

## Biology of Aging

### Plenary Lecture:

#### **S1 AGING IS NO LONGER AN UNSOLVED PROBLEM IN BIOLOGY.**

Leonard Hayflick, Department of Anatomy, University of California, San Francisco.

There are four aspects of the finitude of life: aging, longevity determination, disease and death. Age changes result from the increasing rate of biomolecular disorder that, after reproductive maturation, exceeds repair and turnover capacity. These are stochastic or chance events governed by entropy or the tendency for concentrated energy to disperse when unhindered. The hindrance is the relative strength of chemical bonds. The repair of chemical bond breakage is vital until reproductive maturation for species survival. Genes do not cause aging but genes do indirectly drive longevity by maintaining the balance in favor of molecular synthesis and energy status at least until reproductive maturation after which damage exceeds repair capacity. Longevity is indirectly governed by genes because the strategy of producing excess physiological capacity to better insure survival to reproductive maturation allows life to continue beyond that crucial point. Selection for the maintenance of molecular fidelity beyond reproductive success is unnecessary for species survival. Thus, the aging process begins. Aging is not a disease because, unlike any disease, age changes (1) occur in every animal that reaches a fixed size in adulthood (2) cross virtually every species barrier (3) occur in all animals that reach a fixed size in adulthood and only after sexual maturation (4) occur in animals removed from the wild and protected by humans even when that species has not been known to experience aging for thousands or millions of years (5) increase vulnerability to death in 100% of the animals in which it occurs and (6) occur in both animate and inanimate objects. The only aspect of the finitude of life that humans have manipulated is disease or pathology. If all causes of death written on death certificates were to be resolved, average human life expectancy at birth could not exceed about 93 years. The only way that this number can be exceeded is by intervention in the fundamental aging process or in the determinants of longevity. The belief that the resolution of age-associated diseases will increase our understanding of the fundamental aging process is spurious. Aging is a process that is only experienced by humans and the animals that we choose to protect like zoo and domestic animals. We, and those animals, now survive well beyond young adulthood. That did not occur for the majority of time that we have been a species and it is, in fact, an aberration of civilization attributable to our discovery of how to eliminate

or postpone many causes of death. Immortality does not exist in biology because cells and their constituent molecules turnover or are replaced. The only long lasting biological property on an evolutionary time scale is the information coded in the DNA of the genome and mitochondria, but even that information is subject to mutation or change. There is an almost universal belief by physicians and others that the greatest risk factor for all of the leading causes of death is aging. Why then are we not devoting significantly greater resources to understanding what changes occur in biomolecules that lead to the manifestations of aging at higher orders of complexity and then increase vulnerability to all age-associated pathology?

### Plenary Lecture:

#### **S2 MAKING THE POLITICAL AND SCIENTIFIC CASE FOR AGING RESEARCH.**

Huber R. Warner, College of Biological Sciences University of Minnesota.

In spite of the well-documented graying of the population in developed countries, support for aging research in most countries is not robust. The USA founded the NIA as a separate entity of the NIH in 1975 as the result of intense lobbying by private citizens. In contrast, the IA as a separate entity of the CIHR did not occur until 2000. Although biogerontology research is supported through a variety of strategies in European countries such as Denmark, Great Britain, France, Germany, Belgium, The Netherlands, etc., it seems clear that a solid political basis for such funding remains weak. Often the case is made indirectly through arguments that supporting research on biogerontology is also a way of funding research on the causes of a variety of age-related degenerative pathologies, such as Alzheimer's disease, sarcopenia, diabetes, osteoporosis, etc. While this is certainly true, a direct case should be made for support for biogerontology research, although it is far from clear that the best political route would be by a call for promoting human life span extension per se as the primary goal.

## SYMPOSIUM I: Nutrition as a Determinant of Successful Aging

### S3 FOOD GROUP CONSUMPTION OF ELDERLY COMMUNITY-DWELLING CANADIAN MEN AND THEIR PERCEPTIONS OF DIET, HEALTH AND LIFE SATISFACTION. THE MANITOBA FOLLOW- UP STUDY.

Christina O. Lengyel, Department of Human Nutritional Sciences, Faculty of Human Ecology, University of Manitoba, Winnipeg, MB.

Healthy eating practices, self-rated health and life satisfaction are predictors of health outcomes in individuals. Research examining food group consumption and quality of life measures are largely unexplored in elderly men. This session will discuss the relationships between frequency of food group consumption on self-rated diets, self-rated health and life satisfaction of men participating in the Manitoba Follow-up Study (MFUS). The MFUS is a long term prospective study that began in 1948 with a cohort of 3, 983 healthy males (mean age = 31 years) with the primary objective of investigating the development of cardiovascular disease. MFUS continues to gather data from the remaining members (n=900; mean age = 86 years). The findings presented are important for the development of effective nutrition education programs targeting the oldest-old (individuals aged 85 years and older).

### S4 WHAT ARE ELDERLY CANADIANS EATING?.

Katherine Gray-Donald PhD, McGill University, Montreal, QC

Abstract not available

### S5 NUTRITION AND FRAILITY. WHAT DO WE KNOW? THE NUAGE LOGITUDINAL STUDY.

Hélène Payette PhD, Centre de recherche sur le vieillissement, CSSS-IUGS, Université de Sherbrooke.  
**Source of Research Funds:** CIHR and FRSQ (Research Network on Aging).

Lifestyle risk factors, such as nutrition, are powerful predictors of the rate and severity of functional decline throughout aging. Indeed, nutrition is consistently associated with the development and evolution of frailty. The increased vulnerability to stressors, a marker of frailty, may well be induced by negative energy balance. In the elderly, undernutrition proceeds as a spiral. Early signs such as loss

of appetite lead to decreased food intake which in turn rapidly leads to weight loss, nutrient deficiency, decreased muscle mass, increased fatigue, metabolic and endocrine abnormalities and diminished immunity; all cited as features of frailty. As frailty exacerbates further undernutrition by affecting ability to procure, prepare and eat nutritious food, nutrition is thus a key component of frailty and has the potential to modulate transitions in and out of the frailty state and to disability. Epidemiological studies have shown that thinness and obesity are both associated with frailty and that low serum micronutrients, low protein intake and weight loss are predictive of functional decline and frailty. The NuAge research program (2003-2008) is a longitudinal study of 1793 men and women, aged 67-84 yrs and generally healthy at baseline. It is collecting data on all aspects of nutritional status, including dietary, anthropometric, biochemical and functional measures, and employing basic, clinical, epidemiological and social approaches. It will then have the potential to assess the impact of diet, body composition and biological markers on transitions from vulnerability, frailty and disability, thereby clarifying the role of optimal nutrition in fostering successful aging by delaying frailty and the subsequent ensuing disability in an aging cohort. Preliminary analyses of the NuAge data already suggest that appetite could be a marker of successful aging and that low dietary protein intake (g/kg BW) predicts 1-y body weight loss of at least 5%.

