Univ. Louisville Med. Sch.*

Board #

58 **10.31** IUGR Alters COX-2 Expression through Steroid Signaling and Affects 11-β–Hydroxysteroid Dehydrogenase Type 2 Chromatin Structure in the Rat Kidney. **M. Baserga, M. Hale, X. Yu, Q. Fu, C. Callaway, R. McKnight, and R. Lane.** *Univ. of Utah.*

SUNDAY, AUGUST 12, 2007

Symposium VII

11.0 **SEX STEROIDS, PREGNANCY, PRE-ECLAMPSIA, AND FETAL PROGRAMMING**

Sun., 9:00 - 10:30 AM, Texas Ballroom II/III.

Chair: **Barbara Alexander**, *Univ. of Mississippi Med. Ctr.*

9:00 AM **11.1** Introduction. **Barbara Alexander.** *Univ. of Mississippi Med. Ctr.*

9:05 AM **11.2** Ang-(1-7) and ACE2 in Human Pregnancy. **K. Bridget Brosnihan.** *Wake Forest Univ.*

9:25 AM **11.3** Pathophysiology of Hypertension During Pre-eclampsia. **Joey Granger.** *Univ. of Mississippi Med. Ctr.*

9:45 AM **11.4** Pre-eclampsia and Angiogenic Factors. **S. Ananth Karumanchi.** *Harvard Univ. Med.Sch.*

10:05 AM **11.5** Sex Differences in Fetal Programming of Cardiovascular Disease. **Barbara Alexander.** *Univ. of Mississippi Med. Ctr.*

This meeting has been made possible through the generous support from:

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2007 APS Conference
Sex Steroids and Gender in Cardiovascular-Renal Physiology and Pathophysiology

Abstracts of Invited and Contributed Presentations

1.0: SEX STEROIDS IN CLINICAL AND EPIDEMIOLOGICAL STUDIES

1.2

THE LATEST ON THE CARDIOVASCULAR EFFECTS OF HORMONE THERAPY IN POSTMENOPAUSAL WOMEN

Pamela Ouyang[1]
[1]Cardiology/School of Medicine, Johns Hopkins University, 4940 Eastern Ave, Baltimore, MD, 21224.

Women have lower coronary heart disease (CHD) risk than men though this is attenuated after menopause. Whether estrogen loss contributes to this is debated. The increased androgenic state in postmenopausal women is associated with an adverse metabolic risk profile. The effects of estrogen on endothelial function, vasodilation, adhesion molecules and lipids could result in cardiovascular protection. This, along with observational studies data support potential CHD benefit from estrogen replacement therapy. However, the randomized placebo-controlled trials of conjugated equine estrogen (CEE) and medroxyprogesterone, and of unopposed CEE, show no reduction in CHD events and an increased stroke risk. It was postulated that selective estrogen receptor modulators might provide both CHD and breast cancer protection. However, the Raloxifene Use for the Heart Trial showed no cardiovascular protection from raloxifene. The explanation for the different findings of randomized and observational trials include healthy individual bias explaining the CVD benefit seen in observational studies, the physiologic effects of different types and doses of estrogen therapy, potential adverse cardiovascular effects of progesterone, and different vascular effects dependent on the timing of hormone therapy related to menopause, and resulting from the degree of underlying vascular disease and changes in hormone receptors due to the age of the woman. Studies are ongoing to test some of these hypotheses.

1.3

SEX STEROIDS AND RENAL DISEASE IN HUMANS

Sharon Silbiger[1]
[1]Dept. of Medicine/Division of Nephrology, Albert Einstein College of Medicine/Montefiore Medical Center, 111 E. 210th St, Centennial 3, Bronx, New York, 10467.

In a manner similar to animals, men with a variety of renal diseases progress to end-stage renal failure at a rate faster than women. This rate is independent of blood pressure control or serum lipids levels. The exact physiologic mechanisms underlying this gender disparity are unclear, but are speculated to include gender differences in renal and systemic hemodynamics, glomerular size and/or number and the direct local effects of sex hormones. In rodents models of renal disease, hormonal manipulation such as ovariectomy in females, castration in males or the supplementation of estrogens or testosterone, modulates the course of renal disease. In these models, in general, estrogens have been found to be "protective", while testosterone has been found to be "detrimental". Naturally, such specific parallel data in humans is unavailable. Based on our meta-analysis evaluating the effect of gender on the renal disease progression rate in Membranous nephropathy, Polycystic kidney disease, IgA nephropathy and Chronic renal disease of mixed etiology, we can conclude that males with these underlying diseases have a more fulminant course. The role of gender on the course of human diabetic nephropathy is less clear, but data suggest that diabetic nephropathy in males may progress at a faster rate than this disease in women. REFERENCES: Neugarten J, Acharya, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. J Am Soc Nephrol 11:319-329, 2000. Silbiger S, Neugarten J. The role of gender in the progression of renal disease. Adv Renal Repl Ther 10:3-14, 2003.

2.0: UPDATE ON SEX STEROID RECEPTORS AND CARDIOVASCULAR DISEASES

2.2

SEX STEROID RECEPTORS AND ATHEROSCLEROSIS

Matthias Barton[1]
[1]Internal Medicine, University Hospital Zurich, Ramistrasse 100, Zurich, 8091, Switzerland.

Clinical manifestations related to atherosclerotic vascular disease show marked gender differences with regard to time of onset and clinical presentation. Although endogenous sex hormones, particularly 17β-estradiol, non-selective estrogen receptor agonist, have been implicated in cardiovascular protection, the underlying mechanisms are unknown. In contrast to endogenous hormones, hormone therapy with oral contraceptives and with equine estrogens in postmenopausal women is associated with increased venous thombotic events. Of note, testosterone exerts its effects not only via binding to the androgen receptor, but also after conversion to 17β-estradiol by aromatase. The exact roles of sex steroids and individual sex steroid receptors in atherogenesis and vascular homeostasis is still largely unclear. This information will be important for the understanding of vascular activities and clinical side effects of sex hormones. Most recent data suggest that natural estrogens and receptor-elective ligands for individual estrogen receptors have specific functions in arterial and venous vascular beds in humans and animals possibly offering new therapeutic opportunities. (Support: SNF 32-058426.99, 3232-058421.99, 32-108258/1). Traupe T., Stettler C, Li H.G., Haas E., Bhattacharya I., Minotti R., Barton M. (2007) Distinct roles of estrogen receptors alpha and beta mediating acute vasodilation of epicardial coronary arteries. *Hypertension* (in press); Haas E., Meyer M.R., Schurr U., Bhattacharya I., Minotti R.,Nguyen H.H., Heigl A., Lachat M., Genoni M., Barton M. (2007) Differential effects of 17β-estradiol on function, ERα, ERβ and GPR30 expression in arteries and veins of patients with atherosclerosis. *Hypertension* (in press). www.athero.ch.

2.3

INCREASED HEPATIC STEATOSIS AND INSULIN RESISTANCE IN MICE LACKING HEPATIC ANDROGEN RECEPTOR VIA MODULATION OF PTP1 β/PPARα INVOLVED IN LIPID AND GLUCOSE HOMEOSTASIS

Chawnshang Chang[1], Hung-Yun Lin[2], Ruey-Shen Wang[2], I-Chen Yu[2], Ning-Chun Liu[2], Wen-Lung Ma[2], Janet D. Sparks[2], Shuyuan Yeh[2]
[1]Pathology, and Urology, the Cancer Center, and George Whipple Lab for Cancer Research, University of Rochester Medical Center, 601 Elmwood Ave, Box 626, Rochester, NY, 14642, [2]Pathology, University of Rochester Medical Center, 601 Elmwood Ave, Box 626, Rochester, NY, 14642.

Early studies showed that whole body androgen receptor (AR) knockout (T-AR$^{-/y}$) mice with hypogonadism exhibit insulin resistance. However, the detailed mechanism how androgen/AR signaling regulates insulin sensitivity in individual organs remains unclear. Here we generated hepatic AR knockout (H-AR$^{-/y}$) mice and found obese male H-AR$^{-/y}$ mice, but not female H-AR$^{-/-}$ mice, fed with high fat diet had hepatic steatosis with insulin resistance, whereas lean male H-AR$^{-/y}$ mice fed with normal chow exhibited normal insulin sensitivity. Mechanism dissection found increased hepatic steatosis in obese male H-AR$^{-/y}$ mice could be due to decreased fatty acid β-oxidation and increased de novo lipid synthesis that may come from decreased PPARα and increased SREBP1c expressions with its downstream target genes expressions. Furthermore, reduced insulin sensitivity with PI3k activity and increased PEPCK expression in obese male H-AR$^{-/y}$ could be due to increased PTP1b expression. Together, hepatic AR alone might play vital roles to prevent the development of insulin resistance and hepatic steatosis. AR agonists that specifically target hepatic AR might be developed to provide better strategies for treatment of metabolic syndromes in men.

2.4

ESTROGEN RECEPTOR STUDIES USING TRANSGENIC ANIMALS

Pascale Lane[1]
[1]Pediatrics, University of Nebraska Medical Center, 982169 Nebraska Medical Center, Omaha, NE, 68198-2169.

The development of targeted disruptions in the murine genes for estrogen receptors (ER) α and β in the 1990s has provided many lessons regarding the role of estrogens in various organ functions. While reproductive tract abnormalities in females were anticipated, reduced fertility in males also occurred. Lack of ERα eliminates neuroendocrine feedback, resulting in high circulating levels of both estrogens and androgens in female mice with ovaries. In mice, the kidney is the most ERα-regulated organ outside of the neuroendocrine system. ERα knockout mice (αERKO) show no differences in adult kidney size in males, while female αERKO mice show greater kidney weights than wild-type littermates, similar to values seen in males. No differences in glomerular size have been noted in this model; however, glomerular growth induced by diabetes is suppressed in female αERKO mice, suggesting a sex-specific effect of this genotype on the diabetic state. Another model of kidney enlargment, compensatory kidney growth 48 hours after uninephrectomy, also shows suppression in αERKO females. These effects may be mediated by the lack of ERα or via increased stimulation of ERβ. No renal phenotype has been described for the βERKO mouse, although this animal has not yet been studied in the same manner. βERKO mice do show hypertension and vascular dysfunction with aging, so renal effects of this genotype seem likely. Study strategies to determine effects of each receptor include studying females after ovariectomy to remove elevated hormone levels, and the use of selective estrogen receptor stimulation or blockade. Much has been learned from ERKO mice, and much more can be determined using this tool. (Supported in part by NIH DK59869).

2.5

REDUNDANT, DIVERGENT OR OPPOSING FUNCTIONS OF ESTROGEN RECEPTOR SUBTYPES, ERα AND ERβ IN HYPERTENSION, CARDIAC HYPERTROPHY AND HEART FAILURE?

Theo Pelzer[1]
[1]Medicine I, University of Wuerzburg, Josef Schneider Str. 2, Wuerzburg, D-97080, Germany.

Gender and ageing are determinants for the incidence and the prognosis of cardiovascular diseases including hypertension, cardiac hypertrophy and chronic heart failure. Clinical observations on a low incidence of cardiovascular disease in women during their reproductive age that is lost with the decline of sex hormone levels after menopause served as the starting point for clinical and basic research into estrogens as class of potentially cardioprotective hormones. In support of this concept, both estrogen receptor subtypes, ERα and ERβ, are expressed throughout the cardiovascular system and mediate important vascular functions such as NO-dependent vasorelaxation. Importantly, the myocardium represents another established target for female sex hormones. But against this evidence and the initial dogma, clinical endpoint trials on the primary or secondary prevention of coronary artery disease including the HERS and WHI trials have failed. Thus, a better understanding on the role of estrogens and progestogens in the cardiovascular system is warranted to (1) understand the mechanism(s) of gender effects in heart disease, (2) to improve the safety of hormone replacement therapy in women with a co-existing cardiovascular morbidity and (3) to develop innovative ER and PR ligands that are safe, efficacious and suitable to treat heart diseases in women. This presentation will provide an update on cardiovascular function in ERα and ERβ knock out mice and on the properties of novel subtype selective agonists for ERα (16α-LE2) and ERβ (8β-VE2) and novel progestins with anti-mineralocorticoid functionality that were tested in different animal models of hypertension, cardiac hypertrophy and chronic heart failure.

2.6

THE GLUCOCORTICOID RECEPTOR: ONE GENE, MANY PROTEINS-NEW MECHANISMS FOR TISSUE SPECIFIC ANTI-INFLAMMATORY ACTIONS OF GLUCOCORTICOIDS IN HEALTH AND DISEASE

John Cidlowski[1], Nick Lu[1], Christine Jewell[1], Onard Schoneveld[1], Danielle Duma[1], Kathy Gross[1], Javier Revollo[1], Robert Oakley[1]
[1]Laboratory of Signal Transduction, NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC, 27709.

Glucocorticoids are necessary for life after birth and regulate numerous homeostatic functions in man, including glucose homeostasis, protein catabolism, skeletal growth, respiratory function, inflammation, development, behavior and apoptosis. They are also one of the most prescribed classes of anti-inflammatory drugs in the world. Our understanding of how one hormone or drug regulates all of these diverse processes is limited, although most of these actions are thought to be mediated via the glucocorticoid receptor, which is a product of a single gene. However, recent studies in our laboratory have shown that multiple glucocorticoid receptor isoforms are produced from one gene via combinations of alternative mRNA splicing and alternative translation initiation. In addition these glucocorticoid receptor isoforms are subject to several post-translational modifications including ubiquitination, phosphorylation and sumoylation which also modulate receptor function. In this lecture, we will show that these GR receptor isoforms regulate specific subsets of genes and selectively regulate distinct cellular functions such as apoptosis. Finally, we will also describe new studies on the human glucocorticoid receptor â protein whose expression is associated with various states of glucocorticoid resistance in human inflammatory disease. Reference: Lu, N. Z. and Cidlowski, J.A. (2006). Glucocorticoid receptor isoforms generate transcription specificity. TRENDS in Cell Biology, Vol. 16, No.6.

3.0: SEX STEROIDS AND VASCULAR FUNCTION

3.2

ESTROGEN AND MITOCHONDRIA: A NEW PARADIGM FOR VASCULAR PROTECTION?

Sue Duckles[1], A Razmara[1], DN Krause[1], V Procaccio[2]
[1]Pharmacology, Univ Calif, Irvine, Sch Med, Irvine, CA, 92697, [2]Pediatrics, Univ Calif, Irvine, Sch Med, Irvine, CA, 92697.

There is much evidence that E decreases the incidence of cardiovascular disease and prolongs lifespan. Mitochondrial reactive oxygen species (ROS) cause lasting mutations of mitochondrial DNA. Thus the mitochondrial theory of aging links aging, exercise and diet. E receptor α was detected in mitochondria. Therefore we investigated whether E alters mitochondrial function in brain blood vessels isolated from ovariectomized female rats, treated 3 weeks with or without 17- β E by subcutaneous implant. Nuclear respiratory factor-1 protein, a primary regulator of nuclear gene-encoded mitochondrial genes, was significantly increased by E. Treatment with E increased levels of mitochondrial proteins: E receptor α, cytochrome c, subunits I and IV of complex IV, and MnSOD. E treatment increased activity of mitochondrial citrate synthase and complex IV, key rate limiting steps in energy production. In cultured human brain microvascular endothelial cells, 10 nM E decreased mitochondrial superoxide production and increased mitochondrial aconitase activity, an enzyme inactivated by mitochondrial superoxide. MnSOD protein, mRNA and activity were unchanged. We find that E modulates mitochondrial function in two ways: increasing energy-producing capacity and decreasing ROS production. The effectiveness of E against age-related cardiovascular disorders, including stroke, may arise in part from hormonal effects on mitochondrial function. However, E may be unable to reverse existing disease. E-mediated increases in mitochondrial efficiency may contribute to the longer lifespan of women. NIH RO1 HL50775.

3.3

SEX STEROIDS AND VASCULAR RESPONSES IN AGING

Raouf Khalil[1]
[1]Brigham & Women's Hospital, Boston, MA, 02115.

Cardiovascular disease (CVD) is less in pre- than post-menopausal women, suggesting vascular benefits of estrogen (E2). In adult female animals, E2 promotes endothelium-dependent vascular relaxation via the NO, prostacyclin and hyperpolarization pathways. Also, E2 receptors (ER) inhibit $[Ca^{2+}]_i$, protein kinase C and perhaps Rho kinase-dependent vascular smooth muscle (VSM) contraction. However, HERS, HERS-II and WHI clinical trials did not support the experimental findings, and demonstrated adverse CV events of hormone therapy (HT) in aging women. The lack of vascular benefits of HT may be related to the hormone used, the ER, or subject's CV condition or age. Experiments on vascular strips from aging (16 month) female-SHR have shown reduction in ER-mediated endothelial NO production, and decreased inhibitory effects of E2 on Ca^{2+} entry in VSM. The age-related decrease in ER-mediated vascular relaxation may explain the decreased effects of HT on CVD in aging women. New HT strategies should examine natural E2 and phytoestrogens for potential benefits over synthetic E2. Transdermal E2 may be more effective than oral E2, and specific ER modulators (SERMs) could maximize the vascular benefits, with little side effects on breast cancer. Variants of vascular ER should be screened for genetic polymorphism and postmenopausal decrease in amount or downstream signaling mechanisms. HT during menopausal transition could be more effective than in late menopause. Progesterone, testosterone or their specific modulators, combined with E2, may provide alternative HT strategies. Thus, HT type, dose, route of administration and timing should be customized depending on the subject's CV condition and age, and thereby enhance the vascular benefits of HT in aging women. (HL-65998, HL-70659).

3.4

RAPID NONGENOMIC EFFECTS OF ANDROGENS ON THE VASCULAR WALL

John N. Stallone[1]
[1]Michael E. DeBakey Institute and Department of Veterinary Physiology & Pharmacology, Texas A&M University, College of Veterinary Medicine, College Station, TX, 77843-4466.