### S6 FISH, OMEGA-3 FATTY ACIDS AND BRAIN HEALTH DURING AGING: HOW GOOD IS THE EVIDENCE?

Stephen Cunnane, University of Sherbrooke, Sherbrooke, QC

Abstract not available

## SYMPOSIUM 2: Muscles: From Molecules to Mobility

### S7 THE IMPACT OF STRETCH, EXERCISE AND DRUG TREATMENTS ON STRUCTURE, FUNCTION AND STEM CELL ACTIVATION IN AGING SKELETAL MUSCLE.

Jeff Leiter, University of Manitoba, and PanAm Clinic.  
**Source of Research Funds:** Parent Project Muscular Dystrophy and Canadian Space Agency.

Several age-associated morphological and functional changes occur in skeletal muscle however; the mechanisms responsible for these changes are unknown. Myogenic

satellite cells (SCs), which can be activated by nitric oxide (NO) through stimuli such as stretch and exercise, are required for muscle maintenance, repair, and hypertrophy. The purpose of this research was to determine if the nitric oxide pathway of SC activation is perturbed with age by using models of stretch, exercise and drug treatments to activate SCs. Extensor digitorum longus (EDL) muscles from 8 and 18 mo old mice randomized to 1 of 7 groups: control (C), stretch (S), S + L-Arginine (LA), S + Isosorbide Dinitrate (ISDN), S + N $\omega$ -nitro-L-Arginine methyl ester (LN), S + LA + LN, and S + ISDN + LN). Immediately following the stretch (or not) cycle (8 s on, 7 s off, 20% length increase) and drug treatments, muscle cultures were treated with tritiated thymidine (4  $\mu$ l/2 ml BGM) and harvested 24 or 48 hrs later to determine SC activation via scintillation counts per  $\mu$ g DNA. In separate experiments, 8 and 18 mo old mice were exposed to voluntary wheel running (or not) for 3 weeks to measure the effects of exercise on body mass, muscle mass, endurance capacity, grip strength, SC activation, gene expression, and muscle cross-sectional area (CSA). Results from stretch experiments suggest NO administration in 18 mo old muscle had an opposite affect on SC activation compared to younger muscles treated with NO. Data from exercise experiments indicated 18 mo old mice have decreased body mass, muscle mass, CSA and SC pool size compared to 8 mo old mice. Three weeks of exercise restored the endurance capacity of 18 mo old mice. Future experiments are in progress to determine if exercise combined with NO administration can ameliorate sarcopenic changes in muscle.

### **S8 SKELETAL MUSCLE FLEXIBILITY: FROM BASIC SCIENCE TO PRACTICAL APPLICATION.**

Jason Peeler, Department of Kinesiology & Applied Health, University of Winnipeg.

Muscle flexibility has a large impact on health, physical performance, and the aging process. It significantly influences our ability to handle the physical demands of work, study and leisure activity. While innovations in science and technology have advanced our understanding of basic muscle structure and function, to date they have had little impact on the assessment and prescription of flexibility protocols used by health care practitioners (ie. physicians, physiotherapists, etc.) in the treatment of musculoskeletal dysfunction. In fact, the Philadelphia Panel (2001) on Evidence Based Clinical Practice Guidelines found insufficient evidence to warrant clinical recommendations regarding the use of stretching programs by health care practitioners in the treatment of musculoskeletal dysfunction. Currently, the vast majority of clinical assessment and rehabilitative techniques are developed through trial and error methods, which employ non-scientific, anecdotal approaches similar to single case reports. This practice often leads to short-lived or ineffective treatment interventions. This presentation will explore the disconnect between basic

science and clinical application of stretching protocols, and focus on the practical application of validated assessment and rehabilitation protocols that are designed to enhance muscle flexibility.

### **S9 WHAT INFLUENCES HEAD MOTION DURING GAIT? -- CHANGES IN MOTOR CONTROL FOLLOWING LOW-VELOCITY WHIPLASH PERTURBATIONS.**

Michael Pierrynowski\*, (Sponsored by Judy Anderson), School of Rehabilitation Science, McMaster University. **Source of Research Funds:** The University of Guelph and McMaster University.

Motor deficits in the form of muscle inhibition and altered patterns of muscle recruitment resulting in a loss of joint control have been recognized in cervical spine and shoulder disorders. Recent work in our laboratory has shown that neck pain causes a disturbance in the rhythmical motion of the head during gait. The influence of this disturbance can be quantified using an extension of the long-range power law correlation, a measure we call the Neck Walk Index (NWI). To investigate the sensitivity of the NWI to detect coordination changes in head motion during gait we subjected three groups of healthy volunteers (n=6+9+8) to a series of 9, 49 or 100 mild (peak velocity change of 3.0 km/h) whiplash-like perturbations. This perturbation has been previously used to elicit reflex-like neck muscle activation in healthy volunteers and has the potential to cause mild neck muscle soreness similar to that experienced following mild whiplash. The NWI was derived from 3D body and head motion data collected during a 5 minute treadmill walk prior and following the perturbations {0h, Perturbation, 1h, 1d, 2d, 6d}. Our results clearly demonstrate that the NWI increased 1 and 2 days post-perturbation for both the 49 and 100 groups and as expected the 100 group had a greater change. Unexpectedly, the 9 group presented with a small decreased NWI 1 day post-perturbation. These findings demonstrate that the NWI is sensitive to detect a change in head coordination during gait following a series of mild whiplash-like perturbations. These data suggest that the NWI may be a useful clinical tool to examine the effectiveness of interventions used to treat patients with neck pain.

### **S10 MOBILITY AMONG OLDER ADULTS: THE ROLE OF PERSONAL AND ENVIRONMENTAL FACTORS.**

Verena H. Menec, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba.

Background Mobility encompasses many different aspects, from performance in specific activities, such as climbing stairs, to more broadly being able to get around via a range of transportation modes, such as walking or driving. All

aspects are important for continued participation in society, health, and well-being. For the present purposes, mobility was defined in terms of walking, given the current emphasis on increasing activity levels in the population. Increasingly, the importance of the neighbourhood environment in promoting activity participation, such as walking, is being recognized in the health promotion domain; however, relatively few studies have examined this issue among older adults. The purpose of the present paper was, therefore, to examine the relationship between both personal and environmental factors and walking among older adults.

**Methods.** In-person interviews were completed with 1,015 individuals aged 45 and over living in Winnipeg, 370 (36.5%) of whom were 65 years or older. Questions focused on a wide range of issues, including socio-demographics, health and well-being, neighbourhood walkability, perceptions of safety, etc. Participants were also asked to wear a pedometer for three days, with 807 (80%) agreeing to do so. Walking was measured as the average number of steps per day derived from the recorded number of steps over the three days.

**Results.** Older adults (aged 65+) walked considerably less than younger individuals (aged 45-64), with 17.7% taking on average less than 2000 steps per day, relative to 9.9% of younger participants. Analyses were conducted to identify which personal factors (age, sex, marital status, education, self-rated health, and chronic health problems) and environmental factors (neighbourhood walkability (e.g. walking paths), and neighbourhood safety) were associated with more walking. Among older adults, being aged 65-69 (relative to aged 70+) and being in better health was associated with more walking. Neighbourhood walkability was not significantly associated with walking. However, neighbourhood safety (feeling safe after dark and not letting safety concerns limit activities) was significantly related to walking.