Our laboratory has demonstrated that TES produces rapid, nongenomic vasorelaxation that is endothelium-, sex-, and androgen receptor-independent; however, little is known about TES mechanisms in vascular smooth muscle (VSM). Therefore, TES mechanisms in rat aortic and mesenteric arteriolar (MA) VSM were examined. In aorta, TES induced full relaxation (100%, EC50 36±4 uM), while reactivity to dihydrotestosterone, the nonpolar ester TES-enanthate, TES-hemisuccinate conjugated to BSA, and the excretory metabolite androsterone exhibited a fundamentally different rank order of efficacy/potency than in reproductive tissues. In MA, TES produced vasorelaxation at physiological concentrations (50±7%, EC50 2.3±0.5 nM). Precontraction of vessels with 80 mM KCl markedly reduced maximal response to TES (by 91±4%). 4-aminopyridine (4-AP, 2 mM) inhibited TES-induced relaxation by 65±5%. Pretreatment of MA with ICI 182,780 (1 uM) did not alter TES effects. In whole-cell patch clamped MA myocytes, TES increased outward K+ current >tenfold; this was nearly eliminated by 4-AP. In single MA myocytes, TES activated the fluorescent nitric oxide (NO) indicator DAF-2DA; ICI 182,780 (1 uM) did not alter this effect, while L-NMMA (10 uM) eliminated it. These data suggest that: 1) TES exerts a direct vasorelaxing effect on VSM at physiological concentrations which involves, at least in part, activation of the Kv channel, perhaps through the NO signal cascade; and 2) TES-induced vasorelaxation is a structurally-specific effect of the androgen molecule, which is enhanced in more polar analogs with lower permeability to the VSM cell membrane, and does not require aromatization to estrogen. Supported by NIH: HL-080402.

5.0: SEX STEROIDS IN HEART AND VASCULAR FUNCTION

5.1

SEX-BASED DIFFERENCES IN THE ARCHITECTURE OF THE HYPER-TROPHIED HEART IN SALT STRESSED BORDERLINE HYPERTENSIVE RATS

Johanna Krontiris-Litowitz[1], Rita Fulton[2]
[1]Biological Sciences, Youngstown State University, One University Plaza, Youngstown, Ohio, 44555, [2]Biology, Belmont Technical College, 120 Shannon Place, St. Clairsville, Ohio, 43950.

The Borderline Hypertensive Rat (BHR), the first generation offspring of a mating between a female spontaneously hypertensive rat and male normotensive Wistar-Kyoto rat, exhibits borderline hypertension and left ventricular hypertrophy at maturity. If exposed to an environmental stressor or dietary stressor such as sodium, BHR will develop hypertension. In these experiments we investigate the effect of elevated dietary sodium on the perivascular collagen deposition (PVC) in the hearts of 20 male and 20 female BHR. Half or the male and female BHR were fed a high salt diet (8% NaCl) for 12 weeks and half were fed a normal salt diet (0.6% NaCl). At the end of the experiment the animals were euthanized and the hearts harvested and analyzed. Animals on a high salt diet exhibited an increase in systolic pressure ($p<.05$) and ventricular hypertrophy ($p<.05$ n=20, 20). The PVC fraction in the ventricles of high salt females was significantly less than in high salt males ($p<.05$, n=6,6). Additionally, the distribution of PVC was regulated differently in males than females. PVC deposits in males were thicker than females in both control and high sodium animals ($p<.05$, $p<.05$, n= 6,6). Males also appeared to be sensitive to dietary sodium, exhibiting a significantly decreased PVC thickness when on a high sodium diet ($p<.001$, n= 6,6). In contrast, PVC deposits in females on a high sodium diet were not significantly thicker than their control counterparts. These studies suggest that there is a gender-based difference in perivascular collagen deposition in the hypertrophied heart and that dietary sodium may influence the reorganization of perivascular collagen differently in males and females.

5.2

ESTROGEN RECEPTOR ALPHA INTERACTS WITH 17β-HYDRO-XYSTEROID DEHYDROGENASE TYPE 10 AND REGULATES ITS ENZYMATIC ACTIVITY IN THE HEART

Theo Pelzer[1], Virginija Jazbutyte[2]
[1]Medicine I, University of Wuerzburg, Josef Schneider Str. 2, Wuerzburg, D-97080, Germany, [2]Department of Medicine I, University of Wuerzburg, Josef Schneider Str. 2, Wuerzburg, 97080, Germany.

Background: Studies in MCF7 cells have indicated that both estrogen receptor subtypes, ERα and ERβ localize not only to the nucleus and the cytosol but also to the mitochondrial compartment. Because estrogens might influence cardiac energy homeostasis that depends critically on mitochondrial function, we determined whether heart mitochondria contain ERα protein and whether ERα may act on the heart also via protein-protein interactions. Results: Confocal studies in cardiac myocytes localized ERα to the nucleus and to the cytosol in a pattern that overlapped partially with that of cardiac mitochondria. Candidate protein-protein interaction partners of ERα including 17β-hydroxysteroid dehydrogenase type 10 (17β-HSD10) were identified by two-hybrid screens using the ERα LBD as a bait. 17β-HSD10 co- localized with ERα in heart mitochondria and was co-precipitated with ERα (and vice versa) in pull-down experiments. The enzymatic activity of endogenous 17β-HSD10 was analyzed spectrophotometrically in cardiac mitochondrial fractions. 17β-HSD10 was expressed to comparable amounts in the mitochondria of ERα KO and WT hearts. But 17β-HSD10 activity was higher in control compared to KO animals. Conclusion: Heart mitochondria contain ERα protein. ERα may modulate estrogen metabolism via protein-protein interactions with 17β-HSD10 which catalyses the conversion of 17β-estradiol to estrone.

5.3

CHARACTERIZATION AND FUNCTIONAL ANALYSIS OF THE 5'-FLANKING REGION OF THE ERa GENE IN THE HUMAN HEART

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Estrogen receptor (ER)-mediated effects have been associated with the modulation of myocardial hypertrophy, but the regulation of ER expression in the human heart has not yet been analyzed. It has been shown that the human ERalpha (ERa) mRNA is transcribed from at least seven different promoters with unique 5'-untranslated regions (UTRs), which are utilized in a cell- and tissue-specific manner. Therefore, we determined the 5'-UTR promoter variants of the ERa gene in left ventricular biopsies from patients with dilated cardiomyopathy and control hearts using 5'-RACE and PCR. The promoter activity of the most frequent promoter variant was investigated by transfection experiments in a human cardiomyocyte cell line followed by Luciferase reporter assay. The PCR-based results showed that four 5'-UTR variants, namely A, B, C and F are expressed in the human heart, and furthermore pointed to the predominance of the F-promoter variant. Luciferase reporter assays with the F-promoter variant revealed regulatory regions, containing enhancer and suppressor elements. Database analysis showed the presence of several putative consensus sequences for transcription factors including CDP, NF-Kappa and NF-KappaB within the suppressor region. Site directed mutagenesis within the CDP- and NF-Kappa-binding sequences greatly increased the promoter activity. The results indicate that the expression of ERa-gene is predominantly controlled by the F-promoter and the expression of ERa-gene might be regulated by the CDP and NF-kappa-family of transcription factors in the human heart.

5.4

VOLUNTARY EXERCISE INDUCES SEX-SPECIFIC PHYSIOLOGICAL CARDIAC REMODELING

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Background: Physical activity leads to sex-specific protection of the heart against cardiovascular diseases. Therefore it is of great interest to identify how the sex of an individual determines physiological hypertrophy. **Methods:** Male and female mice, exercised for 5½ weeks on a wheel, were characterized by echocardiography to evaluate morphological and physiological cardiac adaptation in response to voluntary physical activity. RNA was isolated from the left ventricle and analyzed by quantitative PCR. **Results:** We found that female mice revealed a higher exercise performance (9.2km/d vs. 6.4km/d in males, $p<0.001$). Females showed a greater increase in LV mass (15% vs. 5% in males, $p=0.007$) in comparison to their sex-matched sedentary controls. β/α-MHC ratio was decreased by 41% in running females ($p=0.035$) but unaltered in males. Exercise led to a decrease by 20% of CTGF mRNA in females ($p=0.036$) but not in males. Furthermore CTGF mRNA was inversely correlated with LV/TL ratio only in females ($p=0.045$). IGF1 mRNA in exercised females was significantly higher than in males ($p=0.011$) and strongly correlated with daily running distance and time ($p<0.001$). **Conclusions:** Moderate long-term exercise provokes a sex-dependent cardiac adaptation. Female

mice develop a stronger hypertrophy. In opposition to pathological hypertrophy, this adaptation is characterized by anti-fibrotic gene expression pattern and IGF1 dependent pathways which are know to mediate physiological hypertrophy via PI3K. Therefore our findings can be of importance to explain the sex bias of physical activity as a protektiv cardiovascular factor.

5.5

COMPARISON OF THE SECOND DERIVATIVE PHOTOPLETHYSMOGRAPHY a-a INTERVAL METHOD AND ELECTRO-CARDIOGRAM R-R INTERVAL METHOD

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Objective: To examine the relationship between two methods for the assessment of autonomic nervous activity: the Second Derivative Photoplethysmography a-a Interval Method (SDPTG method), and Electrocardiogram R-R Interval Method (ECG method). Methods: 10 healthy males aged 22.1 (SD 2.0) years volunteered as subjects. ECG (standard techniques) and SDPTG (obtained from three sites: (A) forehead, (B) left middle fingertip, and (C) 1st digit MP joint of left foot), were simultaneously measured for 5 minutes. Power spectrum of heart rate and pulse beat variability was obtained by the maximum entropy method. Results: The average value of the a-a interval measured at site A was significantly correlated with R-R interval, at 978.8 (53.6) vs. 978.8 (52.9) ms, r=0.99, p<0.001. There was no significant difference between the two intervals. As for the value of low-frequency peak power (LF: 0.04-0.15 Hz), high-frequency peak power (HF: 0.15-0.40 Hz) and LF:HF ratio, there were significant correlations between the value measured at site A using the SDPTG method and the value obtained from ECG method (r>0.99, p<0.001). The same results were obtained between the value measured at site B and the value obtained from ECG and between the value measured at site C and the value obtained from ECG. Conclusions: At three measurement sites, the SDPTG method for the assessment of autonomic nervous activity may serve as a replacement for the ECG method.

5.6

CARDIAC SIZE AND PLASMA VOLUME: POTENTIAL MECHANISMS FOR POTS?

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We tested the hypothesis that Postural Orthostatic Tachycardia Syndrome (POTS) is associated with a small cardiac size and a low plasma volume. Eight young female POTS patients, 15 healthy women and 11 men, matched for age and body mass index, were studied. All subjects consumed a constant diet three days prior to study. Heart rate (HR) and blood pressure (BP) responses were assessed during 10 minutes of standing. Plasma volume (PV) was measured by the Carbon-Monoxide rebreathing technique. Left ventricular (LV) mass was determined using MRI. POTS patients had the greatest elevation in HR after 10 minutes of standing compared with healthy women and men (ΔHR, 32±10 beats/min *vs* 18±12 and 12±6, between groups $P<0.001$). Systolic BP was greater in men than in women and POTS patients ($P<0.001$), but diastolic BP was not different between groups in the supine and upright positions ($P=0.134$). POTS patients had the smallest normalized PV (41±6 mL/kg *vs* 48±7 and 50±7, between groups $P=0.008$) and normalized LV mass (45±6 g/m^2 *vs* 58±8 and 80±6, between groups $P<0.001$) compared with healthy women and men. However, normalized PV did not differ between healthy women and men ($P=0.516$), while normalized LV mass was significantly smaller in women than in men ($P<0.001$). Multiple linear regression analysis showed that HR responses could be predicted from a linear combination of both normalized LV mass and PV in all subjects ($R=0.618$, $P<0.001$). These results suggest that there is a sex-specific difference in cardiac size, even in the healthy population. This difference is exaggerated in female patients with POTS. It seems likely that a small cardiac size coupled with a low plasma volume can be important contributor(s) to the pathophysiology of POTS.

5.7

DEVELOPMENTAL CHANGES OF AUTONOMIC CONTROL OF HEART RATE IN THE CONSCIOUS BEHAVING RAT: STATE AND SEX INFLUENCES.

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Investigations into the postnatal development of autonomic control of the cardiovascular system have suggested that neonatal heart rate (HR) is primarily controlled by the sympathetic nervous system until postnatal day 16. At this critical developmental period, the parasympathetic system begins to influence HR control, paralleling changes in respiration. Though studies have examined this development in depth, the interaction of sex and sleep states on the development of HR control has not been investigated. The current study examined these factors on normal postnatal developmental changes in the cardiorespiratory interaction. At days 10, 17 & 28, Sprague Dawley pups were instrumented with ECG leads and placed in a plethysmograph where respiration rate (RR) and HR was measured for one hour. Heart variability (HRV) was determined by spectral analysis of heart beat to beat interval during different sleep/wake states. Preliminary data suggests that RR is significantly lower in all pups during sleep irrespective of sex at 28 days compared to 10 days of age. At day 17, HRV appeared to be greater in females irrespective of sleep stage versus to males. Indices of increased parasympathetic tone were greater in females compared to males at this time point. These preliminary findings suggest that male rat pups may develop tonic vagal tone more slowly than females. Supported by FL-Dept.of Health.

5.8

TESTOSTERONE MODULATES HEART RATE AND QT INTERVAL IN SWINE

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QT interval, the duration between the Q wave and T wave of an ECG heart beat, provides an in-vivo measure of cardiac ventricular repolarization. Women have a longer QT interval, even when corrected (cQT) for heart rate (HR) than men and thus, are at a higher risk for arrhythmias. Clinical data suggests testosterone shortens QT interval. Using a swine model with regulated sex hormone levels, the purpose of this study was to determine whether the male sex steroid hormone, testosterone influences regulation of HR and QT. Methods: Adult Yucatan swine were divided into 3 groups: control intact (IM), castrated (CM), and castrated with testosterone replacement (MHR) with topical Androgel (10mg/d). In addition, we examined the effects of 3 weeks of treatment with an androgen inhibitor, flutamide (FLUT, 500mg q12h). HR and QT intervals were calculated from 24-hour ambulatory ECG recordings prior to and after treatment. cQT was calculated using the Bazzett's formula and measured from 50 heart beats during both an active time period (10:00 AM) and a resting time period (1:00 AM) to represent data from high and low HR. Results: CM and FLUT had lower average 24-hour HR (79± 2.4, 80± 1.2bpm, respectively) compared to pre-treatment IM (92±3, 90± 3.5bpm respectively) and MHR (94± 3.2bpm). cQT interval of CM 94±7.5msec) was significantly increased compared to IM (363 ± 7msec) or MHR (364±8msec). FLUT also exhibited increased cQT interval compared to paired, pre-treatment control males (410±12msec). These data suggest that 1) castration alters HR and cQT, and 2) testosterone appears to mediate the effects of castration as a) testosterone therapy maintains HR and cQT levels comparable to IM, and b) androgen receptor blockade with FLUT altered HR and cQT comparable to CM.

5.9

TESTOSTERONE MODULATES HEART RATE VARIABILITY IN SWINE

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Heart rate variability (HRV) analysis, variation in beat to beat intervals of heart rate, reflects autonomic nervous system activity and can be used as an assessment of cardiovascular disease. Control of HRV differs between males and females with females exhibiting greater parasympathetic influence. To date, the influence of androgens on HRV has not been examined. This study tests the hypothesis that androgens influence HRV. Methods: 24-hour ECG recordings were obtained from adult Yucatan pigs in the following groups: normal males (NM, n=15), castrated males (CM, n=8), and castrated males treated daily with topical testosterone (AndroGel, 10 mg) (MHR, n=7). HRV was interpreted with time domain analysis. A second group of swine was treated for 3 weeks with placebo, following by 3 weeks with androgen receptor blocker, flutamide (500mg twice daily (FLUT, n=3)). Results: Overall 24-hour HRV (SDNN) and long term HRV (SDANN) were greater in CM (207.2± 14, 150.5± 11.7) than in NM (162.89± 18.6, 83± 3.4). Testosterone replacement restored SDNN comparable to NM, but SDANN remained higher than NM (99± 12.2). There were no differences in short-term HRV (RMSSD) between any group. Diurnal variation in HRV also existed with an increased nighttime SDNN (172.7± 8.2) and SDANN (83.3± 11) in MC vs NM (121± 7.3, 41.5± 3.4). Similar data were obtained using natural paired sampling and also revealed a difference in nighttime RMSSD between NM prior to (80.8± 9.1) and after castration (107.7± 8.8). Similar to castration, treatment with flutamide increased SDNN (207.5± 13.1) and SDANN (173.3± 12.4) compared to pre-treatment (186.6± 18, 141.3± 15.4). These data indicate that testosterone does modulate HRV with greatest effects on long term variability. Study supported by NASA and T32RR007004.

5.10

ROLE OF OXIDATIVE STRESS IN PARITY-INDUCED CORONARY DYSFUNCTION

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Multiparity is associated with increased risk of cardiovascular disease in postmenopausal women. During pregnancy, there is increased oxidative burden. However, it is not clear whether this persists *long-term*. We examined the effect of parity on coronary artery function, and on vascular reactive oxygen species (ROS) and nitric oxide levels (NO), in multiparous and age-matched virgin rats. Vascular reactivity to acetylcholine (ACh) was measured by wire myography using small coronary arteries preconstricted with U46619, in the presence of superoxide dismutase (SOD) or FeTPPs (peroxynitrite scavenger). Oxidative stress was measured using the luminol derivative L-012, and NO was measured by the Griess reaction. There was reduced ACh-mediated maximal relaxation in coronary arteries from multiparous rats (Parous: 49.2±2.9 %; Virgins: 94.6±3.1 %; P<0.05). ACh-mediated relaxation was abolished in both groups by L-NAME. Superoxide anion formation was increased in parous rats by 171.77±42.29 % URL (vs. virgins). Incubation of parous vessels with 100U/ml SOD or 10 μM FeTPPs improved maximal vascular relaxation to ACh (76.6±3.0 % and 65.8±4.2 % respectively). Parity also reduced eNOS protein levels in aorta, and reduced total nitrite/nitrate levels in heart tissue from 1.72±0.27 to 0.98±0.12 μM/mg protein. In addition, coronary arteries from parous rats exhibited reduced maximal relaxation to the NO donor SNAP (Parous: 73.5±2.8 % vs. Virgin: 96.8±1.8 %). These data suggest that pregnancy causes long-term coronary vascular dysfunction through decreased NO availability and increased ROS formation. Funding: CIHR.