**Conclusions.** Mobility, defined here in terms of walking, was associated with both personal characteristics, such as age, as well as certain neighbourhood-related factors, particularly perceptions of safety. This suggests that the neighbourhood environment should be a focus of health promotion interventions.

## SYMPOSIUM 3: Calpain: a Molecular Monkey Wrench Involved in Aging and Cell Death Mechanisms

### S11 STRATEGIES FOR INHIBITING CALPAINS.

Peter L. Davies, Queen's University, Kingston, ON.

Abstract not available

### S12 SURVIVAL AND DEATH FUNCTIONS OF CALPAIN.

Peter A. Greer, Queen's Cancer Research Institute, Kingston, ON.

Abstract not available

### S13 THE ROLE OF CALPAINS VERSUS CASPASE-3 IN DIFFERENT FORMS OF NEURONAL CELL INJURY.

Kevin K.W. Wang<sup>1,2</sup>, <sup>1</sup>Center of Innovative Research, Banyan Biomarkers, Inc., Alachua, FL, USA. <sup>2</sup>Center for Neuroproteomics and Biomarkers Research, Department of Psychiatry, McKnight Brain Institute, University of Florida, Gainesville, FL, USA. **Source of Research Funds:** NIH Award# R01 NS049175-01 and US Dept. of Defense (DoD-Army) Grant #DAMD17-03-1-0066.

In the central nervous system (CNS), physiological controlled activation of calcium activated cysteine proteases calpain-1 and -2 (calpains) may be critical to synaptic function and memory formation, with possible substrates including various structural and scaffolding proteins, enzymes, and glutamate receptors. During regulated activation of calpain, only a small number of calpain molecules are activated transiently. Similarly, activity of another cellular cysteine protease, caspase-3 is important in neural cell pruning during neurodevelopment in the form of controlled apoptosis. Yet, both of these proteases can operate in a hyperactivated mode during CNS pathology, contributing the neuronal cell death. For example, during ischemic and traumatic brain injuries, calpains are overactivated by sustained calcium overload in affected brain regions (involving almost all available calpain molecules), contributing the acute phase of neuronal necrosis (oncosis). Subsequent to that, caspase-3 is over-activated by pro-apoptotic signals, including the intrinsic, extrinsic and ER-pathways, contributing to the delayed phase of neuronal apoptosis. Calpain also participates during this apoptotic phase of neuronal injury. In fact, calpain and caspases-3 generated distinct neuronal protein breakdown products, such as  $\alpha$ II-spectrin breakdown products of

different molecular weight. These SBDPs are released from the injured brain tissue into biofluid compartments such as cerebrospinal fluid and circulating blood, allowing them to be used as biomarkers for neuronal necrosis and apoptosis, respectively. Lastly, our new data show that an emerging form of neuronal cell death (Type II; autophagic cell death) is also involved in acute brain injury. I will further discuss the intricate interplays among caspase-3, calpain, autophagy and autophagic cell death in the context of acute neuronal injury.

**S14**  
**CALPAIN MEDIATED PATHWAY OF DEATH IN PARKINSONS DISEASE.**

David S. Park, Neuroscience East – Ottawa Health Research Institute (OHRI).

Abstract not available

**SYMPOSIUM 4:**  
**Cardiovascular System and Aging:**  
**Exercise Blood Flow**

**S15**  
**EXERCISE TRAINING REVERSES AGE-RELATED ENDOTHELIAL DYSFUNCTION IN THE SKELETAL MUSCLE RESISTANCE VASCULATURE: ROLE OF NO AND OXIDANT STRESS.**

Judy M. Delp, Center for Interdisciplinary Research in Cardiovascular Sciences, West Virginia University School of Medicine, USA. **Source of Research Funds:** NIHR01 HL077224-01.

Advanced age is associated with a reduction in skeletal muscle vascular conductance and impairment of endothelium-dependent vasodilation. Old age-associated reductions in flow- and agonist-mediated endothelium-dependent vasodilation of arterioles from skeletal muscle occur through a decrease in nitric oxide (NO) signaling. Aerobic exercise training reverses the age-related impairment of endothelium-dependent, NO-mediated vasodilation. Several possible mechanisms may underlie this deficit in NO signaling, including limited availability of substrate (L-arginine) or cofactor (tetrahydrobiopterin [BH4]), reduced endothelial NO synthase (eNOS) abundance, and increased scavenging of NO. In skeletal muscle arterioles, eNOS protein content increases with age, and L-arginine levels are preserved in skeletal muscle arterioles from aged rats. Neither inhibition of arginase activity or addition of exogenous L-arginine alters flow-mediated vasodilation in arterioles from old rats. In contrast, age reduces BH4 in skeletal muscle arterioles, and addition of sepiapterin, to increase BH4 through the salvage pathway,

improves flow-induced vasodilation of skeletal muscle arterioles from old rats. These data indicate that the age-induced impairment of NO-mediated vasodilation does not result from increased arginase activity or limited availability of L-arginine. Direct measures of NO and superoxide anion suggest that the age-related deficit in BH4 availability contributes to uncoupling of eNOS, resulting in eNOS-mediated production of superoxide in arterioles from old rats. The age-related decrease in NO-mediated vasodilation appears to be accompanied by an increase in vasodilation induced by reactive oxygen species (ROS). Although ROS-mediated dilation may increase with age, the resultant vasodilation to agonists and flow remains impaired in arterioles from old rats, suggesting that NO is a more potent dilator of vascular smooth muscle, and that the loss of NO-mediated signaling results in reduced responsiveness to flow and agonists with age.

**S16**  
**TIPPING THE BALANCE: PRO AND ANTIOXIDANT INFLUENCES ON SKELETAL MUSCLE HYPEREMIA IN THE ELDERLY.**

David Walter Wray, Ph.D.\*, Department of Medicine, Division of Physiology, University of California San Diego, La Jolla; Department of Medicine, Division of Geriatrics, University of Utah, Salt Lake City, UT, USA. **Source of Research Funds:** Supported by the Tobacco-Related Disease Research Program (15RT-0100) and the Parker B. Francis Fellowship in Pulmonary Research.

While the link between the aging process, free radicals, nitric oxide (NO) bioavailability, and vascular dysfunction have been recognized, the details of the interaction between these factors remain incomplete. It has become increasingly apparent that the balance between antioxidant defence and “oxidative stress” may directly regulate the fundamental vascular function of NO, and that this balance is altered even during healthy aging. To further explore these issues, we have recently examined the efficacy of an oral antioxidant cocktail (Vitamin C, Vitamin E, and alpha-lipoic acid) to improve vascular function in the elderly in a variety of experimental settings. A host of methodologies have been employed to achieve this goal; vascular oxidative stress and antioxidant efficacy have been evaluated utilizing a unique electron paramagnetic resonance (EPR) spectroscopy technique, while skeletal muscle hemodynamics and vascular function have been assessed by ultrasound Doppler and nuclear magnetic resonance techniques. Examination of skeletal muscle hyperaemia in response to ischemic cuff occlusion (the flow-mediated vasodilation test), acute exercise, and exercise training collectively suggest that antioxidant interventions have little positive (and sometimes negative) effect on vascular function in young, healthy adults, while elderly individuals appear to benefit from acute antioxidant administration. Together, these recent findings emphasize the importance of considering both pro and antioxidant influences on the vasculature, the balance of

which appear to dictate overall vascular responsiveness to a given perturbation with advancing age.