5.11

ANALYSIS OF THE EFFECT OF E2 ON THE HUMAN MMP2 EXPRESSION IN HT1080 CELLS: A PROMOTER BASED ANALYSIS

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Background: It is known that MMP-2 plays an important role in cardiac remodeling and is regulated by E2 in different cell lines. Therefore we study the regulation of the human MMP-2 gene and the molecular mechanism involved in the E2-dependent control of the MMP-2 promoter. Methods: To understand the regulation of the humane MMP2 gene, a series of MMP-2 promoter constructs of varying length were transiently transfected in HT1080. MMP-2 promoter-activity was analyzed by luciferase reporter assays. To investigate the effect of E2 on the MMP-2 promoter activity, MMP-2 promoter constructs were co-tranfected with the human ERa in HT1080 cells. After treatment with E2 or vehicle, luciferase reporter assays were carried out. To evaluate direct regulation of E2 on the MMP-2 promoter EMSA was performed. Results: We identified within the human MMP-2 promoter sequence two sections, which show most luciferase activity, suggesting that these regions may contain enhancer elements. The co-transfection experiments in HT1080 cells showed an increase in MMP-2 promoter activity in the presence of ERa and a significantly decrease when the transfected cells were treated with E2. The luciferase reporter assays and EMSA suggest that E2 exerts its inhibitory effect upon binding sites located in the proximal region of the human MMP-2 promoter. Conclusion: Our study shows that ERa is capable to diminish the MMP-2 promoter activity in response to E2 in HT1080 cells. A deficiency or excess of E2 may cause a dysregulation of the ECM turnover in the human heart.

5.12

CUTANEOUS VENOARTERIOLAR RESPONSE IS NOT IMPAIRED IN POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

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Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by excessive tachycardia during orthostasis, which appears to be a compensatory mechanism for a small stroke volume. One of the major factors affecting stroke volume is the amount of venous return which may be determined in part by the venoarteriolar response (VAR). We tested the hypothesis that POTS is associated an impaired cutaneous VAR. Thirteen female POTS patients, 13 healthy females, and 10 healthy males, age (16-51 yr.) and body mass index matched, were studied. Skin blood flow (SkBF, laser-Doppler flometry), was measured in the calf at heart level and during leg dependency of 17-36 cm below the heart for two minutes each while supine. Blood pressure (BP, Portapres) and heart rate (HR, ECG) were monitored continuously. HR was higher in POTS patients when compared to both healthy females and males (79±12 bpm vs. 67±7 vs. 60±7, P<0.001). Between groups, BP was not different at baseline and during VAR, however diastolic BP increased slightly during VAR in males (61±4 mmHg baseline vs. 64±4 VAR, P=0.015). VAR, determined by the relative decrease in SkBF, was if anything, slightly greater between POTS patients and healthy females (39±15% vs. 28±12, P=0.056) and not different than males (45±15%, P=0.275). However VAR was lower in healthy females compared with males (P=0.015). These results suggest that POTS is not associated with an impaired VAR. Other mechanisms rather than this cutaneous local axon reflex may contribute to this syndrome. *Supported by NIH K23 (HL0752 83) and the GCRC grant (RR00633).*

5.13

DIHYDROTESTOSTERONE MODULATES CEREBRAL VASCULAR TONE IN PART BY ENHANCING COX-2

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Sex steroids modulate cerebral vascular responses: testosterone augments and estrogen attenuates vascular tone. Therefore, we investigated the effect of the more potent testosterone metabolite, dihydrotestosterone (DHT), on cerebral vascular function. Cerebral arteries were isolated from orchiectomized male rats treated chronically (3 wk) with either DHT 25 mg pellets (DHT25), DHT 45 mg pellets (DHT45), or placebo (ORX). In isolated, pressurized middle cerebral artery segments (MCA) passive diameters were not different among groups; however, vascular tone was significantly greater in DHT25 vessels compared to ORX. In contrast, vascular tone in DHT45 MCA was not different from ORX. Following endothelial removal, myogenic tone in DHT25 and DHT45 MCA was suppressed compared to ORX. The NOS inhibitor, L-NAME (100 μM), constricted all arteries with no differences among groups. Indomethacin (non-selective cyclooxygenase inhibitor, 10 μM) in the presence of L-NAME dilated DHT25 and DHT45 MCA, but constricted ORX MCA. Chronic DHT had no effect on eNOS or COX-1 protein levels measured by Western blot; however, COX-2 protein and NFκB activation were greater in DHT25 and DHT45 cerebral vessels. In conclusion, DHT has a dose dependent effect on vascular tone in cerebral vessels. At both doses effects of DHT involved COX-2-dependent constriction. AHA National Scientist Development Award (RJG).

5.14

GENDER AND CIRCULATING ENDOTHELIAL PROGENITOR CELL NUMBER AND APOPTOSIS

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Clinical interest in bone marrow-derived circulating endothelial progenitor cells (EPCs) has increased due to their importance in vascular repair processes as well as their emerging role as a biomarker of cardiovascular risk. We have previously shown that EPC clonogenic and migratory capacity are higher in middle-aged women than men, suggesting gender-related functional phenotypic differences with EPCs. In the present study we tested the hypothesis that: 1) circulating EPC number is higher and 2) EPC susceptibility to apoptosis is lower in middle-aged women vs men. EPCs were isolated from peripheral blood samples collected from 42 healthy, sedentary adult humans: 21 men (M: age 58±1 yr) and 21 women (W: 67±1 yr). EPC number was determined by flow cytometry and apoptotic tendency by active caspase-3 concentrations. There was no difference in % of CD45 low/CD34/VEGF-R2/CD133 positive cells between M (0.0019±0.0005%) and W (0.0016±0.0005%). Although, M demonstrated higher (55%; P<0.05) basal EPC caspase-3 activity vs W, active caspase-3 levels in response to the apoptotic stimulant staurosporine was not different (2.5±0.2 vs 2.2±0.2 ng/mL; P<0.30). In contrast to our hypothesis, these results demonstrate no gender-related differences in circulating EPC number and apoptosis susceptibility in middle-aged and older adult humans.

5.15

GENDER DIFFERENCES IN ENDOTHELIAL FUNCTIONS, VASCULAR ESTROGEN RECEPTORS, ENOS AND TRIGLYCERIDES

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The lower incidence of cardiovascular disease in women than men has been, in part, correlated with estrogen's protective effects on endothelial functions. We test the hypothesis that whether the higher estrogen level in female rats exhibited higher vascular nitric oxide (NO) content and acetylcholine-induced endothelial dependent relaxation (EDR) through up-regulation of estrogen receptors (ER) and endothelial NO synthase (eNOS). Our data showed that acetylcholine-induced EDR and vascular NO content were significantly higher in female compared to male rats. Quantitative real-time RT-PCR analysis demonstrated that mRNA expression of ER-α was significantly higher in female compared to male rats, but ER-β and eNOS did not differ between genders. Several lines of evidence indicated that the lower bioactive NO in vascular tissue was partially correlated with higher serum triglycerides. We further examined several biochemical parameters and found that serum triglyceride was significantly lower in female than male rats. Thus, the higher vascular NO output and endothelial function (EDR) in female rats correlated with higher expression of ER-α and lower level of serum triglyceride but not eNOS mRNA. (Supported by CMRPD 140152 NSC95-2320-B-182-030 to Y.T. Lau).

5.16

ESTRADIOL INHIBITS APOPTOTIC SIGNALING AND MICROVASCULAR ENDOTHELIAL CELL HYPERPERMEABILITY

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Disruption of endothelial cell-cell junction following ischemia-reperfusion (IR) has been shown to increase vascular hyperpermeability. Recent studies have also demonstrated that activation of the apoptotic signaling cascade is involved in endothelial dysfunction, which may result in hyperpermeability. We hypothesized that mitochondrial (intrinsic) apoptotic signaling pathway is involved in vascular hyperpermeability in endothelial cells and factors that inhibit this pathway may prevent hyperpermeability. The purpose of this study was to identify if estrogens such as 17β-estradiol, that are known to inhibit intrinsic apoptotic signaling, are effective in preventing hyperpermeability. Rat lung microvascular endothelial cells (RLMEC) grown on Transwell membranes as monolayers were treated with 17β-estradiol (1 or 10 nM) followed by pro-apoptotic BAK (BH3) peptide (5μg/ml) transfection. The permeability changes were determined based on FITC-albumin flux across the monolayer. Cytosolic cytochrome *c* levels were measured by ELISA. BAK (BH3) transfection induced monolayer hyperpermeability ($p < 0.05$). 17β-Estradiol (10 nM) attenuated BAK (BH3)-induced hyperpermeability ($p < 0.05$). Further, BAK (BH3) transfection induced cytochrome *c* release to the cytosol. 17β-Estradiol (10 nM) inhibited BAK (BH3)-induced cytochrome *c* release. This suggests 17β-estradiol as an important regulator of vascular permeability in RLMEC through cytochrome *c*-induced apoptotic signaling cascade.

5.17

GENDER MODULATION OF VENOUS FUNCTION IN SPONTANEOUSLY HYPERTENSIVE RATS.

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Our previous work suggested that increased venous tone contributes to the onset of hypertension. We also showed that male sex steroids amplified venous tone (18%) during hypertension development. This study tested the hypothesis that endogenous estrogens reduce venous tone in the female spontaneously hypertensive rat (**SHR**). Female SHR rats (5 weeks old) underwent sham operation (**Sham**) or ovariectomy (**OVX**). At 10 weeks of age, mean arterial pressure (**MAP**) and mean circulatory filling pressure (**MCFP**) were recorded in chronically instrumented conscious rats. MCFP, an index of venous tone, was calculated during brief right atrial balloon-induced circulatory arrest. Postsynaptic adrenergic responsiveness was assessed by constructing cumulative dose response curves to intravenous norepinephrine (**NE**) infusion. MAP was not significantly affected by ovariectomy (Sham 127±6 vs OVX 130±3 mm Hg). Conversely, MCFP was moderately, but significantly, increased in OVX SHR by 14% (Sham 5.2±0.2 vs OVX 5.9±0.2 mm Hg). Ganglionic blockade markedly decreased MAP and MCFP, however these responses were not different between sham (MAP:-60±8 mm Hg; MCFP: -2.1±0.3 mm Hg) and OVX (MAP: -54±4 mm Hg; MCFP: -1.9±0.2 mm Hg) SHR. NE dose dependently increased MAP and MCFP. There were no marked differences in these responses between Sham and OVX rats. Accordingly we conclude that endogenous ovarian hormones effect a modest reduction in venous tone that does not involve adrenergic mechanisms. Supported by NIH HLBI 63053 and 69886.

5.18

SEX DIFFERENCES IN THE RESPONSE TO VASOCONSTRICTOR AND VASODILATOR SUBSTANCES IN CHRONICALLY STRESSED MALE AND FEMALE RATS

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Chronic stress, which increases plasma NPY, has been reported to increase atherosclerotic-like lesions following angioplasty. While this is intriguing, whether there are sex differences in response to stress in normal vasculature is unknown. Stress has been shown to reduce circulating estrogen and testosterone levels, with the loss of estrogen potentially having a negative vascular effect. Adult male and female rats were separated into control and cold-water stress groups. After two-weeks, mesenteric arteriolar vascular reactivity to the vasoconstrictor PE and vasodilator ACh was performed on a wire myograph. Stress increased plasma NPY in both male and female rats (P<0.05 vs sham). An inverse response to ACh was observed between the sexes; vessels from stressed males had a 115% increase in ACh response compared to controls (P<0.05), versus a 56% decrease in females (P<0.05). While stress had no effect on PE reactivity in either sex, L-NAME incubation before PE challenge resulted in an increase in PE reactivity in the stressed female but not male. This indicates that vessels from the stressed female, but not stressed male, increase constitutive NO production versus control non-stressed vessels. Finally, NPY incubation before PE resulted in a decrease in sensitivity (-25% from controls) in stressed male vessels, while vessels from stressed females increased the responsiveness to NPY (+35% from controls). These findings support the concept that chronic stress induces early sex-related changes in vascular remodeling, which may put the stressed female at greater risk for developing vascular disease. *(supported by NIH R01 DK064916 and the National Kidney Foundation of the National Capital Area).*

5.19

ESTROGEN DECREASES MITOCHONDRIAL OXIDATIVE STRESS IN HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELLS

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Mitochondrial reactive oxygen species (ROS) and endothelial dysfunction are key paradigms in cerebrovascular pathophysiology. 17β-estradiol (E) enhances efficiency of mitochondrial energy production and suppresses mitochondrial ROS in cerebral blood vessels. Cultured human brain microvascular endothelial cells (HBMEC) were exposed to 10 nM E for 24 hr, and mitochondrial superoxide measured with MitoSOX Red dye. E decreased mitochondrial superoxide in an E-receptor dependent manner. Raloxifene suppressed mitochondrial superoxide, but tamoxifen did not. Aconitase activity is a functional indicator of mitochondrial ROS production as the iron-sulfur core of aconitase is inactivated by superoxide. E increased aconitase activity, confirming less mitochondrial ROS production. Enzyme reactivation with reducing agents showed that E did not affect enzyme levels per se. E had no effect on Mn superoxide dismutase mRNA, protein, or enzyme activity. E increased levels of the peroxisome proliferator-activated receptor-gamma

coactivator-1 family of transcriptional co-activators in an ER-mediated manner, suggesting that mitochondrial ROS may be decreased by E via these co-activators. The ability of E to decrease cerebral endothelial mitochondrial ROS and protect against damage to mitochondrial DNA may contribute to differences in lifespan as well as stroke morbidity and mortality between men and women. NIH RO1 HL50775.

5.20

EFFECT OF ESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS ON VASCULAR REACTIVITY IN THE PERFUSED MESENTERIC VASCULAR BED.

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Estrogen and SERMs such as raloxifene (RAL) and tamoxifen (TAM) acutely relax arteries, but the long term effects of estrogens and SERMs on vascular reactivity in the mesenteric vasculature are unknown. In this study, we used an isolated perfused mesenteric vascular bed technique to investigate the effect of chronic treatment of estrogens and SERMs on vascular reactivity of the mesenteric bed. Female Sprague Dawley rats were ovariectomized (ovx) at 4 weeks of age. After 2 week recovery the rats were treated by gavage with vehicle (CTL, 2-hydroxypropyl-β-cyclodextrin), ethinyl estradiol (EE), estradiol benzoate (EB), equilin (EQ), TAM, or RAL for 3 weeks. Mean arterial blood pressure (BP, mmHg) was significantly increased in EQ (134±4) and decreased in TAM (104±4) compared to CTL (117±4). EQ, EE, and TAM treatment increased the perfusion pressure response to KCl induced depolarization compared to CTL. The ED_{70mmHg} for KCl was significantly lower for EQ and TAM vs. CTL. EQ and TAM treatment increased the perfusion pressure responses to norepinephrine (NE) compared to CTL. The $ED_{125\ mmHg}$ for NE was significantly lower for EE vs CTL and higher for EB vs. CTL. EQ and EE treatment increased the perfusion pressure at the maximal dose of serotonin (5HT) compared to CTL. The ED_{30mmHg} for 5HT was significantly lower for EQ vs. CTL. These data demonstrate that chronic treatment with estrogens and SERMs affect vascular reactivity in the mesenteric vascular bed. Supported by NIH HL 69886 & 63053.

5.21

SEX DIFFERENCES IN THE RELATIONSHIP BETWEEN RAT MESENTERIC VENULAR PROTEIN LEAKAGE AND TISSUE PROTEIN CLEARANCE

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We tested whether protein flux from individual venules was indicative of net protein clearance from the rat mesenteric tissue, whether high dose insulin alters this relationship, and whether it does so differently with sex and age. Following intravenous injection of Alexa 594™ labeled bovine serum albumin (Alexa-BSA) the exposed mesenteric vasculature was suffused for 30mins with bicarbonate-buffer solution (BBS), then 75mins BBS with or without 10-7M porcine insulin. Microvascular BSA flux for a postcapillary venule was assessed by fluorescence microscopy (indicated as leak index; LI). The suffusate flowing off the mesentery was collected and Alexa-BSA concentration was measured. No correlation existed between protein leakage (LI) and clearance (indicated by %BSA of total protein in suffusate) in the adult males either with or without insulin treatment. Protein leakage and clearance were negatively correlated in juvenile males treated with (r=-0.78; p=0.01) or without (r=-0.71; p=0.03) insulin. A positive correlation existed between protein leakage and clearance (r=0.80; p=0.01) for adult females treated with insulin. In conclusion, the handling of proteins by individual venules and overall mesenteric tissue can differ significantly depending not only on the sex of the animal, but also its maturity and metabolic status. NIH-HL078816 & HL075186, RR017353, NASA-NNJ05HF37G, AHA0615515Z(RS).

5.22

SEX DIFFERENCE IN THE REGULATION OF MUSCLE BLOOD FLOW DURING STATIC HANDGRIP EXERCISE.

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There exists sex difference in the vasodilatory response to reactive hyperemia and flow-mediated vasodilation (FMD) is larger in females than males. We hypothesize that muscle blood flow response to active muscle is different between females and males because of sex difference in endothelial function. To elucidate the sex difference in the regulation of blood flow to the active muscle during exercise, we examined the regulation of muscle blood flow during static handgrip exercise (20 % MVC) in female and male subjects. In the female subjects, we conducted experiments three times; menstrual (M), ovulatory (O), and luteal (L) phases. FMD in the brachial artery was larger in females than males, and in females FMD tended to be larger during O phase than the other phases. The percent increase in blood flow during exercise in females during O phase was higher than in males. Mean arterial pressure increased by about 15 mmHg in males, but did not significantly increase in females regardless of phases. The increase in vascular conductance during exercise in females during O phase was higher than in males. Thus, the muscle blood flow during exercise is regulated differently between males and females. The contribution of increased perfusion pressure is significant in males, but peripheral vasodilation contributes almost all to the increase in blood flow to the muscle in females. In addition, the magnitude of vasodilation was influenced by menstrual cycle. These results suggest sex and menstrual cycle affect the regulation of muscle blood flow to the exercising muscle.