**S17**  
**DYNAMICS OF MICROCIRCULATORY FUNCTION AND OXYGEN DELIVERY IN AGED MUSCLE.**

David C. Poole, Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, U.S.A.  
**Source of Research Funds:** National Institutes of Health, NHLBI RO1-50306 and the American Heart Association, Heartland Affiliate.

Aging is accompanied by an impaired ability to distribute blood flow and therefore oxygen delivery within and among active muscles. Indeed, this may occur despite maintenance of cardiac output and limb blood flow in aged individuals and may contribute to the decreased ability to extract oxygen from the blood. The control of muscle blood flow during exercise is complex with an array of mechanical, chemical and neural mechanisms participating in the response. These mechanisms summate to match the temporal and spatial blood flow and oxygen/substrate delivery to requirements. Recent evidence in humans and animals demonstrates that, during contractions, the net output of these control mechanisms in muscles from aged, compared with young, individuals is reduced. One consequence of this reduction, that has been identified in muscles from aged Fischer 344 X Brown Norway rats (26-30 month old, equivalent to 65-70 yr old humans), is that the oxygen delivery-to-utilization balance during contractions is fundamentally changed which lowers microvascular oxygen pressures much further. This is of crucial importance because it decreases the pressure head responsible for driving oxygen across the microcirculatory blood-myocyte barrier and each molecule of oxygen necessary to power the energetic requirements of exercise must cross that barrier. To address the hemodynamic basis for this response novel intravital microscopy approaches in rat muscle have, for the first time, resolved capillary hemodynamics during contractions in aged muscles. In resting muscle of aged individuals capillary red blood cell (RBC) flux and velocity are increased which, compared with young controls, normalizes oxygen delivery in the face of a reduced lineal density of flowing capillaries. During contractions of precisely the same stimulus intensity that increase capillary RBC flux two to four-fold in young muscles, capillary hemodynamics are completely different in aged muscles. Specifically, RBC flux and velocity do not increase significantly and there are occasional instances of capillaries where RBC flow either slows down or stops. These observations indicate the presence of multifaceted derangements in microvascular control that conspire to reduce microcirculatory blood flow and microvascular oxygen pressures during muscle contractions.

**S18**  
**BLOOD FLOW TO CONTRACTING MUSCLES OF THE AGING HUMAN: ADAPTIVE OR MAL-ADAPTIVE?**

David Proctor\*, Beth Parker\*, Sandra Smithmyer\*, and Samuel Ridout\*, Noll Laboratory, Dept. of Kinesiology, and Penn State College of Medicine, Penn State University, University Park, PA, USA. **Source of Research Funds:** NIH grants R01 AG-018246, T32 AG-00048, and M01 RR-10732.

The full impact of the aging process on the regulation of blood flow to contracting muscles remains poorly understood. Reports of reduced, preserved, and even augmented whole limb hyperemic responses to graded exercise in older vs. younger men suggests there are myriad factors, both physiological and biomechanical, that influence local O<sub>2</sub> delivery, O<sub>2</sub> extraction, metabolic demand, or the matching between blood flow and metabolism. However, a fundamental question with respect to exercise hyperemia is whether or not primary aging (i.e., aging in the absence of extreme conditioning or deconditioning and disease) alters the matching between limb blood flow and metabolic demand during submaximal exercise work rates. Results from our laboratory suggest that the matching between leg O<sub>2</sub> delivery and O<sub>2</sub> demand during both large and small muscle graded exercise is well preserved with healthy aging in men; in women, the impact of age on this matching appears to be mode-dependent (better preserved during large compared to small muscle dynamic exercise). Aerobic fitness influences the relation between leg hyperemia and power output in all groups except older women. With respect to vascular control of the observed blood flow responses, there is little question of age-related alterations given the higher perfusion pressure required by older adults to achieve a given exercising limb blood flow response. However, the mechanisms by which older men and women raise leg vascular conductance during exercise in the face of heightened baseline vascular resistance have not been determined. We find that the leg vasculature of healthy, normal fit older men exhibits a well preserved ability to dilate in response to both large and small muscle mass exercise, while older (estrogen deficient) women of similar relative fitness do not, suggesting sex-specific alterations in local vascular control. Likely mechanisms underlying the persistent attenuation of leg vasodilator responses to dynamic small muscle mass (isolated knee extensor) exercise in older women include structural alterations in the leg arterial vasculature, functional alterations that limit their ability to overcome heightened tonic vasoconstriction (e.g., reduced bioavailability of endothelium-derived vasodilator substances and attenuated sympatholysis), and reduced hyperemic adaptability with advancing age. Unraveling the mechanisms underlying these sex-specific alterations in leg hyperemia and vascular control with aging, as well as determining if these responses are adaptive or maladaptive under a variety of exercise challenges, will be important

steps toward understanding the full impact of physiological aging on muscle blood flow regulation during exercise and developing appropriate (perhaps sex-specific) interventions.

**SYMPOSIUM 5:  
Neuromuscular Function and  
Resistance Training in Older Adults  
– From Laboratory Research to  
Clinical Implications**

**S19  
CHANGES IN MOTOR OUTPUT AND THE  
CONSEQUENCES FOR MUSCLE FUNCTION.**

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University of Colorado Boulder, CO, USA. **Source of  
Research Funds:** National Institute on Aging  
(AG0090000).

The motor unit remodeling that accompanies advancing age reduces the size of motor unit populations and alters the properties of motor units. The adaptations in motor unit properties include an increase in innervation number, a decrease in contraction speed, a decline in maximal discharge rates, and a reduction in the recruitment range of the population. The challenge has been to determine the functional consequences of these adaptations. Our approach has involved comparing the performance of young and old adults on a simple motor task and attempting to identify differences in motor unit activity between the two groups of individuals. The task requires participants to perform brief isometric contractions at a range of intensities and to keep the force as steady as possible. When humans perform this task, the force is never constant but varies about an average value, which influences the capacity of an individual to achieve a desired force and to produce an intended limb trajectory. The fluctuations in force provide an index of the steadiness of the contraction. Old adults are often less steady than young adults, especially during low-force contractions. Experimental measurements and a computational model have indicated that the variation in steadiness across the operating range of a hand muscle are strongly influenced by the variability in the discharge times of the action potentials for the involved motor units. However, there does not appear to be any difference between young and old adults in the variability of motor unit discharge times when the task involved brief (< 10 s) submaximal contractions and the old adults were less steady only at the lowest force examined (2% of maximum). When the task involved longer contractions and various amounts of visual feedback of the performance, there were more substantial differences in steadiness between young and old adults, which suggested that either the intrinsic properties of the motor neurons or the synaptic input they received changed differently for the two groups of individuals during the longer contractions. Consistent with this interpretation, manipulation of

physiological arousal by exposing individuals to a stressor intervention (electric shock) worsened steadiness during a pinch grip task, but more so for old adults compared with young adults. Furthermore, motor units recruited in the biceps brachii muscle of old adults during a submaximal contraction appear to exhibit discharge characteristics that differ from those observed in young adults. Also, old adults are more variable and less accurate when they perform rapid goal-directed contractions that require the generation of a feed-forward activation signal before the task is executed. These findings suggest that adjustments in the intrinsic properties of motor neurons and in the synaptic input received by the motor neuron pool contribute to the impairment in motor performance that can be observed in old adults.