5.23

SKELETAL MUSCLE ARTERIOLES DEMONSTRATE SEXUAL DIMORPHISM WITH RESPECT TO MACROMOLECULE TRANSVASCULAR EXCHANGE PATHWAYS.

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We have demonstrated that sex can be a primary determinant of basal coronary microvessel permeability (Ps, 10^{-7} cm/s) and, independently a determinant of the magnitude and direction of response to acute vasoactive stimulants or chronic adaptation to exercise. In this study we hypothesized that arterioles (art) isolated from skeletal muscle (*tricepts brachii*) of adult male (M) and female (F) pigs would not differ with respect to basal Ps, but like coronary arterioles, would differ with respect to the change in Ps (ΔPs) in response to adenosine (ADO, 10^{-5} M). Ps to porcine serum albumin (PSA, 29 F & 19 M) and alpha lactalbumin (a-lact, 29 F & 13 M) were measured in the absence and presence of ADO. Not only was sex without influence on Ps but there was no difference in Ps to PSA and a-lact despite the difference in size (66.5 vs 14 kD). While ADO was without influence on Ps to PSA in either M or F, Ps to a-lact was increased in arterioles from F and decreased in arterioles from M ($p<0.05$). In aggregate the basal Ps data to the two proteins and the responses to ADO are consistent with the interpretation that under basal conditions these molecules use different routes to traverse the vessel wall. Further, the sex influences the mechanisms whereby ADO alters the paracellular pathway used by a-lact while being without influence on the pathway used by PSA. These data differ from the results observed in the heart. In both organs the data support sexual dimorphism in the regulation of exchange and mechanisms regulating volume homeostasis. Supported by NIH PO1 HL 52490; RO1 HL078816 and NASA NNJ05HF37G.

5.24

DOES GENDER INFLUENCE CARDIOVASCULAR AND RENAL RESPONSES TO WATER IMMERSION?

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Human female responses to water immersion remain poorly studied when compared to the huge body of literature obtained from male subjects. We hypothesized that women and men exhibit similar cardiovascular and renal responses to thermoneutral water immersion (WI) to neck level after adjustment of renal responses per kg body weight. Ten women and nine men underwent two sessions in random order: 1) seated non-immersed for 5.5 h (control); and 2) WI to neck level for 3 h, with subjects sitting non-immersed for 1.5 h pre- and 1 h post-WI. We measured left atrial diameter, heart rate, arterial pressure, urine volume and osmolality, and urinary endothelin, urodilatin, sodium, and potassium excretion. No significant gender differences emerged in cardiovascular responses. Women and men also exhibited largely similar renal responses to WI after adjustment for body mass. However, female urodilatin excretion per kg during WI was 128% greater than men ($P < 0.05$). Also, women exhibited a delayed kaliuretic response to WI relative to men, and women excreted 24% less potassium per kg during the third h of WI. Men may excrete more potassium than women during WI because men possess greater lean body mass (potassium per kg body weight). Alternatively, anti-kaliuretic effects of urodilatin may be responsible. Selected responses of men to WI may be cautiously extrapolated to women, yet urodilatin and potassium excretion responses exhibit gender differences.

5.25

EFFECT OF ESTROGEN REPLACEMENT ON OSMOREGULATORY AND CENTRAL ANGIOTEISIN II-INDUCED FLUID REGULATION IN OVARIECTOMIZED RATS

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We examined the effect of estradiol (E2) replacement in ovariectomized rats on the fluid intake and c-Fos expression of the arginine vasopressin (AVP) neurons at the paraventricular (PVN) and supraoptic (SON) nuclei in response to iv hypertonic saline infusion and icv angiotensin II (ANGII) injection. We also examined the c-Fos expression induced by these challenges at the organum vasculosum of the lamina terminalis (OVLT), subfornical organ (SFO) and median preoptic nucleus (MnPO). E2 replacement significantly attenuated osmotically-induced fluid intake and c-Fos expression of AVP neurons at the PVN and SON. E2 replacement did not affect the c-Fos expression at the osmosensitive regions, such as OVLT, SFO or MnPO following systemic osmotic challenge, suggesting that E2 does not modify osmoreceptor sensitivity. E2-effect on osmoregulation might be located on the pathway between osmoreceptors and the centers generating thirst and AVP secretion, or on these centers directly. E2 replacement also attenuated fluid intake and AVP neuron's activity induced by icv ANGII injection, and also attenuated the c-Fos expression at the SFO and MnPO, indicating that the central sensitivity to ANGII is attenuated by E2 replacement. Thus, the reduced central sensitivity to ANGII might be at least in part involved in the attenuated osmoregulatory responses by E2, because central ANGII plays an important role in osmoregulatory thirst and AVP release.

5.26

ALDOSTERONE EXCRETION DURING CHRONIC INTERMITTENT HYPOXIA IN MALE AND FEMALE RATS

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We have shown that chronic intermittent hypoxia (CIH) increases blood pressure in male (M), but not female (F) rats. This protection in F is dependent on F sex hormones because ovariectomized (OVX) females responded to CIH with an increase in blood pressure similar to M. CIH in M and OVX suppressed pressure-natriuresis/diuresis, while CIH in F enhanced pressure-natriuresis/diuresis. We hypothesize that F sex hormones facilitate renal sodium and water excretion during CIH by suppressing aldosterone production. We investigated the effect of CIH on aldosterone excretion in M (n=8), F (n=6) and OVX (n=6) rats. Rats were exposed to 7 days of CIH, defined as continuous cycles of 3 minutes of room air (21% O2) and 3 minutes of 10% O2 for 8 hours/day. Urine volume and aldosterone levels were measured during the CIH periods of the day. Following a similar increase in aldosterone excretion on the first day of CIH in all groups, aldosterone excretion subsequently decreased in F (-29%) and M (-8%). In contrast, CIH resulted in a sustained increase in aldosterone excretion in OVX (+13%). The reduction in aldosterone excretion in F was significantly different from M and OVX ($p<0.05$). We conclude that CIH reduces aldosterone excretion in females, and this effect is dependent on the presence of female sex hormones. We speculate that female sex hormones protect against elevations in blood pressure associated with CIH by facilitating renal sodium and water excretion mediated by a suppression of aldosterone production.

5.27

GENOME-WIDE SCAN FOR GENOMIC DETERMINANTS OF ALCOHOL AND TOBACCO USE IN FRENCH CANADIAN FAMILIES

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We investigated the genomic factors in alcohol and tobacco use in a cohort of 120 families with at least 1 sib pair affected by hypertension and dyslipidemia from the Saguenay-Lac-St-Jean region. Phenotyping was performed by questionnaire. Joint sex-specific and non-specific linkage and association analyses were carried out with dense map (3 haplotypes per cM; r2 > 0.4) generated by merging 58000 SNPs and 437 microsatellites. Alcohol and smoking were strongly correlated with sex. Several loci with strong evidence of linkage and association were identified (LOD score > 3, P-value <0.001). A common locus on chromosome (chr) 1 was found for alcohol and tobacco use. Fine mapping for alcohol revealed a LD block located downstream of LPHN2 gene; female-specific SNPs were also uncovered inside the block for smoking. Moreover, on chr 1 at 233 cM, where we previously reported a QTL for diastolic blood pressures (DBP), a locus for smoking emerged. We noted SNPs inside GRID2 gene on chr 4; male-specific analyses revealed associated SNPs inside this gene for alcohol. At 168-180 cM on chr 3, where we previously observed loci for night and pre-math stress DBP, we uncovered a locus for alcohol. Along with the results of segregation mating tables indicated a pattern of X-linked inheritance for alcohol; SNPs emerged within POU3F4 gene on X chromosome. Besides, female-specific SNPs were found for smoking inside HTR2C gene. Common loci were identified for alcohol and tobacco use and for BP, suggesting common genomic determinants pointing to novel mechanisms of BP modification by these substances and the importance of sex. This work was supported by the NIH, CIHR, HSFC and the GENESIS Team.

6.0: SEX STEROIDS AND METABOLIC SYNDROME

6.1
SEX DIFFERENCES IN SLEEP APNEA

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Sleep apnea (SA) is characterized by repetitive episodes of apnea-induced arterial hypoxemia during sleep. Repeated exposure to SA results in an increase in arterial pressure during waking hours, and disturbances in sodium and volume homeostasis. SA also associates with other cardiovascular risk factors that are components of metabolic syndrome such as obesity, dyslipidemia, and insulin resistance. Pre-menopausal women have a lower occurrence of SA than males, while in post-menopausal women the incidence is the same as in males. However, the cardiovascular complications associated with SA represent a significant health problem in both men and women. The mechanisms for the cardiovascular and renal effects of SA are not well understood, but evidence suggests that activation of the sympathetic nervous system, and the renin-angiotensin-aldosterone system are contributing factors. Chronic intermittent hypoxia (CIH) is a model for the repetitive bouts of apnea-induced arterial hypoxemia that occur during SA. Using this model, we have studied blood pressure, sodium and water homeostasis, renal pressure natriuresis, and aldosterone production in male and female rats during a 7 day exposure to CIH. We have demonstrated significant sex differences in the response to CIH. These findings and the clinical observations of sex differences in the effects of SA underscore the importance of further research of the mechanism of these sex-dependent responses. Reference: Hinojosa-Laborde C and Mifflin SW. (2005) Sex Differences in Blood Pressure Response to Intermittent Hypoxia in Rats. Hypertension, 46:1016-1021.

6.3
THE PARENTAL ORIGIN OF THE X CHROMOSOME AND METABOLIC RISK FACTORS

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Some important gender disparities in metabolic profile and longevity aren't explained by sex steroid effects. Despite random inactivation of the 2nd X chromosome in females, the finding of a distinct phenotype in 45,X females with Turner syndrome (TS) indicates that the second X chromosome is important for normal female development. Our study of women with TS suggests that parental imprinting of X-linked genes involved in body composition and lipid metabolism contributes to gender differences in risk for atherosclerosis. Normal men are monosomic for X_{mat} while women are mosaic for X_{mat} and $X_{pat.}$ If X-chromosome gene or genes that prevent visceral fat accumulation were imprinted (silenced) on X_{mat} and selectively expressed from $X_{pat,}$ that could explain some of the observed differences between male and female risk profiles. To test this hypothesis, we compared regional fat distribution and lipid profile in women monosomic for X_{pat} vs. women monosomic for X_{mat} . Although BMI and total body fat were similar in our age-matched groups, women with a single maternally inherited X-chromosome (X_{mat}) had more than twice as much visceral fat vs. women with a paternal X (P=0.001, JAMA, 2006). Lipid profile was also significantly more atherogenic in the X_{mat} group of women. This male-type fat distribution and lipid profile in 45, X_{mat} women supports the view that differential X-chromosome gene dosage, determined by genomic imprinting, contributes to the excess mortality from ischemic heart disease in 46, X_{mat}Y men as well as 45, X_{mat} women. The identification of these genes clearly is of clinical importance.

7.0: SEX STEROIDS, THE RENIN-ANGIOTENSIN SYSTEM AND HYPERTENSION

7.2
SEX DIFFERENCES IN ANGIOTENSIN II, ANGIOTENSIN CONVERTING ENZYME 2 AND ANGIOTENSIN-(1-7)

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The mRen2.Lewis (mRen) is a congenic hypertensive model that exhibits sex-dependent differences in blood pressure and tissue injury. We tested the hypothesis as to whether the tissue renin-angiotensin system (RAS) is enhanced in the male versus female mRen. Age-matched hemizygous male [200 ± 4 mmHg] and female mRen [146 ± 7 mmHg] were utilized in these studies. Renal cortical Ang II content was 2-fold higher in the male mRen [9.2 ± 0.4 vs. 4.2 ± 0.3 fmol/mg]. Conversely, cortical levels of Ang-(1-7) were lower in the male strain [1.1 ± 0.5 vs. 3.4 ± 0.8 fmol/mg]. To determine the potential enzymatic contribution, we assessed cortical ACE2 and neprilysin activities as both enzymes are capable of degrading Ang II and producing Ang-(1-7). Neprilysin was 3 fold higher in the female cortex [919 ± 73 vs. 290 ± 51 fmol/min/mg] consistent with the higher expression of Ang-(1-7). Surprisingly, ACE2 activity was significantly higher in the male mRen [69 ± 3 vs. 31 ± 3 fmol/min/mg]. We conclude that the gender differences in the mRen strain involves differential regulation of the RAS that may favor Ang II over Ang-(1-7) in the kidney. However, increased ACE2 may reflect a compensatory response to the greater pressure and tissue injury in the male. NIH HL-56973, HL-51952 & AHA-Grant-in-Aid. References: Chappell MC, Yamaleyeva LI, Westwood BM. Estrogen and Salt-Sensitivity. *Am J Physiol:* 291: H2166-H2172,2006.

7.3
GONADAL HORMONE-INDEPENDENT SEX CHROMOSOME EFFECTS IN ANGIOTENSIN II-INDUCED HYPERTENSION

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Men have higher blood pressures (BP) and a higher incidence of hypertension than women up to the 6th decade of life after which point, women catch up. To determine if sex chromosomes contribute to this sex difference in BP independently of the gonadal hormone milieu, we studied the magnitude of angiotensin II (Ang II)-induced hypertension in the Sry transgenic mouse on an MF-1 background. The Sry gene is the testis-determining factor and thus its presence (phenotypic male) or absence (phenotypic female) determines an individual's sex. The Sry gene was moved from the Y chromosome to an autosome resulting in 4 genotypes: 2 females [XX and XY^-(lack Sry)] and 2 males [XY^-Sry and XXSry] differing only in their sex chromosomal complement, respectively. Six weeks after birth, both the males and females were castrated. At 6-8 mo, radiotransmitters were inserted and baseline recordings were made for 3 days after the mice had recovered from surgery (1 week). Once a stable baseline was established, Ang II was infused by osmotic minipump (800ng/Kg/min) and BP was recorded by radiotelemetry at 10s intervals for 10 min/hour from 8 pm to 6 am for 8 d. A mixed effect statistical model was used to compare the differences in BP (DBP) between basal and Ang II treatment. The DBP was significantly higher in the XX compared to the XY^- female ($p < 0.013$) [DBP±SEM (mm Hg): XX, 36.8±7.6; XY^-, 26.5±7.8; XYSry, 26.3±8.0; XXSry, 32.8±6.1; n=9-11]. These data suggest that under conditions of gonadal steroid deficiency such as menopause, the XX sex chromosomal complement makes the female more susceptible to hypertension than the XY male. Supported by NIH grant AG19291.

7.4
ROLE OF THE RAS IN SEX DIFFERENCES IN HYPERTENSION

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Sexual dimorphism in arterial pressure (AP) exists in human and animal models. Hypertension is more prevalent in post-menopausal compared to pre-menopausal women. The RAS likely plays a prominent role. Estrogen induces increased circulating RAS components in women and in users of oral contraceptives (OCs) and hormone replacement therapy (HRT); estrogen induces downregulation of ACE activity and AT1 receptors, and upregulation of AT2 receptors. Human studies document RAS functional differences between the sexes and between high and low estrogen states: The luteal phase is characterized by elevated circulating RAS components, a blunted response to Ang II, and an inability to maintain AP in response to simulated orthostasis. Women exhibit augmented hemodynamic responses to RAS blockade. Exogenous estrogens also impact RAS function: OC users exhibit elevated AP which is abolished by RAS blockade and increased AT1 receptor expression compared to non-users; HRT induces discordant Ang II and AP responses to orthostasis in post-menopausal women. The Nitric Oxide (NO) pathway as a counterregulatory system may offer insight into sexual dimorphism in AP, in that women who are users and non-users of OCs exhibit differences in response to NO system stimulation. Funding Source: Canadian Institutes of Health Research. (Miller JA, Cherney DZ, Duncan JA et al: Gender differences in the response to renin angiotensin system blockade. J Am Soc Nephrol 17:2554-2560, 2006; Harvey PJ, Morris BL, Miller JA et al: Estradial induces discordant angiotensin and blood pressure responses to orthostasis in healthy post-menopausal women. Hypertension 45:399-405, 2005).

7.5
2-METHOXYESTRADIOL: A SAFE AND EFFECTIVE CARDIORENAL PROTECTIVE HORMONE THERAPY FOR WOMEN AND MEN

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2-Methoxyestradiol (2ME) is a non-estrogenic metabolite of estradiol. In smooth muscle cells, cardiac fibroblasts and mesangial cells 2ME potently inhibits cell growth. Moreover, 2ME reduces endothelin-1 production, yet increases prostacyclin biosynthesis. In rats with the metabolic syndrome, treatment with 2-hydroxyestradiol, the precursor of 2ME, decreases body weight, improves vascular endothelial function, decreases nephropathy, exerts antidiabetic actions and lowers blood pressure and blood cholesterol. Also, 2ME protects against nephrotoxins and pulmotoxins. The beneficial effects of 2ME are such that it makes sense to evaluate the drug's potential as a safe and effective hormone therapy for both women and men. 2ME is not feminizing in men nor would it be expected to increase the risk of uterine or breast cancer in women. Indeed, 2ME is anti-carcinogenic. Although the pharmacokinetic properties of 2ME are challenging, progress has been made in developing a long-acting formulation of 2ME that provides pharmacologic levels of the drug in humans for several weeks after a single dose. An interesting finding in the phase I studies with this preparation is that approximately 25% of men have significant basal levels of 2ME as determined by state-of-the-art mass spectrometric methods. In conclusion, 2ME may play an important physiological role and is an important molecule to consider in the quest for a safe and effective hormone therapy.

7.6

THE ROLE OF ESTROGENS AND POLYPHENOLS IN HYPERTENSION AND DIABETES.

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Cognitive loss, hypertension, cardiovascular disease, diabetes and stroke increase dramatically after menopause. In SHR, estrogen deprivation increases hypertension, insulin resistance and stroke. We have demonstrated that in female ovariectomized SHR three polyphenols (i.e., genistein [soy], puerarin [kudzu] and proanthrocyanidins [grape]) blunt hypertension, cognitive decline and insulin resistance. Of these, puerarin is most easily tracked, largely because the C-glucoside remains unmetabolized as it crosses the gut/blood barrier, circulates and is eliminated. Puerarin blunts <50% of the blood pressure rise that occurs in the non-treated SHR on a high salt diet. Suppression of both sympathetic nervous system activity and superoxide production play a role in these effects. Puerarin also reduces blood glucose, insulin and leptin in the SHR. Glucose tolerance and glucose sensitivity are improved by <20% in chronic studies and by about 50% when the puerarin and glucose are administered simultaneously. In the later effects puerarin appears to act via Na-dependent glucose transporters. Both of these effects occur in young and aged SHR, but there are several changes in the effects with age. Clearly, treatment of the animals is always beneficial, but the greatest effects occur when the animals are treated prior to 12-15 months of age. (NIH/ODS P50AT000477; NINDS P30NS047466 and P30NS057098; Peng, et al., Antihypertensive and cognitive effects of grape polyphenols. *Amer J Physiol, 289:771,* 2005. Meezan E, et al., Contrasting effects of puerarin and daidzin on glucose homeostasis in mice. *J Agric Food Chem*, 53:*8760,* 2005.)

8.0: SEX STEROIDS AND TARGET ORGAN INJURY

8.2

SEX STEROIDS, CORONARY SMOOTH MUSCLE, ATHEROSCLEROSIS AND RESTENOSIS

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Sex differences in the prevalence of coronary artery disease (CAD) have led to the belief that testosterone increases the risk of CAD in men. However, recent clinical studies have failed to support a detrimental effect of testosterone on CAD or carotid atherosclerosis in men. On the contrary, epidemiological and clinical trials indicate that low testosterone levels in men are associated with a higher risk of cardiovascular disease. Accumulation of smooth muscle cells (SMC) in the intima is a hallmark of coronary atherosclerosis and restenosis, reflecting the balance between proliferation and apoptosis. We have recently shown that 1) PKCδlevels are higher in coronary smooth muscle cells (CSMC) of males, 2) endogenous testosterone increases PKCδ protein levels in CSMC and 3) both testosterone and dihydrotestosterone (DHT) increase PKCδ expression and activity in CSMC in vitro. PKCδ has been shown to be anti-proliferative and pro-apoptotic in other cells types. Accordingly we have shown that testosterone induced a PKCδ-dependent G1/S phase cell cycle arrest and stimulated apoptosis in CSMC, providing a potential mechanistic basis for observed effects of testosterone on coronary vasculoproliferative diseases. Using a swine model of coronary restenosis we found both intimal to medial ratio (I/M) and I/M normalized to rupture index (RI) were increased in castrated males, but not those with testosterone replacement, compared to intact males. Thus, both in vitro and in vivo data support beneficial effects of endogenous T on post-angioplasty restenosis in males. The effect of testosterone on complex atherosclerotic lesions is likely context dependent, e.g. vulnerable plaque vs. stable plaque, warranting caution when extrapolating to human clinical outcomes. Support: NIH HL 071574 and NASA.

8.3

CRITICAL ROLE FOR ET_B RECEPTORS IN ATTENUATING THE RESPONSE TO ENVIRONMENTAL STRESS IN FEMALE, BUT NOT MALE RATS

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The endothelin (ET) system contributes to blood pressure regulation through both vascular and renal tubular mechanisms with ET_A and ET_B receptors having contrasting effects. Genetic ET_B receptor deficiency or pharmacological blockade of the ET_B receptor results in salt-dependent hypertension. When ET_B receptor deficient rats were placed on a high salt diet, female rats were observed to have a greater increase in blood pressure compared to male rats when assessed by the tail cuff method. When we sought to confirm these observations using telemetry, the gender difference was no longer observed. This led us to hypothesize that female ET_B receptor deficient rats have an exaggerated pressor response to acute stress such as would occur during the tail cuff procedure. Male and female ET_B receptor deficient rats along with receptor intact control rats were implanted with telemetry transmitters to monitor blood pressure and heart rate changes in response to an acute stressor. Rats were placed in a restrainer and subjected to a 3 min period of air pulses directed at their head. We observed that the total pressor response (area under curve) to air jet stress was greater in ET_B deficient female (67±6 mmHg/3min, n=6) compared to male rats (50±5 mmHg/3min, n=5, $p<0.05$) while there was no gender difference in controls. After a high salt diet (8% NaCl) for 3 weeks, both male and female ET_B receptor deficient rats had similar increases in baseline blood pressure (165±10 and 160±5 mmHg during the 4th week of high salt in male vs. female, respectively). Air jet stress increased pressure more in the female rats (61±9 mmHg/3min), an effect that was again more pronounced compared to male rats (37±9 mmHg/3min, n=5, $p<0.05$). These studies highlight an important gender difference between ET_B receptor function in the response to stress and suggest that the ET_B receptor functions to attenuate the stress response in female, but not male rats.

8.4

SEX, DIABETES AND RENAL INJURY

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The incidence and progression of renal disease is lower in women than in men, however, in the setting of diabetes, this relationship no longer exists. While the data are inconclusive, mainly due to inadequate analyses, the current view is that the incidence and progression of diabetic renal complications in women is either equal or exceeds that in men. Our studies have suggested that diabetes is associated with reduced estradiol levels (1), which may explain why the female gender is lost as a protective factor in diabetes. We have recently shown that supplementation with 17β-estradiol is renoprotective in attenuating and reversing albuminuria and renal structural damage in the streptozotocin-induced rat model of diabetic renal disease, suggesting that restoring estradiol levels in diabetes protects from the development of the disease.
While estradiol is generally believed to be renoprotective in the non-diabetic kidney, testosterone is thought to contribute to non-diabetic renal disease. Interestingly, in the setting of diabetes, this no longer holds. Similar to diabetic women, who exhibit low circulating levels of estradiol, diabetic men exhibit decreased levels of testosterone. Our studies in an experimental model have shown that absence of testosterone contributes to more rapid progression and more severe renal damage in diabetes. Collectively, these observations suggest that sex hormones play a significant role in the pathophysiology of diabetic renal disease and that it may not be the absolute levels of hormones, but rather the relative ratio of androgens to estrogens that determines the overall contribution and effect of the hormone in the diabetic kidney. 1. Wells CC, Riazi S, Mankhey RW, Bhatti F, Ecelbarger C, Maric C. Gender Medicine 2: 237-247, 2005. 2. Mankhey RW, Bhatti F, Maric C. AJP-Renal Physiol 288: 399-400, 2005.

8.5

SEX, NO AND AGING

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With advancing age the kidney shows falls in GFR due to renal vasoconstriction and structural damage. This usually occurs slowly and does not cause severe renal impairment unless additional insults are superimposed. There is a pronounced sexual dimorphism in kidney aging with females protected. Pre-menopausal females produce more NO than men and total NO production falls with age, although there is no clinical data on sex differences. NO is a major factor in regulation of vascular tone, growth and structural integrity and becomes deficient with advancing age, as endothelial dysfunction develops. Although the substrate, L-arginine is maintained, the concentration of the circulating endogenous nitric oxide synthase (nNOS) inhibitor ADMA increases with age; this is delayed in women. There may be falls in vascular eNOS abundance, decreased membrane association and decreased stimulatory protein-protein interactions with age as well the cumulative oxidative stress of aging promoting superoxide rather than NO formation by the eNOS. Within the kidney, declines in abundance and activity of the neuronal (nNOS) correlate with development of disease in the male rat, whereas in the protected female, renal nNOS abundance is maintained. The impact of sex steroids is complex and includes NO stimulatory and direct antifibrotic actions of estrogens and possible damaging effects of androgens, although in man this is not clear cut. Taken together, it is likely that age-dependent declines in NO generation contribute to age-dependent kidney damage. REFERENCE: Baylis C. Changes in renal hemodynamics and structure in aging kidney; sexual dimorphism and the NO system Exp Geront 40: 271-278, 2005.

8.6

SEX STEROIDS, PLATELET AGGREGATION AND INFLAMMATION

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In women, risk of cardiovascular disease and thrombosis increases exponentially at menopause suggesting that estrogen may influence both processes. Infection also increases risk for venous thrombosis. Platelet activation is required for formation of thrombin, development of arterial vascular lesions, and activation of leukocytes. Hormones and infection-associated factors, i.e. lipopolysacharide (LPS), will influence the phenotype of circulating platelets through gene transcription and translation in platelet precursors, megakaryocytes. Genetic polymorphisms in receptors which bind hormones or LPS will cause variation in platelet characteristics. For example, platelets were more reactive in mice lacking estrogen receptor beta whereas platelets derived from mice lacking toll-like receptor 4 were less responsive to thrombin compared to their wild type counterparts, respectively. Therefore, a platelet procoagulant phenotype may be characteristic of an individual which could predispose that individual to risk for adverse thrombotic events under certain environmental influences, for example, with hormone therapy or infection. The concept of using platelet phenotype to define thrombotic risk for individuals is a new and is being tested in women enrolled in an ancillary study to the Kronos Early Estrogen Prevention Study (KEEPS), a study of hormone therapy to prevent progression of cardiovascular disease in early menopausal women. Reference: Miller, V.M., et al., *Estrogen therapy and thrombotic risk.* Pharmacology & Therapeutics, 2006. **111**(3): p. 792-807.

8.7

ANDROGENS STIMULATE PROXIMAL TUBULE TRANSPORT

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Disrupting the enzyme CYP4A14 in mice leads to hypertension, which is more severe in the male mice and appears to be due to androgen excess. Androgens are known to increase expression of angiotensinogen, but the effect of androgens on proximal tubule transport is unknown. PCTs from knockout (KO) and wild type (SV/129) mice were perfused *in vitro*. Volume absorption was elevated in tubules from the KO mice as compared to the wild type mice (1.11±0.06 vs 0.77±0.12 nl/min/mm, $p<0.05$). Expression of the sodium-proton antiporter (NHE3) was found to be higher in brush border membrane vesicles (BBMV) from KO mice than that in wild type mice. To determine if this effect could be reproduced in a model of androgen excess, male Sprague-Dawley rats were given dihydrotestosterone (DHT) injections IP for ten days. The PCT volume reabsorptive rate was significantly higher in treated rats than in control rats given vehicle injections (4.57 ± 0.31 vs. 3.31 ± 0.23 nl/mm • min, $p < 0.01$). Luminally perfusing with either enalaprilat or losartan decreased the PCT reabsorptive rate in DHT treated rats to a significantly greater degree than in control vehicle injected rats. The renal expression of angiotensinogen and BBMV protein abundance of NHE3 was higher in the DHT treated animals using Northern analysis. DHT treated rats had higher blood pressures and lower serum angiotensin II levels than the control rats. These results suggest that androgens may directly upregulate the proximal tubule renin-angiotensin system, increase the volume reabsorptive rate, and thereby increase extracellular volume and blood pressure and secondarily decrease serum angiotensin II levels.

10.0: SEX STEROIDS IN HYPERTENSION, DIABETES, AND PREGNANCY

10.1

ALDOSTERONE/NaCI-INDUCED HYPERTENSION: THE ROLE OF GENDER, SEX HORMONES AND CENTRAL REACTIVE OXYGEN SPECIES

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Elevated aldosterone (Aldo) contributes to hypertension and vascular and renal injury. Little is known about the role of sex differences in Aldo/salt-induced hypertension and the role of central reactive oxygen species (ROS) in this form of high blood pressure. The purpose of the present study was to test the hypothesis that male and female Sprague-Dawley rats respond differently to subcutaneous infusion of Aldo (0.75 μg/h, 28 days) combined with 1% NaCl as the sole drinking fluid and the effects in males of superoxide mimetic treatment. Blood pressure was measured by DSI telemetry. Aldo+1% NaCl-treated male rats progressively developed hypertension (101.6±2.8 to 124.6±3.6, Δ23.2±3.7 mmHg, n=6), but blood pressure in females was not different from controls (98.4±1.7 to 101.8±3.5, Δ3.4±1.4 mmHg, n=4). Gonadectomy augmented Aldo+1% NaCl-induced hypertension in females (Δ17.1±2.3 mmHg, n=3) but had no additional effect in males (Δ20.9±2.2 mmHg, n=4). Systemic infusion of 17β-estradiol (250 μg/day) totally blocked Aldo+1% NaCl-induced hypertension in intact males (Δ-1.5±2.4 mmHg, n=3). In males, central, but not peripheral infusions of tempol (200 nm/kg/min), prevented the development of hypertension (Δ6.0±1.9 mmHg n=4 vs Δ17.6±2.0 mmHg, n=3). These results indicate that estrogen may play a protective role in the development of Aldo+1% NaCl-induced hypertension and that central ROS are involved in the development of Aldo+1% NaCl-induced hypertension. (NIH HL-59676; HL-62261; HL-14388; DK-66086).

10.2

MPA BUT NOT DROSPIRENONE AGGRAVATES RENAL INJURY IN ALDOSTERONE-SALT TREATED RATS

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Background: Clinical trials on the prevention of cardiovascular disease by combined hormone replacement therapy (HRT) revealed negative or neutral results. The HERS and WHI trials employed medroxyprogesterone acetate (MPA), which binds not only to the progesterone receptor (PR) but transactivates also the androgen- (AR), the glucocorticoid- (GR) and the mineralocorticoid receptor (MR). In contrast, the recently developed progestin drospirenone (DRO) is not only devoid of partial AR and GR agonist activities but also possesses a strong anti-mineralocorticoid functionality. The aim of this study was to compare the effect of different hormone replacement regimes including 17b-estradiol (E2) plus either MPA or DRO in uni-nephrectomized rats receiving chronic aldosterone infusion plus a high salt diet for 8 weeks (AST rats). Elevated water consumption, sodium uptake and renal potassium excretion in AST rats increased further by co-treatment with MPA whereas DRO attenuated fluid and sodium turnover in AST rats. Only MPA but not DRO increased kidney mass and caused extensive inflammatory kidney injury resulting in glomerular and peritubular fibrosis. MPA but not DRO enhanced the expression of regulatory NADPH oxidase subunits including p67phox as well as eNAC alpha expression. DRO completely prevented kidney hypertrophy as well as glomerular and tubular damage. In conclusion, MPA aggravates and DRO attenuates renal injury in aldosterone salt treated rats that relates to enhanced ROS generation. We conclude that drospirenone confers nephroprotective effects under conditions of excess MR activation that are superior to MPA.

10.3

DIFFERENTIAL EXPRESSION OF NEPRILYSIN AND ANGIOTENSIN CONVERTING ENZYME 2 (ACE2) MAY CONTRIBUTE TO DECREASED ORGAN DAMAGE IN THE FEMALE HYPERTENSIVE mRen2.LEWIS RAT

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The mRen2.Lewis (mRen) strain exhibits a gender difference in blood pressure and tissue injury. At 14 weeks of age, males exhibit higher blood pressure to that of the females [200 ± 4 vs. 146 ± 7 mm Hg; p<0.01; n=5-6], as well as greater cardiac hypertrophy [4.0 ± 0.1 vs. 3.2 ± 0.1 mg/g] and increased proteinuria [156 ± 32 vs. 29 ± 3 mg protein/kg/day; p<0.01; n=5-6]. Serum C - reactive protein, a marker for inflammation was 1.3 fold higher in the male mRen compared to females [595 ± 20 vs. 468 ± 31 μg/mL; p<0.01; n=6]. The aim of the present study evaluated the enzymatic pathways in cardiac and renal tissue that contribute to the gender differences in organ damage. We utilized a sensitive method to detect the metabolism of angiotensin peptides (Ang), Ang II to Ang-(1-7) for ACE2 and Ang I to Ang-(1-7) for neprilysin. Cardiac ACE2 activity was 1.4 fold higher in male mRen than females [19.3 ± 0.9 vs. 14.3 ± 0.9 fmol/min/mg; p<0.01; n=4]. In renal cortical membranes, ACE2 activity was 1.7 fold higher [69.4 ± 2.9 vs. 40.8 ± 3.1 fmol/min/mg, p<0.01; n=4]. In contrast, neprilysin activity in the renal cortex was 3 fold higher in the female mRen [919 ± 73 vs. 290 ± 51 fmol/min/mg, p<0.01; n=4]. We conclude that the higher expression of neprilysin may confer a protective mechanism in the female kidney through: 1) the enhanced metabolism of Ang II; and 2) the increased formation of Ang-(1-7). A preferred pathway for Ang I to Ang-(1-7) in the female mRen kidney may negate the reliance on ACE2 given the reduced levels of Ang II as the ACE2 substrate. In contrast, the higher ACE2 activity in the male mRen may reflect a compensatory mechanism for the lower expression of neprilysin and the greater degree of hypertension and tissue injury. Supported by NIH grants HL56973, HLS56973, & HL51952.

10.4

TESTOSTERONE SUPPLEMENTS PROMOTE RENAL INJURY AND EXACERBATE HYPERTENSION IN AGING SHR

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Testosterone supplements are commonly prescribed to aging men, who are frequently hypertensive and have increased risk of developing hypertensive renal injury. Endogenous androgens may promote hypertension and renal disease. Spontaneously hypertensive rats (SHR) develop androgen-dependent hypertension at a young age but are relatively protected from any hypertensive renal injury until after 9 months of age. We hypothesized that testosterone supplementation of aging male SHR exacerbates hypertension and renal injury. Intact, castrated (at 8 months) and testosterone-supplemented male SHR (n=4/group) were followed from 9 to 13 months of age, when blood pressure (BP, indwelling arterial catheters) and urinary protein excretion were determined. Testosterone supplementation with Silastic® pellets led to approximately 2-fold increase of plasma testosterone concentration. At 13 months of age, BP was significantly higher in testosterone supplemented male SHR as compared with intact rats (199±2 vs 188±3 mmHg, p<0.05) whereas castration did not alter BP levels (187±6 mmHg). Testosterone supplemented SHR excreted more urinary protein than intact rats (150±8 vs 96±8 mg/day, p<0.05) and castration reduced proteinuria (34±6 mg/day). These results suggest that testosterone supplementation of aging male SHR promotes renal injury and thereby exacerbates hypertension. On the other hand, removal of endogenous androgens later in life (8 months) prevents the development of hypertensive renal injury without altering established hypertension.