**S20  
ANABOLIC SIGNALING IN AGING SKELETAL  
MUSCLE: IMPLICATIONS FOR SARCOPENIA..**

Roger Fielding, Tufts University, Boston, MA, USA

Abstract not available

**S21  
NUTRITIONAL SUPPLEMENTATION FOR  
INCREASING MUSCLE MASS AND STRENGTH IN  
OLDER INDIVIDUALS.**

Philip D. Chilibeck, University of Saskatchewan. **Source of  
Research Funds:** CIHR Experimental and Applied Sciences,  
Iovate Health Sciences Research Inc., Gatorade Sport  
Science Institute, Saskatchewan Flax Development  
Commission, Saskatchewan Health Research Foundation,  
NSERC.

We have conducted a number of clinical trials combining nutritional supplementation and heavy resistance training in older individuals. Protein supplementation has minimal effect on muscle mass and strength; however, small benefits are realized if protein is consumed immediately before resistance training sessions indicating that blood flow during exercise may enhance the uptake of amino acids into muscle. Creatine monohydrate supplementation increases muscle mass and strength, and inhibits muscle and bone catabolism. It is effective when given in small doses, especially when combined with protein. Smaller dosing results in reduced side-effects. Flax oil supplementation reduces inflammation and may have small benefits for increasing muscle mass when combined with resistance exercise training.

**S22**

**RESISTANCE TRAINING: PROMOTING FUNCTION AND INDEPENDENCE AMONG OLDER ADULTS.**

Teresa Liu-Ambrose, Centre for Hip Health, Department of Physical Therapy, University of British Columbia. **Source of Research Funds:** Michael Smith Foundation for Health Research, Vancouver Foundation (BCSMF), Canadian Institutes of Health Research

Resistance training is a mode of exercise that most older adults do not uptake. However, resistance training has very specific benefits for the older adult, including the reduction of falls risk, the promotion of independent mobility, and the promotion of bone health. More recently, there is evidence to suggest that resistance training benefits cognitive performance. Thus, resistance training may be an essential tool in the promotion of healthy aging.

**SYMPOSIUM 6:  
The AAA Alarm: Antioxidants,  
Atherosclerosis and Aging**

**S23**

**DIETARY HABITS AND CARDIOVASCULAR CONCERNS AMONG CANADIAN ELDERLY.**

Mohammed H. Moghadasian, Department of Human Nutritional Sciences, and Canadian Centre for Agri-food Research in Health and Medicine, St. Boniface Hospital Research Centre and University of Manitoba.

Dietary habits and lifestyle play a major role in cardiovascular health. Adequate and appropriate amounts of nutrients may delay the onset of atherosclerotic vascular disorders. Data from Canadian Community Health Survey Cycle 2.1 (2003) have been analyzed to learn about dietary habits and the reasons behind food choices among Canadian elderly. Approximately 47% of elderly participants reported consumption of fruit and vegetables five times or more a day. Fruit and vegetable consumption was positively associated with total household income and education. Gender and the province of residence were among other significant contributing factors. Further analysis of data revealed that approximately 50% Canadian elderly choose their food to be low in fat and high in calcium and fiber. Approximately 30% of the participants reported that heart disease is a major concern for their food selection. These data suggest that Canadian elderly are aware of the role of diets on cardiovascular health. Additional information will further enhance their knowledge of prevention of chronic diseases through alterations in dietary habits and lifestyle modifications, resulting in improving quality of life and reducing financial burden on health industry.

**S24**

**LDL-OXIDATION, ANTIOXIDANTS AND CORONARYARTERY DISEASE IN THE ELDERLY.**

John Hill, St. Paul's Hospital and University of British Columbia, Vancouver, BC

Abstract not available

**S25**

**NATURAL ANTIOXIDANTS AND ANTIOXIDANT SUPPLEMENTS IN HEALTH PROMOTION AND DISEASE REDUCTION.**

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Free radicals are culprits in the etiology of a number of chronic diseases such as cardiovascular disease, arthritis, diabetes, cancers, and the ageing process, amongst others. *In vivo*, antioxidant enzymes neutralize excess free radicals (e.g., reactive oxygen species) that are formed by the body's metabolic/oxidative pathways, and dietary antioxidants can augment their effect in healthy individuals and especially in those suffering from a chronic disease state. Antioxidants themselves are substances, which when used at low concentrations, neutralize free radicals by donation of hydrogen atoms or single electrons. In some instances, they may function as chelators of pro-oxidant metal ions. Studies continue to suggest that diets rich in fruits and vegetables lead to health promotion on account of the presence of vitamin C, E, carotenoids and endogenous phenolic compounds; however, other plant-based food materials such as cereals, legumes, and oilseeds also provide an excellent source of dietary phenolics. Furthermore, certain beverages and tree nuts are well documented to contain a variety of bioactive phenolic compounds with health-promoting potential. Though the mechanism of action of phenolic antioxidants is often ascribed to their free-radical scavenging capabilities, there are in fact a number of possible mechanisms: some include the effect of phenolics on cell differentiation, increase in apoptosis of cancer cells, and maintenance of DNA repair. The process of ageing is often in parallel with a decline in body's efficacy to maintain a proper pro-oxidant/antioxidant balance; thus, an adequate intake of dietary antioxidants may help to address increasing demands on the ageing body and to assist in retarding conditions such as macular degeneration, cataracts, diabetes, heart disease, and cancers. The presentation will provide an overview of the role of selected dietary antioxidants and their potential sources for improving the quality of life, especially in the ageing population.

S26

### PERIPHERAL ARTERIAL DISEASE – THE PLAGUE OF OUR AGE.

Asad Junaid, University of Manitoba, Winnipeg, MB.

Abstract not available.

### SYMPOSIUM 7: Dilemmas of Drug Therapy in the Elderly

S27

### AGING AS A DETERMINANT OF DRUG DISPOSITION AND EFFICACY.

Daniel Sitar, Department of Pharmacology and Therapeutics, University of Manitoba.