10.5

SEX DIFFERENCES IN RENAL 11β-HYDROXYSTEROID DE-HYDROGENASE TYPE 2 IMMUNOREACTIVITY IN RAT KIDNEYS

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Female control rats, as compared to male control rats, exhibit increased renal abundances of aldosterone-sensitive electrolyte transporters, suggesting that constitutive mineralocorticoid activity is increased in female as compared to male rats. The purpose of this study was to test the hypothesis that decreased renal abundance of 11beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) contributes to increased constitutive mineralocorticoid activity in female rats. Vehicle or aldosterone (200 μg/day) was infused in male and female rats fed a 1% NaCl diet for 4 weeks. Four groups were studied: male control rats (n=5), male rats infused with aldosterone (n=6), female control rats (n=6), and female rats infused with aldosterone (n=6).. There were significant effects of sex (p<0.001) and treatment (p<0.001) on renal 11β-HSD2 abundance as determined by Western blot. 11β-HSD2 abundance was 1.00±0.02 absorbance units (AU) in male control rats and was significantly (p<0.001) less in female control rats (0.63±0.04 AU). Aldosterone infusion did not significantly change 11β-HSD2 abundance in male rats, but in female rats, aldosterone infusion significantly reduced 11β-HSD2 abundance to 0.39±0.05 AU. The results of this study demonstrate that renal 11β-HSD2 abundance is decreased in female as compared to male rats. We propose that reduced 11β-HSD2 abundance contributes to increased constitutive activation of mineralocorticoid receptors by endogenous glucocorticoids in female as compared to male rats.

10.6

TESTOSTERONE MEDIATES HYPERTENSION AND RENAL INJURY IN DAHL RATS DESPITE HIGH SODIUM DIET-MEDIATED DECREASE IN TESTOSTERONE LEVELS

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Recent epidemiological studies suggest that low levels of plasma testosterone (PT) are associated with cardiovascular diseases in men. However, a cause-effect relationship between the two parameters has not been conclusively established. High sodium (HS) diet in Dahl salt sensitive rats (DS) causes hypertension and renal damage. To test the hypothesis that HS diet reduces PT in DS males and yet castration protects against hypertension and renal damage, DS males (5/group) were challenged with HS diet for 3 weeks, starting at 4, 6, 9 and 15 weeks of age. Age matched animals on low sodium (LS) diet were used as control. At the end of the experiment PT was measured by RIA. On LS diet, PT increased at 11 weeks and remained constant until 15 weeks of age. On HS diet, PT did not rise at 11 weeks and remained significantly lower compared to high sodium group up to 22 weeks of age. Other group of intact and castrated DS male rats (11/group) maintained on LS diet were challenged with a HS diet for 4 weeks. Mean arterial pressure was measured by radiotelemetry. Renal injury was determined by urinary albumin excretion by ELISA and glomerular sclerosis by histology. Castration significantly attenuated HS diet induced hypertension and renal injury. Our study suggests that although HS diet decreases PT in males DS, androgens still play a major role in the pathogenesis of hypertension and renal injury associated with HS diet.

10.7

POPULATION EXTREMES-BASED APPROACH DEFINES GENDER DIFFERENCES IN ADRENERGIC AND RENAL GENES CONTRIBUTING TO BLOOD PRESSURE

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Recent studies indicate that gender impacts genetic expression of complex traits & diseases. To investigate the differential contribution of genetic variants to BP in men vs. women we exploited the power of sampling subjects from the top and bottom 5th percentiles of BP from a community-based sample of >53,000 people in a health maintenance program. With a sample of 611 men and 656 women White-Americans, we had >90% power to detect genes contributing as little as 3% to trait (BP) variation. We assayed for >60,000 genotypes in the subjects including 48 SNPs at 33 autosomal and 2 X-linked genes in adrenergic and renal pathways that regulate BP and observed different effects on BP in males and females: In females, polymorphisms at β1-adrenergic receptor (AR) and α2A-AR contributed to BP, while in males polymorphisms at β2-AR and angiotensinogen (AGT) were associated. Combination of SNPs within a single gene (haplotypes) also influenced BP differentially in males and females: An α2A-AR haplotype influenced BP in females, while two AGT haplotypes were associated with increased BP in males. The results thus reveal gender-specific effects of SNPs and haplotypes that determine BP in Caucasian-Americans and demonstrate the power of an approach based on population extremes for identifying genetic contributors to physiological (e.g.cardiovascular) traits, even ones that can be influenced by multiple genes with small contributions to variance. Moreover, the findings imply that gender should be taken into account in the development of genotype-based diagnostic and therapeutic treatment for hypertension.

10.8

EFFECT OF AGE AND ESTROGEN LOSS ON ESTROGEN RECEPTOR ALPHA AND BETA IN KIDNEY OF DAHL SALT SENSITIVE RATS

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We have shown that renal estrogen receptors alpha and beta (ERa and ERb) from female Dahl salt sensitive (DSS) rats are affected by either age or ovariectomy (OVX). At middle age, there is an increase in ERb compared to young rats, while old age was associated with an increase in both ERa and ERb . OVX in young DSS rats was associated with a decrease in ERa and an increase in ERb. Estrogen replacement in OVX rats reversed the over expression of ERb, but had no effect on ERa. In this study we determined the combined effect of aging and estrogen loss on renal ERa and ERb. We compared young (4 months), middle age (12-13 months) and old (15-18 months) DSS rats that were OVX, and OVX with estrogen replacement (OVX+E), which were initiated at 2 months of age. Western blot analysis was used to determine ERa and ERb levels reported as optical density. In OVX rats, renal ERa at middle age (0.20±0.01) and old (0.22±0.03) were significantly greater ($p < 0.01$) than young (0.05±0.01), while ERb was similar in young (0.29±0.01), middle age (0.26±0.02) and old (0.24±0.02). In OVX+E, renal ERa at middle age (0.19±0.04) was significantly greater than young (0.04±0.01) and old (0.07±0.01) rats, while ERb was similar in young (0.13±0.02), middle age (0.14±0.09) and old (0.10±0.01). These results indicate that renal ERa levels increased with age in OVX and OVX+E. In contrast, renal ERb was not altered by aging, in OVX and OVX+E. We conclude that renal ERa levels are affected by aging, while renal ERb are affected by circulating estrogen.

10.9

SEXUAL DIMORPHIC REGULATION OF AQP2 IN DOCA-SALT HYPERTENSION

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Hypertension is more prevalent and more severe in men than pre-menopausal women. We used the DOCA-salt hypertensive rat model to examine if a sexual dimorphic relationship is seen in the development of hypertension in this model. Further, we determined if an altered role of aquaporin 2 (AQP2) regulation occurs in this sex-associated difference in the regulation of blood pressure in this hypertensive model. Radio-telemetry units were implanted for measurement of mean arterial blood pressure in conscious, unrestrained DOCA-salt hypertensive male and female rats. Chronic measurement of blood pressure in conscious DOCA-salt rats demonstrated that intact male rats had higher blood pressures compared to intact females (intact male=164±3; intact female=136±4, $p<0.05$) thereby replicating the differential between men and women. Twelve days following induction of hypertension, AQP2 expression was determined by semi quantitative immunoblotting of kidney homogenates from cortex. In cortical homogenates, a down regulation of AQP2 was seen in DOCA-salt intact female compared to intact male rats (intact male = 100±6; intact female = 53±6, % of control, $p<0.05$). This down regulation of AQP2 expression may in part be involved with the diminished severity of hypertension in female DOCA-salt rats compared to their male counterparts.

10.10

ROLE OF HYDROGEN PEROXIDE IN MEDIATING HYPERTENSION AND PROTEINURIA IN FEMALE SHR

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Reactive oxygen species (ROS) such as superoxide anion (O2-) and hydrogen peroxide (H2O2) are implicated in the development of hypertension. Males exhibit greater oxidative stress (OS) and blood pressure (BP) than females. O2- is important in the maintenance of hypertension in male SHR, since the superoxide dismutase mimetic tempol and the NAPDH oxidase inhibitor apocynin reduces the BP in male but not female SHR. In light of these observations, we hypothesized that H2O2, rather than O2-, is responsible for mediating the hypertension in female SHR and that treatment with the glutathione peroxidase mimetic ebselen will reduce both BP and proteinuria. Methods: Female SHR (245-300 g) were assigned to receive either vehicle (5% Carboxymethylcellulose) or ebselen (7.5mg/kg) twice a day by gavage for ten days. BP was recorded by telemetry. Proteinuria was assessed prior to administration of the drug and at the end of the experimental protocol. Results: Ebselen has no effect on BP (last 24 hs MAP [mmHg]: 132+1 vs. 127+1 control) or protein excretion (2.8+0 vs. 3.8+1 mg/24Hs, vs. control). These data suggest that H2O2 is not important in the hypertension of female SHR. Taken together with our previous observations, it is likely that OS mediates hypertension in male but not female SHR.

10.11

EARLY DIABETIC KIDNEY DAMAGE IN THE MOUSE VCD MODEL OF MENOPAUSE.

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Perimenopause, the 5-10 years preceding menopause in women, is increasingly recognized as a critical period in the development and treatment of many diseases. The extent to which ovarian hormones impact the development of diabetic nephropathy is not well studied. We hypothesized that changes in ovarian hormones across the menopausal transition promote the development of diabetic kidney damage. We used the 4-vinylcyclohexene diepoxide (VCD) model of menopause, which mimics the perimenopause period (PE) and postmenopausal (PO) ovarian androgen production, in combination with the streptozotocin (STZ) model of diabetes. B6C3F1 female mice were injected with STZ during PE or 2 weeks PO; 6 weeks later kidneys were processed for microarray and real-time PCR or immunohistochemistry. Blood glucose was elevated in PO diabetic mice compared to PE and cycling diabetic mice (336 ± 31 vs 238 ± 32 and 218 ± 37 mg/dL). Proliferating cell nuclear antigen protein expression, a marker of early kidney damage, was greater in PO diabetic than in cycling diabetic mice ($P<0.05$). Using microarray, we identified 66 genes that are differentially expressed in diabetic kidneys dependant on hormonal status. Midkine (Mdk) was identified by the microarray as increased 1.68 fold in PO diabetic kidneys compared cycling diabetic kidneys ($P<0.05$). Mdk is regulated by estrogen, and Mdk knockout mice develop less severe diabetic nephropathy. These data suggest changes in ovarian hormone production across the menopausal transition promote the development of diabetic kidney disease. Funding: NIH AG-021948 to PBH.

10.12

SEX DIFFERENCES IN THE RESPONSE TO VASOACTIVE SUBSTANCES IN EARLY UNCONTROLLED DIABETES

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Diabetes is associated with development of vascular disease, and we hypothesize that there are early changes in vascular reactivity in the diabetic animal that are sex-related. Adult male and female S-D rats were divided into sham, diabetic (STZ), or STZ+GH to mimic the human diabetic milieu. After eight weeks, mesenteric arteriolar vascular reactivity to PE and ACh was performed on a wire myograph. STZ caused a profound decrease in the vasodilatory response to ACh in both male and female vessels, independent of GH. While there was no change in the constrictor response to PE in vessels from male diabetic rats, PE response increased 103% ($P<0.05$ vs sham) in vessels from female STZ rats, which was prevented in STZ+GH rats (ns from sham). In the presence of L-NAME (to block NO), female sham had a larger change in PE reactivity than STZ (7- vs 5-fold), indicating a reduction of NO in the STZ rat. This contrasted with the male, with STZ producing more NO than sham. In both sexes, STZ+GH increased NO. The effects of GH on vascular reactivity affirm its importance in the rat model of human diabetes. Together, these findings support the hypothesis of early vascular changes in diabetes, which may include a loss of endothelial function in female vasculature before major changes are observed in the male, suggesting females may be more susceptible to early vascular disease development. *(Supported by NIH R01 DK064916 and National Kidney Foundation of the National Capital Area).*

10.13

SEX DIFFERENCES IN DIABETIC RENAL REMODELING: EFFECTS OF GROWTH HORMONE

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While GH levels are elevated in human diabetes, pulsatile GH release is abolished in the streptozotocin (STZ) diabetic rat. We hypothesize that replacement GH will result in a more human-like disease process including early renal remodeling, which will be exacerbated in the male kidneys. Male and female S-D rats were divided into three groups; Sham, STZ (55 mg/kg ip), and STZ+GH (2.5µg GH, 2X daily) and sacrificed after 8 weeks. The Glomerular Sclerotic Index (GSI) was increased in female STZ kidneys (0.79±0.06 vs 0.20±0.03 in Sham, $P<0.05$), without additional effects of GH (0.87±0.07); kidneys from male STZ rats, however, had an increased GSI (0.90±.02 vs 0.26±0.05, $P<0.05$), and there was a greater effect in STZ+GH (1.08±0.11, $P<0.05$ vs STZ). Males also exhibited a greater GH response in the Tubular Interstitial Fibrotic Index (TIFI): STZ increased the TIFI in both male and female rats from Sham [F (1.21±0.06 vs 0.44±0.07); M (1.37±0.03 vs 0.54±0.02), $P<0.01$] and while GH significantly increased the female TIFI (1.67±.05, $P<0.05$ vs STZ) the male response was significantly higher than the female (1.99±.09, $P<0.05$ vs F STZ+GH). STZ increased albuminuria, [F (0.42±0.08 vs 11.3±2.71 mg/dL); M (10.38±0.82 vs 1.96±0.07 mg/dL) $P<0.01$)], but again, while GH had no additional effects in females (8.62±1.78 mg/dL), in males there was a marked increase in the presence of GH (16.15±1.67, $P<0.05$ vs STZ). This data supports our hypothesis that GH is important in diabetic renal disease, and has a preferential effect on male kidneys to exacerbate renal remodeling, that is not observed in females. Funded by R01DK064916.

10.14

ROLE OF ESTROGENS IN POSTMENOPAUSAL OBESITY AND HYPERTENSION

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Protection against cardiovascular and renal disease in women is lost when they reach menopause. The incidence of obesity also increases in this low estrogen environment, which can raise blood pressure (BP) by activating the renin angiotensin system (RAS) or via leptin induced increases in sympathetic nervous system (SNS) activity. We hypothesize that estrogen deficiency after menopause leads to obesity related metabolic changes that may activate vasopressor systems, contributing to obesity induced postmenopausal hypertension and renal disease. We used 8 month old intact female and ovariectomized (ovx) rats, with or without estrogen replacement. Ovx rats exhibit higher BP than aged matched intact and estrogen repleted female (126.2±3 vs 110.6±2 and 102.6±3 mmHg respectively). However renal function and hemodynamics indexes remained unchanged. Body weight (BW) gain with age was 2 fold higher in ovx compared to intact females and it was accompanied by increases in metabolic indexes, leptin (70%) and blood glucose (35%). We also found that RAS, determined as plasma renin activity, and SNS, determined as renal norepinephrine, were also increased after ovx by 16% and 39% respectively. All these hormonal and metabolic changes were reverted by estrogen administration. In summary, ovx in old female rat increased BW, leptin and elevated BP together with the activation of RAS and renal SNS. These effects were completely abolished with estrogen replacement. These results suggest that estrogen deficiency in aged female rats may trigger the development of obesity and postmenopausal hypertension in the absence of renal disease. This work was supported by NIH AG029250-01 award.

10.15

FEMALE GENDER PROTECTS OBESE RATS FROM NEPHROPATHY OF THE METABOLIC SYNDROME

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Renal vasculopathy and interstitial fibrosis are more prevalent in men, while premenopausal women seem protected. We hypothesized that female sex (either from gender-specific or estrogen-specific effects) protects kidneys of rats with the metabolic syndrome. These experiments were conducted according to APS guiding principles for the care and use of animals. We fed ad-lib obese male (OM) and female (OF) ZSF_1 hybrid rats two separate diets: 27 % protein (diet A: OMA, n = 10 and OFA, n = 13) or 10 % protein (diet B: OMB, n = 3 and OFB, n = 14) for 36 weeks: Hyperglycemia (mM; M±SE) was present in all: OMA, 19±4; OFA, 10±2; OMB, 32±1; and OFB, 19±1. Body weight (BW, gm) in OMA, 659±23; was higher than OFA, 580±16 ($p<0.01$); highest in OMB, 847±28 ($p<0.01$); while OFB was 575±10. Kidney

weight (gm/100 gm BW) was highest in OMA: 0.51±0.02 ($p<0.01$); and equal in all others: 0.31±0.01; 0.42±0.03, and 0.35±0.01. Interstitial fibrosis (fibrosis index: 1-4) was worse in OMA, 3.8±0.03 than OFA 1.6±0.5 ($p<0.01$), OMB, 1.9±0.10, and OFB, 1.1±0.2. Kidney TGFbeta1 (pg/mg prot.) was highest in OMA 710±65 ($p<0.01$) than OFA, 295±60; OMB, 370±40; and OFB, 270±50. Serum creatinine (uM) was highest in OMA: 100±16, and equal in all others: 46±1; 50±3; and 42±1. Renal fibrosis and failure was more severe in OMA than in OFA eating the higher protein diet. In contrast, kidneys in OMB and OFB were relatively unaffected when eating the lower protein diet. Hyperglycemia did not influence the renal outcome. We conclude that: Female gender offers protection from renal injury and fibrosis in obese rats on high protein diets. The diet composition was a critical determinant for this type of nephropathy, while hyperglycemia by itself was less significant.

10.16

GENDER-DEPENDENT METABOLIC AND RENAL EFFECTS OF 2-HYDROXYESTRADIOL IN OBESE DIABETIC ZSF_1 RATS.

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Previously we have demonstrated that 2-hydroxyestradiol (2HE), an estradiol metabolite with some estrogenic activity, provides cardiovascular and renal protection in young, male, obese ZSF_1 rats. However, these effects were associated with significantly reduced food consumption. Therefore, the objective of this study was to examine the metabolic and renal effects of long-term treatment (32 weeks) with 2HE (10 µg/kg/h) and pair-feeding (vs. 2HE) in obese diabetic male and ovariectomized (OVX) female ZSF_1 rats. 2HE improved the oral glucose tolerance test and reduced HbA1, leptin and cholesterol levels and exhibited significant estrogenic effects in male rats. Ovariectomy did not affect glucose homeostasis and, in the face of increased food consumption and body weight, decreased plasma cholesterol and triglycerides levels, proteinuria and renal injury. In OVX rats, 2HE markedly increased triglycerides and cholesterol levels, augmented proteinuria and renal hypertrophy, and increased glomerulosclerosis. This study suggests limited value of estradiol metabolites with estrogenic activity in metabolic syndrome associated renal disease. Further investigation of non-estrogenic metabolites of estradiol (i.e., 2-methoxyestradiol) in diabetic kidney is warranted.

10.17

DYSREGULATED ESTRADIOL METABOLISM IN PREECLAMPSIA

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There is a line of evidence suggesting that the cardiovascular protective effects of estradiol (E2) are mediated by its non-estrogenic metabolite 2-methoxyestradiol (2ME). 2ME is a product of E2 2-hydroxylation and subsequent O-methylation by catechol-O-methyltransferase (COMT). Placental and umbilical cord E2 levels are similar in preeclamptic (PP) and normal pregnancies (NP). However, induction of E2 metabolism reduces the risk of pregnancy-induced hypertension and eclampsia, whereas low COMT activity is associated with gestational hypertension and reduced fetal growth. No data are available regarding the presence of E2 metabolites in humans. Therefore, in the present study, by using a highly sensitive and selective LC-MS/MS method, we measured plasma concentrations of 2ME and 2-methoxyestrone (2ME1) in healthy men and women, and in women with NP and PP. 2ME was detected in 9 of 36 healthy young men (361±73pg/ml). In non-pregnant premenopausal women no 2ME1 and 589±65 pg/ml of 2ME were detected. 2ME1 levels tended to increase and 2ME levels tended to decrease in PP group, and a significantly higher 2ME2/2ME1 ratio was determined in NP compared to PP group (4.4±1.08 vs.1.32±0.30; $p<0.03$). In summary, we report the presence of 2ME in a significant number (25%) of healthy men. Moreover, the present data suggest altered E2 metabolism and E2 metabolite disposition in preeclampsia.

10.18

SLEEP DEPRIVATION AND NOCTURNAL URINE OUTPUT-GENDER DIFFERENCE IN THE EFFECT

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Aim: To investigate the impact of sleep on the nocturnal urine production, salt and water regulating hormones and hemodynamics. **Material:** 20 healthy volunteers (10 males), underwent two 24-hour circadian in-patient studies under standardized conditions regarding diet and fluid intake. Blood samples were drawn every three hours and urine was collected in 3-hour intervals. Blood pressure and heart rate were non-invasively monitored. The participants were randomized to sleep deprivation during one of the two studies. Atrial natriuretic peptide, angiotensin II, aldosterone, and renin were measured in blood. Excretions and clearances were calculated for electrolytes and osmoles. **Results:** During sleep deprivation both genders produced markedly larger amounts of urine, an effect that was more pronounced for males (males 1.05 ± 0.10 ml/h/kg vs. 1.82 ± 0.22 ml/h/kg, females 0.98 ± 0.09 ml/h/kg vs. 1.41 ± 0.11 ml/h/kg, $p<0.001$). An increased urinary excretion of sodium (baseline: 0.06 ± 0.01 mmol/kg/h, sleep deprivation: 0.12 ± 0.01 mmol/kg/h), potassium and osmoles was seen. The night-time dip in blood pressure was less evident during sleep deprivation (baseline: 76.5 ± 12.4 mmHg, sleep deprivation: 83.2 ± 11.0 mmHg, $p<0.001$) but no effect on heart rate was seen. The compromised fall in mean arterial blood pressure correlated significantly to increase in night time urine volume. Sleep deprivation induced a significant fall in night time plasma renin ($p<0.05$), angiotensin II ($p<0.001$) and aldosterone ($p<0.05$) in both genders. **Conclusion:** Sleep deprivation leads to natriuresis, kaliuresis and osmotic diuresis. The increase in urine output was more evident in males. Altered hemodynamics seems to account for these observations.

10.19

GENDER BIAS TOWARD A FUNCTIONAL SUBCLASS OF MYELINATED VISCERAL AFFERENT

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Compelling evidence exists concerning gender differences across the spectrum of cardiovascular function even extending to the vasoprotective effects of hormone replacement therapy. Estrogen as well as estrogen effected autocrine and paracrine mechanisms (e.g. vasoactive endothelial factors, prostaglandins) can impact arterial blood pressure. Most studies have been conducted from a systemic view point. To date, very little is known concerning any potential for gender differences associated with afferent pathways that contribute to neurocirculatory control, despite the compelling evidence that men and women regulate BP differently and have markedly different experiences and sensation thresholds related to cardiac pain. Our lab has recently established analytical and chemical methods for reliable classification of isolated visceral neurons as either one of two functionally distinct classes of myelinated (A-type and Ah-type) or as unmyelinated (C-type) afferents (Li & Schild, 2007). Here we present data from six separate patch recording sessions using enzymatically dispersed nodose neurons from six day old gender identified neonatal rat pups. The female group (4 pups) and the male group (2 pups) yielded current clamped action potential recordings from 54 and 27 randomly selected cells, respectively. Classification methods revealed the following distributions for female pups: A = 10 (19%); Ah = 11 (20%); C = 33 (61%) and for male pups: A = 8 (30%); Ah = 2 (7%); C = 17 (63 %).These data demonstrate a greater prevalence for Ah-type myelinated afferents in female as compared with age-matched male rat pups. We also show that these Ah-type myelinated afferents express a TTX-resistant Na+ current that can be markedly up-regulated by prostaglandin E2 via a cAMP-dependent pathway.

10.20

ESTROGEN ALTERS MYOSIN HEAVY CHAIN ISOFORM EXPRESSION OF RAT VAGINAL SMOOTH MUSCLE.

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Although it has been established that estrogen depletion causes general atrophy of vaginal tissue, altered innervation, and reduced blood flow to this organ, little is known of the influence of estrogen on vaginal smooth muscle (VSM). The carboxyl terminal isoforms (SM1and SM2) of myosin heavy chain (MHC) have been shown to be estrogen dependent in the uterus, bladder and vasculature. The objective of this study was to determine the affect of estrogen status on MHC isoform expression and contractility of VSM. The vagina was harvested from sham operated (S), 3-week ovariectomized (O) and 1-week estrogen-replaced (E) Sprague-Dawley rats. RNA was reverse transcribed and semi-quantitative RT-PCR was performed using primer pairs to amplify SMA/SMB and SM1/SM2 isoforms. MHC and beta-actin protein was detected by Western blotting and SM1/SM2 protein was stained by Coomassie blue. Muscle strip studies were performed to measure maximal velocity of shortening (v_{max}) and muscle stress in response to 110 mM KCl. Densitometric analysis of RT-PCR and Coomassie results indicated that ovariectomy increased the % SM2 expression of the vagina, an effect reversed in E rats. No differences were detected in SMA/SMB or MHC expression. There was a decreased v_{max} and increased muscle stress of vaginal strips from O rats compared to S rats. The results of these studies indicate that estrogen alters molecular and functional characteristics of VSM. Further studies are required to determine whether these changes in smooth muscle contribute to vaginal dysfunction experienced by post-menopausal women. Funding sources: T32-DK007708; P50-DK-052620.

10.21

SEX HORMONES CONTRIBUTE TO GENDER DIFFERENCES IN PROGRAMMED HYPERTENSION INDUCED BY PLACENTAL INSUFFICIENCY IN THE RAT.

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Gender differences in programmed hypertension are well established in animal models and human epidemiological studies; however, the mechanism(s) involved in mediating sex differences are unclear. Our laboratory uses a rat model of placental insufficiency that results in intrauterine growth restricted offspring (IUGR) that develop hypertension at a pre-pubertal age in both sexes. However, after puberty only male IUGR remain hypertensive whereas female IUGR become normotensive. Thus, the purpose of this study was to determine whether sex hormones contribute to gender differences in this model of IUGR. Castration (CTX) or ovariectomy (OVX) was performed at 10 weeks of age in male or female, respectively; mean arterial pressure (MAP) was measured by radiotelemetry from 12 to 16 weeks; testosterone (T) or estradiol (E2) replacement therapy were administered from 14 to 16 weeks in CTX male or OVX female. Gonadectomy abolished hypertension in male IUGR (145±4 vs.104±2 mmHg; $P<0.05$, intact vs. CTX, respectively) and induced hypertension in female IUGR (122±2 vs.140±2mmHg; $P<0.05$, intact vs. OVX, respectively). Hormone replacement reinstated hypertension in male CTX-IUGR (143±3 mmHg; $P<0.05$ vs. untreated counterpart) and abolished hypertension in female OVX-IUGR (111±3mmHg $P<0.05$ vs. untreated counterpart). Therefore, these results suggest that sex hormones contribute to gender differences in programmed hypertension.

10.22

SEX DIFFERENCES IN RENAL FUNCTION OF BETAMETHASONE-TREATED SHEEP: A MODEL OF FETAL PROGRAMMING

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The prenatal exposure of the ovine fetus to clinical doses of glucocorticoids during the time of peak nephrogenesis results in a marked reduction in nephron number in adulthood, as well as a sustained 10-15 mmHg increase in blood pressure. In the present study, we examined the gender difference in renal function to betamethasone at day 80 of gestation in 16 ewes and 15 rams at 1.5 years of age. Following recovery from the surgical placement of vascular and bladder catheters, glomerular filtration rate (GFR) - estimated as clearance of inulin and renal plasma flow (RPF) as determined by clearance of p-aminohppuric acid (PAH) were assayed by an initial loading dose followed with constant intravenous (i.v.) infusion of 0.9% sterile saline containing inulin and PAH. An acute sodium load was administrated by a continuous infusion of hypertonic NaCl (0.0375 mEq/Kg/min at 0.55 ml/min for 60 minutes) within the period of PAH/inulin infusion. In the male betamethasone sheep, inulin clearance significantly decreased (154 ± 18 ml/min) as compared with male controls (213 ± 18 ml/min, $p<0.05$). The PAH clearance was also significantly lower in the male prenatal betamethasone exposed group (883 ± 65 ml/min)

than controls (1079 ± 30 ml/min, p<0.05). In contrast, there were no apparent differences of inulin/PAH clearances between the female control and treated groups. These data suggest that prenatal exposure to glucocorticoids alters renal function in adult male sheep by potentially decreasing GFR and RPF, however, the females are protected from this steroid-induced effect. NIH grants HD-47584, HL-68728 & HL-56973.

10.23

REDUCED UTERINE PERFUSION PRESSURE INCREASES SOLUBLE Flt-1 EXPRESSION IN PREGNANT RATS

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In preeclampsia the balance between pro- and anti-angiogenic factors is thought to be altered to favor an anti-angiogenic state that is evidenced by a marked increase in the soluble VEGF receptor fms-like tyrosine kinase-1 (sFlt-1). Recent evidence suggests that placental hypoxia and possibly poor placental perfusion may initiate this imbalance of angiogenic factors. We hypothesized that the hypertension produced by reduced uterine perfusion pressure (RUPP) in the pregnant rat is associated with increases in plasma and amniotic fluid sFlt-1 concentration and increased expression of sFlt-1 in the placenta of the pregnant rat. AP was increased (130±2.8 v. 100±2.4 mm Hg; P<0.01) and fetal weight (1.9±0.05 v. 2.3±0.05 g; P<0.01) was decreased in the RUPP compared to the normal pregnant (NP) controls. Plasma sFlt-1 concentration (660±270 v. 82±26 pg/ml; P<0.05) was increased 8 fold while amniotic sFlt-1 concentration was increased was increased 10% (5800 ± 160 v. 5200 ± 130 pg/ml; P<0.03) in the RUPP compared to NP dams. Immunoreactive placental sFlt-1, expressed as the ratio of sFlt-1:β-actin, was increased 4 fold (1.1±0.1 v. 0.3±0.1; P<0.01) in the RUPP dams versus the normal pregnant (NP) controls. The present findings support our hypothesis that decreased placental perfusion increases the expression of sFlt-1 and may alter the balance of angiogenic factors in the maternal circulation. These data also indicate that the RUPP model of pregnancy induced hypertension may provide an invaluable model for mechanistic studies into the role of sFlt-1 in the pathogenesis preeclampsia.

10.24

ELEVATED AGONISTIC AUTOANTIBODIES TO THE ANGIOTENSIN TYPE 1 (AT1-AA) RECEPTOR IN RESPONSE TO PLACENTAL ISCHEMIA AND TNF ALPHA IN PREGNANT RATS.

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Circulating factors such as autoantibodies to the angiotensin II type I receptor (AT1-AA) and inflammatory cytokines including TNF alpha may serve as important links between with placental ischemia, maternal endothelial cell dysfunction, and the development of hypertension in women with preeclampsia. Recent studies have demonstrated the presence of AT1-AA in preeclamptic women, factors regulating production of the AT1-AA remain unclear. We report that the increase in mean arterial pressure in response to reductions in uterine perfusion pressure (RUPP) in pregnant rats (137±1mmHg, RUPP vs 101±1mmHg, normal pregnant, NP) is associated with increased circulating levels of TNF alpha (48±13pg/ml RUPP vs 8±1pg/ml NP) and the AT1-AA (RUPP 15.3±1.6 vs NP 0.6±0.3 units). These findings indicate that placental ischemia and inflammatory cytokines may be important stimuli for the production of AT1-AA in preeclampsia. Moreover, TNF alpha induced hypertension (97 ± 2 to 112 ± 2 mm Hg) in pregnant rats is associated with increased production of the AT1-AA (9.2±2.3, TNF rats vs 1.0±0.8 units, NP rats). To determine the importance of AT1 receptor activation in mediating hypertension in RUPP and TNF treated rats, we administered an AT1 receptor antagonist to RUPP, TNF treated and normal pregnant rats. Blood pressure response was attenuated in RUPP rats (Δ 32 mmHg vs Δ 20mmHg, NP) and TNF treated (Δ 10mmHg vs Δ 5mmHg NP). Collectively, these data indicate activation of the AT1 receptor, possibly via AT1-AA, appears to play an important role in the hypertension produced by placental ischemia and TNF in pregnant rats.

10.25

ALTERED CEREBRAL VASCULAR FUNCTION IN RESPONSE TO REDUCTIONS IN UTERINE PERFUSION IN PREGNANT RATS

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Women with preeclampsia, or hypertension with proteinuria during pregnancy, are at increased risk for ischemic stroke and the development of cerebral edema. The underlying mechanisms leading to this remain unclear; however, some evidence suggests that autoregulation of cerebral blood flow may be impaired. In order to test whether autoregulation is altered, we used pregnant rats with reduced uterine perfusion pressure (RUPP) as a model of preeclampsia and normal pregnant rats as controls. Mean arterial pressure was 139±6 mmHg in RUPP rats compared with 107±6 in controls (p<0.001). Middle cerebral arteries (MCA) were isolated, cannulated, and pressurized to 75 mmHg at 37ºC. Basal inner diameter from control and RUPP rats were 178±8 μm and 160±12 μm, respectively (p=0.25). In order to test MCA autoregulatory function, luminal pressure was increased incrementally from 25 to 150 mmHg under active (with Ca^{++}) and passive (0 Ca^{++}) conditions. Tone developed from 4±5% at 25 mmHg to a maximum of 13±3% at 75 mmHg in MCA from control rats. In RUPP rats, tone was maximal at 25 mmHg (21±3%) and did not significantly change across the entire range of pressures (17±5% at 150 mmHg). Therefore while RUPP rats have significant cerebral vascular tone; myogenic vasoconstriction in the MCA appears impaired. These data suggest that altered autoregulation may be a contributing mechanism to the cerebral vascular pathophysiology of preeclampsia.

10.26

VASOMOTOR SYMPATHETIC NEURAL CONTROL IS ENHANCED IN EARLY PREGNANT WOMEN

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Pregnancy-induced hypertension and pre-eclampsia have been proposed to be associated with a hyperadrenergic state. However, the state of sympathetic neural regulation of blood pressure in normal pregnancy, especially during early pregnancy, is unclear. We completed a pilot study in a young healthy Caucasian woman during the very early stage (between 4–5 weeks) and the late stage (~35 weeks) of her pregnancy, and 7 weeks after delivery. Muscle sympathetic nerve activity (MSNA) and hemodynamics were measured in the supine (rotated ~15° into the left lateral) position. We found that during early pregnancy, her supine MSNA was extremely high (43 bursts/min), similar to those of congestive heart failure patients or individuals after chronic severe hypobaric hypoxia exposure. Supine MSNA decreased by ~28%, while blood pressure increased slightly during late pregnancy, associated with plasma volume expansion and increased cardiac output. Seven weeks after delivery, supine MSNA returned to normal (5 bursts/min). Compared with postpartum, her supine MSNA was approximately 9 fold higher during early pregnancy. Consistent with this observation, marked sympathetic activation was also found in additional two healthy young women during the early stages (5 and 7 weeks) of their pregnancies (32 and 42 bursts/min). Interestingly, despite such a dramatic increase in MSNA, both blood pressure and peripheral vascular resistance decreased during early pregnancy in these three women. Some vasodilator factor(s) associated with early pregnancy must have initiated or countered the marked increase in MSNA in these subjects. Further studies are needed to verify these findings and to identify vasodilator biomarker(s) associated with early pregnancy in healthy humans.

10.27

ABILITY TO BUFFER CHANGES IN PH DURING ISCHEMIA – ARE THERE SEX DIFFERENCES IN THE NEWBORN HEART?