With aging comes an accumulation of multiple and chronic diseases that impact on an individual's quality of life and cost of health maintenance to the individual and to society. Drug therapy is a critical tool for health maintenance of the older patient. These patients are prescribed a disproportionate number of medications, and in addition, they will often self-medicate with alternative remedies. The potential for drug interactions increases dramatically with the number of agents ingested concurrently. With increasing age, body composition changes, and this may affect drug concentration in the blood and tissues. As well, liver size decreases relative to body weight and likely contributes to the reduced ability to eliminate an ingested drug dose. The kidneys are often impaired in their ability to excrete drugs, contributing further to the potential of excessive drug accumulation. Diet can also impact the ability of the body to eliminate certain drugs, especially those subject to a high first-pass removal after oral ingestion. Adrenergic nervous system function changes in older persons, and this change may impact on the choice of drugs to treat their hypertension. Studies in healthy elderly adults have assisted in understanding the contribution of age versus concomitant pathology. This presentation provides a basis to determine the relative contributions of age and disease in affecting the choice of a drug for therapy, and in optimizing how it may be best administered to optimize the benefit:risk ratio.

S28

### ADHERENCE TO PRESCRIBED THERAPY BY OLDER ADULTS AND IMPLICATIONS FOR HEALTH MAINTENANCE.

Ruby Grymonpre\* PharmD, FCSHP Professor, Faculty of Pharmacy University of Manitoba. **Source of Research Funds:** Research funded by Merck Frosst, Manitoba Health Research Council, Canadian Institute for Health & Research.

Non-adherence to prescribed medications has been characterized as “America’s other drug problem”. The economic burden of medication non-adherence in Canada is estimated to be at least \$7-\$9 billion per year. Despite the plethora of literature in the area, medication adherence research has been plagued with inconsistencies in definitions, measurement methods, and variability in study designs and samples. It is not surprising that reported rates of medication adherence by older persons have been between 4 and 92%. Studies examining the determinants of non-adherence in community dwelling older adults are equally inconsistent often failing to analyze adherence in the context of a broader range of socio-behavioural factors. Intuitively, one would think that medication adherence improves the therapeutic benefit of a drug. However, there is a paucity of ‘real world’ evidence to support this hypothesis and some speculate that adherence to therapy may, in fact, be detrimental. This presentation will describe a program of research involving community dwelling old-old Manitobans (75+ years). The overall goal is to further our understanding of the measurement, characteristics and impact of medication non-adherence in the older population so that methods for improving this positive health behaviour can be realized. Our specific research questions include: (1) Is refill medication adherence calculated from the Manitoba prescription claims database a valid measure of adherence? (2) How should refill medication adherence be defined? (3) What proportion of older Manitobans are ‘adherent’? (4) What are the determinants of medication non-adherence in older Manitobans? (5) Is medication non-adherence in older Manitobans associated with increased use of health care services or mortality?

**S29**

**LOWERING BLOOD PRESSURE IN THE ELDERLY. EVIDENCE VERSUS GUIDELINES.**

Dr. James M Wright, MD, PhD Coordinating Editor, Cochrane Hypertension Group Departments of Anesthesiology, Pharmacology & Therapeutics and Medicine University of British Columbia. **Source of Research Funds:** CIHR.

Aging is associated with a number of changes that reduces the individual's ability to respond to challenges. One of the ways this manifests in terms of blood pressure is that the older person has more difficulty responding to the challenge of going from a supine to a standing position. This manifests as a predisposition to symptomatic orthostatic hypertension. It also suggests that older people will be more prone to serious adverse events from antihypertensive drugs than younger people. We have good evidence of the benefits of using drugs to lower blood pressure elderly people with hypertension from a Cochrane Systematic Review [Mulrow et al] and from the recent report of the trial in the very elderly [HYVET]. We have much less evidence of the harms. The most difficult process is translating the evidence into the optimal approach in clinical practice. This presentation will assess the degree to which clinical practice guidelines follow the evidence in answering the following questions with regard to the elderly hypertensive. What non-drug therapies are effective? What is the best first-line antihypertensive drug? What is the appropriate target blood pressure? Are the answers different if the patient also has Type 2 Diabetes Mellitus? Is there a limit to how many antihypertensive drugs should be prescribed?

**S30**

**CONTROVERSIES IN THE MANAGEMENT OF TYPE 2 DIABETES IN THE OLDER PATIENT.**

Baiju R. Shah, Department of Medicine, University of Toronto Division of Endocrinology, Sunnybrook Health Sciences Centre, Toronto. **Source of Research Funds:** Canadian Institute of Health Research and the Canadian Diabetes Association.

Diabetes is a common chronic disease that leads to multiple complications, and hence to morbidity and premature mortality. By maintaining excellent glucose, blood pressure and lipid control, patients can reduce their risk of these complications. For most patients, achieving these targets will require pharmacological therapy. The pharmacological management of diabetes, particularly with respect to glucose control, has become more complicated in the past five years, because of the development of many new agents and because of controversies surrounding the safety of existing agents. Drug treatment in elderly patients is particularly complicated, because of heightened concerns about side effects and safety, and because of uncertainty about the long-term benefits of intensive management in this

population. This presentation will evaluate the rationale for glucose, blood pressure and lipid control in the elderly, and will examine the association of cardiovascular disease with thiazolidinediones.

**SYMPOSIUM 8:  
Biology of Alzheimer's and  
Dementia**

**S31**

**IS MONOAMINE OXIDASE-A THE LINK BETWEEN DEPRESSION, HEART DISEASE AND ALZHEIMER DISEASE?**

Darrell D. Mousseau, Cell Signalling Laboratory, Department of Psychiatry, University of Saskatchewan. **Source of Research Funds:** CIHR, Saskatchewan Health Research Foundation.

Monoamine oxidase (MAO) generates peroxy radicals as a product of the oxidative degradation of biogenic amines such as serotonin, dopamine and noradrenaline. There is evidence that the MAO-A isoform contributes to both heart disease and Alzheimer disease, yet dysfunction of this isoform historically has been linked almost exclusively to major depressive illness. Interestingly, depression and heart disease are both risk factors for Alzheimer disease, suggesting a common mechanism might underlie the etiologies of these seemingly unrelated diseases. We provide the first evidence for a post-translational modification of MAO-A that inhibits its catalytic activity and propose that negative feedback based on stressor-induced phosphorylation of the MAO-A protein is a unique pro-survival mechanism, at least during acute or transient instances of oxidative stress. The putative role of this mechanism in disease is discussed.

**S32**

**HOW WELL DOES THE 3XTg-AD MOUSE MODEL REPLICATE ALZHEIMER'S DISEASE NEURO-PATHOLOGY?**

Frederic Calon, University of Laval, Montreal, QC.

The neuropathological correlates of Alzheimer's disease (AD) include amyloid- $\beta$  (A $\beta$ ) and tau pathologies. To better mimic the disease, the laboratory of Frank LaFerla has developed triple-transgenic mice (3xTg-AD) harboring three mutant genes (A $\beta$  precursor protein (APP<sup>swE</sup>), presenilin-1 (PS1M146V), and tauP301L). Our results indicate that 3XTg-AD mice exhibit age-dependent alterations of social behavior following a time-line matching the accumulation of tau and A $\beta$  in the cortex. The influence of gender was critical as females displayed behavior symptoms and, to a lesser extent, tau / A $\beta$  pathologies earlier than males. In parallel, we found a 30% decrease of the cerebrovascular

volume of 12-month-old 3XTg-AD mice compared to controls, without significant changes in blood flow or glucose transport. Increased brain collagen content (+20%) was detected suggesting a thickening of the basal membrane, as seen in individuals with AD. In addition, potential environmental AD risk factors such as low n-3 polyunsaturated fatty acid consumption or high fat calorie intake amplified AD-like pathology in 3xTg-AD mice. Interestingly, n-3:n-6 polyunsaturated fatty acid ratio (-8%) and brain uptake of [<sup>14</sup>C]-docosahexaenoic acid (-26%) were lower in 3xTg-AD mice than in non-transgenic littermates. Overall, our data indicate that the 3xTg-AD mouse displays several critical markers of AD including, but not limited to, Aβ and tau pathologies. Therefore, this model stands as a valuable tool to study the biology of early AD.

**S33**  
**GLIA IN NEURODEGENERATIVE DISEASES AND AGING.**

Alexej Verkhatsky, The University of Manchester, Faculty of Life Sciences, Oxford Road, Manchester, UK and Institute of Experimental Medicine, ASCR, Videnska Prague, Czech Republic. **Source of Research Funds:** NIH, ART(UK).

Abstract not available.

**S34**  
**CHANGES IN LTP AND MEMORY WITH NORMAL AGING AND DISEASE.**

Benedict Albeni, University of Manitoba, Winnipeg, MB.

Abstract not available.

**SYMPOSIUM 9:**  
**The Role of Oxidative Stress in the Decline of Aged Muscle**

**S35**  
**ROLE OF OXIDATIVE STRESS ON POTENTIAL MECHANISMS OF AGE-RELATED SKELETAL MUSCLE ATROPHY.**

Holly Van Remmen, South Texas Veterans Health Care Administration, San Antonio, Texas, USA.

Abstract not available.

**S36**  
**AGE-RELATED MUSCLE DYSFUNCTION: THE ROLE OF PROTEIN MODIFICATIONS.**

LaDora Thompson, Department of PM&R, University of Minneapolis, MN, USA. **Source of Research Funds:** Supported by NIA.

Aging is accompanied by a general decline in muscle strength. The decrease in muscle strength is explained, at least in part, by a decrease in muscle mass. However, strength declines more than would be expected from the reduced muscle or fiber size, thus suggesting other mechanisms are involved. One possibility is there are defects in the myofibrillar proteins responsible for force generation. This idea is supported by the age-related loss in force measured in permeabilized fibers, where muscle membranes are experimentally removed and force generation is entirely dependent on the interaction of myofibrillar proteins. With aging, a disruption in the interaction of myosin and actin is noted also. Electron paramagnetic resonance spectroscopy was used to measure the percentage of myosin that is in optimal interaction with actin to maximize force generation, referred to as the strong binding structural state, vs. when myosin and actin are weakly bound and thus not producing force. In aged muscle, there was a reduction in the fraction of myosin heads in the strong-binding structural state, such that there are fewer myosin-actin interactions capable of generating force. Thus mechanisms that decrease or interrupt the interaction of myosin and actin are likely to explain the age-related reduction in force-generating capacity. This presentation will describe two potential mechanisms that could contribute to the decrease in force-generating interactions of myosin and actin. The first mechanism posits that there is a change in stoichiometry between myosin and actin. Since force generation depends on the interaction of myosin heads with actin molecules, maintaining optimal stoichiometry between myosin and actin is essential. The second mechanism that may play a role in the age-related decline in force generation is oxidative damage to myofibrillar proteins. Evidence to support these two potential mechanisms will be discussed in respect to the

fiber-type composition of the muscle and the lifespan of the rat.

### S37

#### **IMPACT OF AGING ON SKELETAL MUSCLE MITOCHONDRIAL FUNCTION AND THE ROLE OF OXIDATIVE STRESS.**

Russ Hepple, University of Calgary. **Source of Research Funds:** Support provided by CIHR and AHFMR.

A decline in skeletal muscle aerobic capacity occurs with aging. Although a reduction in mitochondrial content secondary to lower levels of habitual physical activity could contribute to this occurrence, there are also functional changes in the mitochondria, some of which implicate the involvement of oxidative damage. For example, mitochondria isolated from aged rodent and human muscles exhibit higher levels of ROS production. Recent studies examining rat muscles contracting in situ and non-invasive imaging studies in human muscle suggest a reduced coupling efficiency in aged mitochondria. The oxidative capacity per volume of mitochondria declines with aging, as demonstrated by reductions in mitochondrial enzyme activity without corresponding reductions in mitochondrial volume or enzyme protein content. Similarly, there are disproportionate changes in different mitochondrial enzymes with aging, with complex IV of the electron transport chain demonstrating larger declines than other enzymes. Not only is this latter event seen at the whole muscle level, but it is also manifest at the cellular level in situ where some myocyte profiles exhibit a relative lack of complex IV activity. Although mtDNA damage increases with aging in skeletal muscle, changes in mtDNA deletion loads do not appear to correlate with functional changes in enzyme activities at the whole muscle level. On the other hand, mtDNA damage at the single myocyte level may be linked to phenotypic changes such as complex IV deficiency and segmental myocyte atrophy. The extent to which this contributes to age-related muscle atrophy remains unclear. Mitochondrial enzymes, particularly those with iron-sulfur centers, accumulate oxidative damage with aging, which may contribute to some of the functional changes observed in aged mitochondria. This and other changes in mitochondria (e.g., increased ROS generation) may be related to a decline in mitochondrial protein turnover with aging that appears to be related to a declining drive on mitochondrial biogenesis. Importantly, although many lines of evidence are consistent with a role for oxidative stress in aged skeletal muscle, the extent to which these are causes versus outcomes of functional changes in aged mitochondria requires further study.

### S38

#### **MITOCHONDRIAL IRON ACCUMULATION WITH AGE AND FUNCTIONAL CONSEQUENCES.**

A.Y. Seo, J. Xu, S. Servais, T. Hofer, E. Marzetti, S.E. Wohlgemuth, M.D. Knutson, H.Y. Chung, and C. Leeuwenburg, University of Florida, FL., USA. **Source of Research Funds:** National Institute of Health to CL (AG17994 and AG21042) and a University of Florida Claude D. Pepper Older Americans Independence Center NIH grant (1 P30 AG028740).