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Clinical studies in children have demonstrated that female sex is a risk factor for mortality following cardiac surgery. Sex differences in the development of lactic acidosis and the ability to buffer changes in pH may determine susceptibility to ischemic injury and affect post-ischemic ventricular function. The purpose of this study was to investigate sex differences in H^+ accumulation during ischemia in the newborn heart, and to determine sex differences in the source and ability to buffer H^+ (buffering capacity). Anaesthetized newborn (3-5 day old) female (n=13) and male (n=7) Yorkshire piglets were intubated, and mechanically ventilated to ensure normal blood gas and pH status. Following left ventricular (LV) *in vivo* biopsies, the heart was excised (onset of ischemia), placed in normothermic Kreb's physiologic solution and a biopsy was taken at 60 minutes of ischemia. All tissues were analyzed for adenosine triphosphate (ATP), creatine phosphate (CP), anaerobic end-products lactate (μmoles/g dry weight) and hydrogen ion (H^+) (x10^{-8} mol/L) and histidine concentration (μmoles/g dry weight). Both sexes demonstrated a similar net decrease in ATP levels by 60 minutes of ischemia. Compared to males however, newborn females accumulated a significant 13% more lactate (females: 221.8±18.5, vs. males: 196.5±19.7, p=0.016) and a significant 47% greater H^+ (females: 68.2±22.4, vs. males: 46.8±8.9, p=0.028). Females also demonstrated 22% lower baseline CP reserves indicating both lower energy levels and a lower buffering capacity. No significant differences in ventricular histidine levels were identified. Thus compared to males, newborn females develop greater lactic acidosis during ischemia that may be due to greater anaerobic glycolysis, ATP depletion, and lower buffering capacity as demonstrated by lower CP levels. These results suggest that the newborn female myocardium is at greater risk of ischemic injury and offers a potential explanation for worse outcome in female children after cardiac surgery.
This work was supported by the Heart and Stroke Foundation of Ontario (T-4926).

10.28

ORTHOTOPIC LIVER TRANSPLANTATION IN NEWBORNS – LOWER SUCCESS RATES FROM FEMALE DONORS AND WHY ISCHEMIC METABOLISM MAY PLAY A ROLE

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Introduction: Outcome following pediatric orthotopic liver transplantation has been reported to be worse in children receiving organs from female donors. Development of tissue lactate acidosis during prolonged periods of liver ischemia prior to transplantation may result in greater ischemic injury and impair graft and patient survival. The purpose of this study was thus to investigate whether sex differences in anaerobic end-product accumulation exist between newborn male and female livers during no-flow ischemia. Methods: 3 day male (n=4) and female (n=6) piglets were anesthetized, intubated and mechanically ventilated to maintain normal blood gas and pH status. *In vivo* liver biopsies were taken from the same lobe in all animals, after which a large section of the liver was excised and placed in a solution of Kreb's Henseleit at 37ºC and ischemic biopsies were taken at 15, 30, and 45 minutes. All biopsies were analyzed for anaerobic end-products lactate (μmoles/g dry weight) and hydrogen ion (H^+) (x 10^{-8} mol/L) content. Results: No sex differences in baseline lactate and H^+ levels were noted. At 15 minutes of ischemia, livers from newborn females accumulated a significant 15% higher lactate compared to those of males (23.6±4.5 vs. 27.6±2.6, p=0.01), and this persisted throughout the remaining ischemic period (p<0.05). A similar profile was noted with H^+ accumulation, where at 15 minutes of ischemia, livers from newborn females accumulated 30% more H^+ compared to males (11.5±1.3 vs. 14.9±2.6, p=0.008), which was also sustained throughout the ischemic period (p<0.05). Conclusion: The larger and more rapid development of tissue lactic acidosis in newborn female livers may result in greater metabolic damage during ischemia and offer a potential explanation for pediatric studies reporting worse outcome of recipients receiving livers from female donors.
This work was supported by the Heart and Stroke Foundation of Ontario (T-4926).

10.29

THE ROLE OF SEXUAL PROCESS IN THE REGULATION OF STRESS-INDUCED CARDIOVASCULAR RESPONSES IN RAT

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Stress is one of the main lines of our studies (Vahabzadeh and Fillenz, 1994). We have already investigated the role of sex hormones in both sexes on the stress-induced responses (Dehghani, et al., 2003). Although we focused in the behavioral responses, in the present studies we monitored the heart rate as a cardiovascular index. The present studies aimed to investigate the effect of changes in the balance of the autonomic nervous system within the sexual process on the regulation of stress-induced cardiovascular responses in rat. Sprague-Dawley rats (200-300g) from both sexes divided to 4 groups for each sex. For each groups 15 rats were used (n=15). Control groups in both sex were intact; and only used for monitoring of the heart rat in normal condition. Second group were subjected to 5 minute tail pinch stress (Antelman, et al., 1975); and the changes in the heart rate were monitored as a stress response. 3rd group were subjected to normal sexual intercourse; and the 4th groups subjected to atropine as well as epinephrine (ip) in pharmacological doses with time course similar to the process of the normal sexual intercourse. With 6 hours interval, all experimental groups were subjected to 5 minutes tail pinch stress; and the changes in the heart rate were monitored as a stress response. Renal out put also

was monitored for all groups. Variation calculated in the percentage base. All statistical analyses were carried out using absolute data and either student paired t-test (within same group) or ANOVA (within the different groups). The results show that regulation of the balance of parasympathetic and sympathetic systems within the sexual process reduce the activity of cardiovascular system by 27+/-4% (P<0.005, n=15); and the renal system by 33+/-3% (P<0.005, n=15) in the present studies. Similar results were obtained with the use of atropine and epinephrine. Stress-induced changes were similar in both sexes. The present data suggest that sexual process reduce stress-induced cardiovascular as well as renal activity; and enhance the tolerance for tail pinch stress. Although the present data may are considered as a pour physiological finding, on the base of these data as well as the light of the current literature one may come to conclusion that ANS balance as a peripheral index of the limbic system reduce the chance of anxiety-induced renal as well as cardiovascular failure in some cases.

10.30

AORTIC COARCTATION-INDUCED HYPERTENSION DURING PREGNANCY: A MODEL OF PREECLAMPSIA IN RATS

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Normal pregnancy entails generalized vasodilatation, increases in blood flow, and decreased responsiveness to vasoconstrictors. Patients with preeclampsia show reduced blood flow to kidneys, uterus and placenta, and increased vasoconstriction leading to maternal hypertension. We induced hypertension in pregnant rats by aortic coarctation (ACOR) and determined hallmarks of human preeclampsia (i.e., proteinuria, decreased fetal viability, and impaired endothelium-dependent relaxations) in such rats. Pregnant (8-day gestation) rats were rendered hypertensive with silver clips (slit opening = 0.279 mm) placed around the aorta immediately distal to the renal arteries; sham rats (SHAM) were surgically opened but without silver clipping of aorta. On gestation days 16 and 17, urinary protein as well as arterial pressures and heart rates were measured. Mesenteric vascular beds were also perfused *ex-vivo* and constricted for acetylcholine-induced relaxation studies. Arterial pressures and urinary protein increased in ACOR ($P<0.05$) *versus* SHAM; fetal viability decreased ($P<0.05$) in ACOR *versus* SHAM rodents. Cirazoline (α_1-adrenoceptor selective agonist) constricted ACOR and SHAM vascular beds similarly but co-infusion of nitro-L-arginine constricted SHAM significantly more than ACOR vessels. Acetylcholine dose-dependently relaxed ACOR and SHAM mesenteric arteries, however, endothelium-derived hyperpolarizing factor (EDHF) via opening of K_{Ca} channels mediate acetylcholine relaxations in SHAM vessels while nitric oxide and EDHF mediate acetylcholine response in ACOR vessels. CONCLUSIONS: The ACOR rodents exhibited arterial hypertension, proteinuria, reduced fetal viability, and modifications in endothelium function and thus may serve as a suitable rodent model of the disease.

10.31

IUGR ALTERS COX-2 EXPRESSION THROUGH STEROID SIGNALING AND AFFECTS 11-β -HYDROXYSTEROID DEHYDROGENASE TYPE 2 (11β-HSD2) CHROMATIN STUCTURE IN THE RAT KIDNEY

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Background: Our research goal is to understand the interplay between steroid biology and IUGR renal morbidities. The IUGR rat is characterized by elevated levels of fetal corticosterone, and altered postnatal chromatin structure. The former is associated with decreased renal expression of COX-2, a gene necessary for nephrogenesis. The latter is associated with decreased expression of 11β-HSD2, an enzyme that protects the kidney from the actions of corticosterone. Whether (1) the decreased expression of COX-2 is secondary specifically due to the elevation in corticosterone, or (2) the postnatal decrease in 11β-HSD2 is due to changes in epigenetic determinants of chromatin structure is not known. **Objective**: We hypothesized that (1) in utero administration of RU486 (a steroid antagonist) moderates the decrease in COX-2 expression; and (2) IUGR leads to postnatal changes in 11β-HSD2 chromatin structure. **Design/Methods:** IUGR and controls (CON) were induced at e19. For hypothesis (1), vehicle, 100 mg or 500 mg of RU486 was given at the time of surgery. Kidney was harvested at term (e21.5). For hypothesis (2), pups delivered spontaneously, litters culled to 6, and kidney harvested at d21 of postnatal life. 11β-HSD2 chromatin structure was analyzed using bisulfite modification (DNA methylation) and chromatin immunoprecipitation. **Results:** The 500 mg dose of RU486 increased IUGR e21.5 COX-2 mRNA levels versus vehicle ($P = 0.004$), in contrast to the 100 mg dose. In the d21 postnatal kidneys, IUGR significantly increased trimethylation of lysine 4 in the IUGR female 11β-HSD2 promoter versus controls, without affecting exon 2 ($P = 0.014$). In contrast, trimethylation of the 11β-HSD2 exon 2 was significantly increased in the IUGR male kidney ($P = 0.006$). **Conclusions:** We conclude that (1) a steroid antagonist RU486 moderates the effects of IUGR upon COX-2 mRNA levels and (2) IUGR alters 11β-HSD2 chromatin structure in the postnatal kidney. The link between the two studies is the concept that the IUGR kidney continues to be exposed to increased levels of corticosterone in the fetal and neonatal periods, whether it is secondary to IUGR or through decreased 11β-HSD2. We speculate that these exposures lead to different renal specific morbidities of IUGR, including decreased nephrogenesis and postnatal hypertension (supported by PCMC grant, MB).

11.0: SEX STEROIDS, PREGNANCY, PRE-ECLAMPSIA, AND FETAL PROGRAMMING

11.2

ANG-(1-7) AND ACE2 IN HUMAN PREGNANCY

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Pregnancy is a condition in which the renin-angiotensin system (RAS) is elevated. With the discovery of angiotensin-(1-7) [Ang-(1-7)] and ACE2, a novel homologue of ACE, studies have shown that these new components of the RAS are regulated during pregnancy. The chorionic villi (CV) are an essential component of the placenta involved in maternal-fetal oxygen and nutrient transport. The presence and regulation of the RAS, in the CV of normal and preeclamptic placentas have not yet been examined. These studies assessed 1) the immunocytochemical distribution of Ang-(1-7) and ACE2 in the placenta of normal and preeclamptic pregnant subjects; 2) the regulation of the placental chorionic RAS during normal and preeclamptic pregnancies. Ang-(1-7 and ACE2 were found in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of primary and secondary villi. CV Ang II levels were significantly increased in preeclamptic subjects, without any change in Ang I and Ang-(1-7). There was a significant increase in the Ang II/Ang-(1-7). Aogen and AT1 receptor mRNAs were significantly increased in preeclamptic CV. No change was observed for renin, ACE or ACE2 mRNA. The mas receptor mRNA was at the detectable limit, but the AT2 receptor mRNA was not detectable. The AT1 receptor was the predominate receptor subtype with less than 15% of the AT2 and AT1-7 receptors. These results provide evidence for enhanced placental chorionic villous tissue expression of Aogen and AT1 receptor mRNA and Ang II levels in preeclamptic CV. These results indicate that the increased Ang II, resulting from increased Aogen, acting through the AT1 receptor may favor vasoconstriction in the chorionic villous tissue of the placenta leading ultimately to the abnormal regulation of maternal-fetal blood flow and thus development of preeclampsia.

11.3

PATHOPHYSIOLOGY OF HYPERTENSION DURING PREECLAMPSIA

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Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not yet been fully elucidated. The initiating event in preeclampsia has been postulated to be reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles. Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium which, in turn, causes hypertension by impairing renal function and increasing total peripheral resistance. Inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF) are thought to be important links between placental ischemia and cardiovascular and renal dysfunction. Supporting a potential role of cytokines in preeclampsia are findings that plasma levels of TNF and IL-6 are elevated in women with preeclampsia. Recent studies from our laboratory have indicated that chronic reductions in placental perfusion in pregnant animals are associated with enhanced production of inflammatory cytokines, such as TNF and IL-6. In addition, chronic infusion of either TNF alpha or IL-6 into normal pregnant rats results in significant increases in arterial pressure and a decrease in renal hemodynamics. TNF alpha activates the endothelin system in placenta, renal and vascular tissues whereas IL-6 stimulates the renin-angiotensin system. Collectively, these findings suggest that inflammatory cytokines play a role in causing hypertension in response to chronic reductions in uterine perfusion during pregnancy by activating multiple vasoactive pathways.

11.4

PREECLAMPSIA AND ANGIOGENIC FACTORS

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Imbalance of angiogenic growth factors in the maternal circulation contributes to the pathogenesis of preeclampsia. Soluble fms-like tyrosine kinase 1 (sFlt1), an endogenous anti-angiogenic protein that antagonizes vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) appears to be a central player in this paradigm. Exogenous gene transfer of sFlt1 into pregnant rats using an adenoviral vector produced hypertension, proteinuria and glomerular endotheliosis, the classical pathological renal lesion of preeclampsia. High serum sFlt1 and low serum free PlGF and free VEGF have been observed in preeclampsia. Abnormalities in these circulating angiogenic proteins also antedate clinical symptoms by several weeks. Another potential soluble factor secreted by the placenta that appears to be elevated in women with preeclampsia is soluble endoglin (sEng). Endoglin (Eng) is an angiogenic receptor expressed mainly on the surface of endothelial cells, but also placental syncytiotrophoblasts. Eng acts as a co-receptor for transforming growth factor-beta (TGF-beta, a potent pro-angiogenic molecule) signaling in endothelial cells. Eng mRNA is up-regulated in the preeclamptic placenta. In addition, the extra-cellular region of endoglin is proteolytically cleaved and that sEng is released in excess quantities into the circulation of preeclamptic patients. Furthermore, sEng appeared to exacerbate the vascular damage mediated by sFlt1 in pregnant rats resulting in severe preeclampsia-like illness including the development of HELLP syndrome and fetal growth restriction. What remains unknown is the etiology of the increased sFlt1 and sEng in preeclamptic patients and whether these markers can be used for the prediction and treatment of preeclampsia.

11.5

SEX DIFFERENCES IN FETAL PROGRAMMING OF CARDIOVASCULAR DISEASE.

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Numerous epidemiological studies report an inverse relationship between birth weight and blood pressure suggesting that hypertension may be programmed by factors initiated in utero. Fetal programming occurs in response to an adverse fetal environment and results in permanent adaptive changes that alter organ growth, structure, and physiology leading to increased risk for development of adult cardiovascular disease. Our laboratory utilizes a model of placental insufficiency in the rat that results in intrauterine growth restricted offspring (IUGR) that develop hypertension by 4 weeks of age. However, sex differences are evident as only male IUGR remain hypertensive after passage through puberty. A role for sex hormone involvement is suggested as plasma testosterone levels are two-fold higher in adult male IUGR and castration abolishes hypertension in adult male IUGR. Thus, testosterone appears to contribute to hypertension in adult male IUGR offspring. Ovariectomy leads to hypertension in female IUGR suggesting estrogen provides a protective status in adult female IUGR offspring. Renin angiotensin system (RAS) blockade abolishes hypertension in adult male IUGR and in adult female IUGR that develop hypertension in response to ovariectomy. Thus, sex hormones and the RAS contribute to sex differences in arterial pressure regulation in this model of fetal programmed hypertension induced by placental insufficiency. (NIH HL074927). REFERENCES: Alexander, BT. Fetal Programming of Hypertension, Am J Physiol. 2006;290:R1-R10. Ojeda NB, Grigore D, Yanes LL, Iliescu R, Robertson EB, Zhang H, Alexander BT. Testosterone contributes to marked elevations in mean arterial pressure in adult male intrauterine growth restricted offspring. Am J Physiol. 2007;292:R758-63.

AUTHOR INDEX

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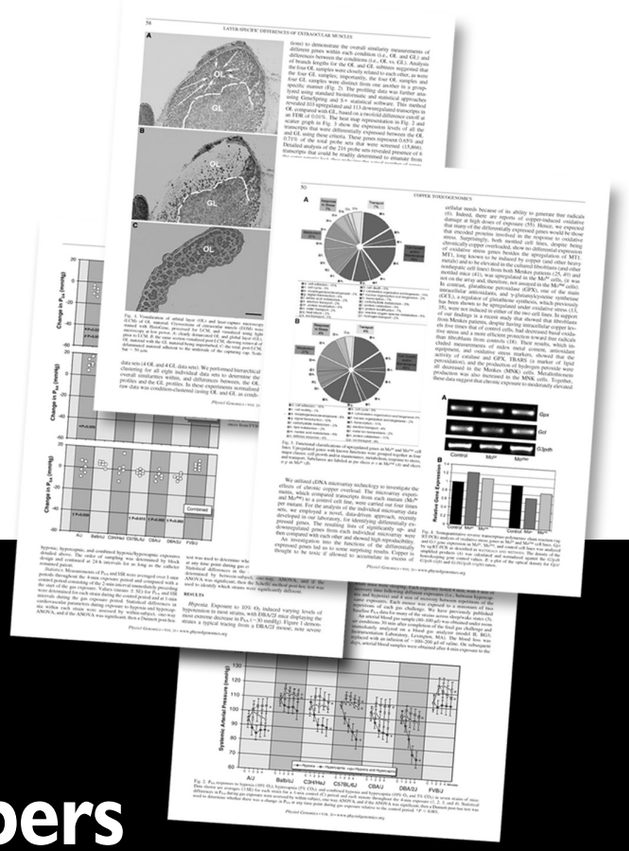

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