Mitochondrial dysfunction, oxidative stress and apoptotic cell death are fundamental mechanisms that drive mammalian aging. Iron (Fe) mediated redox chemistry is particularly important because of its role in mitochondrial oxidative phosphorylation and other life-sustaining functions. Perturbation of mitochondrial Fe homeostasis causes a decline in mitochondrial function and plays a significant role in various neuromuscular degenerative diseases, as well as age-related tissue dysfunction. Hence, we investigated whether non-heme Fe accumulates in mitochondria with advancing age and furthermore, whether Fe overload causes mitochondrial oxidative damage and mitochondrial dysfunction. Specifically, our study investigated whether non-heme Fe levels increased over the course of aging in the quadriceps muscle interfibrillar mitochondria (IFM) and subsarcolemmal mitochondria (SSM) of Fischer 344 x Brown Norway rats. We also assessed mitochondrial susceptibility to apoptosis by measuring mitochondrial permeability transition pore (mPTP) openings and mitochondrial RNA oxidative damage. Furthermore, we investigated whether perturbation of mitochondrial Fe homeostasis differs between post-mitotic myofibers and mitotically active tissue, such as that found in the liver. This study made several significant and novel findings. In particular, we determined for the first time that (i) non-heme Fe levels increase significantly with advancing age in mitochondria (IFM and SSM) of quadriceps muscle and liver tissue; (ii) levels of mitochondrial RNA oxidation increase during the aging process and correlate with mitochondrial levels of non-heme Fe; (iii) mitochondrial Fe is associated with an increased susceptibility of mPTP opening, possibly via the increased oxidative damage that occurs in mitochondria with age; and (iv) significant biochemical and physiological differences exist between skeletal muscle mitochondrial subpopulations (IFM and SSM), in terms of trace metal handling and functional parameters. Our study provides new insights into the role of mitochondrial Fe dyshomeostasis in cellular aging. Our findings also suggest that mitochondrial non-heme Fe represents a potential novel target for targeted interventions to slow aging.

## SYMPOSIUM 10: Physical Activity Guidelines for Canadian Older Adults

S39

### PHYSICAL ACTIVITY MEASUREMENT AND GUIDELINES PROJECT – AN OVERVIEW.

Mark S. Tremblay, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON.

**Source of Research Funds:** Public Health Agency of Canada.

The purpose of this session is to describe Canada's physical activity guidelines project. The public health challenge of physical inactivity is immense and exacerbated by mixed messages regarding how much physical activity is required to preserve and promote health. In 2006 the Canadian Society for Exercise Physiology, in partnership with the Public Health Agency of Canada, initiated a project to examine the research evidence informing physical activity guidelines for Canadians to determine if the existing physical activity guidelines are appropriate and evidence-informed. Fourteen background papers were prepared, including ones targeting older adults. This session aims to describe Canada's physical activity guidelines project and present current evidence informing physical activity recommendations for older adults. Future work of this project will also be discussed.

S40

### PHYSICAL ACTIVITY GUIDELINES FOR OLDER ADULTS: RECOMMENDATION FOR AEROBIC EXERCISE.

Donald H. Paterson, School of Kinesiology, and Canadian Centre for Activity and Aging, University of Western Ontario. **Source of Research Funds:** NSERC.

The purpose is to present an analysis of the epidemiological and experimental research that contributes to evidence-informed recommendations for physical activity for healthy, community-dwelling, older adults (>65 years), and determine the amounts and types of physical activity or purposeful aerobic exercise needed to prevent disease, promote health and maintain function and independence into older age. Data indicating that cardiovascular fitness declines with aging provide evidence that by the mid-70s fitness approaches the threshold for functional daily activities and functional limitations may be consequent to the low aerobic fitness of older adults. A longitudinal 8-year follow-up study of independent-living older adults showed that indeed a lower cardiorespiratory fitness was significantly associated with an increased odds ratio for becoming dependent. Analysis of epidemiological data of the relationship of higher cardiorespiratory fitness and/or

physical activity levels with decreased morbidity (chronic disease) and all-cause mortality shows that the dose and types of physical activity to reduce health risk equate to moderate to moderately vigorous, sustained (>10 min) activities with a duration and frequency to expend 4200 kJ (1000 kcal) per week. For the average older adult this aerobic exercise prescription could be achieved by brisk (or vigorous) walking for 30 minutes or more, 4 to 5 times per week. Adoption of this recommendation would reduce the risk of morbidity and of loss of independence by 30 to 50%. The improved cardiorespiratory fitness would translate into prevention of disease, compression of morbidity and maintenance of function and independence into older age.

S41

### AGING, PHYSICAL ACTIVITY AND HEALTH: MUSCULAR AND OTHER FACTORS.

Gareth Jones, School of Occupational Therapy, Elborn College, London, ON

Abstract not available.

## CAANCB AWARDS LECTURES

## CAANCB M Barr Award Lecture

**AL1  
GENE ENVIRONMENT INTERACTIONS IN TYPE 2  
DIABETES: OF CARBOXYPEPTIDASES, CALCIUM  
AND CALPAINS.**

James D. Johnson, Department of Cellular & Physiological Sciences, University of British Columbia. **Source of Research Funds:** CIHR, CDA, NSERC, JDRF, MSFHR, SC.

Obesity is a principal risk factor for type 2 diabetes and elevated fatty acids reduce  $\beta$ -cell function and survival. An unbiased proteomic screen was used to identify targets of palmitate in  $\beta$ -cell death. The most significantly altered protein in both human islets and MIN6  $\beta$ -cells treated with palmitate was carboxypeptidase E (CPE). Palmitate reduced CPE protein levels within 2 hours, preceding ER-stress and cell death, by a mechanism involving CPE translocation to Golgi and lysosomal degradation. Palmitate metabolism and  $\text{Ca}^{2+}$  flux were also required for CPE proteolysis and  $\beta$ -cell death. CPE null islets had increased apoptosis *in vivo* and *in vitro*. Reducing CPE by ~30% using shRNA also increased ER-stress and apoptosis. Conversely, over-expression of CPE partially rescued  $\beta$ -cells from palmitate-induced ER-stress and apoptosis. Thus, carboxypeptidase E degradation contributes to palmitate-induced  $\beta$ -cell ER-stress and apoptosis. CPE is a novel link between hyperlipidemia and  $\beta$ -cell death pathways in diabetes. Current studies are focused on elucidating the protease(s) involved in CPE degradation. One candidate is calpain-10, a type 2 diabetes susceptibility gene that is partially required for apoptosis induced by the fatty acid palmitate.

## CAANCB JCB Grant Award Lecture

**AL2  
THIRSTY BUSINESS: CELL, REGION AND  
MEMBRANE SPECIFICITY OF AQUAPORINS IN  
THE EFFERENT DUCTS AND EPIDIDYMIS OF  
RATS.**

Louis Hermo<sup>1</sup>, Craig A. Mandato<sup>1</sup> and Charles E. Smith<sup>2</sup>,  
<sup>1</sup>Department of Anatomy and Cell Biology, McGill University and <sup>2</sup>Université de Montréal, Department de Stomatologie, Montreal, QC. **Source of Research Funds:** CIHR.

Water moves across lipid bilayers of plasma membranes in mammalian cells through hydrophilic pores created by integral membrane proteins called aquaporins (AQPs). These proteins are essential for regulation of cell volume, transepithelial water transport and whole body homeostasis. AQPs are a family of 13 small proteins (25-34 kDa) that assemble as homotetramers, with each monomer being composed of six  $\alpha$ -helical domains that enclose a central pore which allows the bidirectional movement of water. Water content within the efferent ducts (EDs) and epididymis of the male reproductive tract is stringently regulated in order to promote sperm concentration and maturation. In this study we explored AQP expression by RT-PCR and LM immunolocalizations using peroxidase and wide-field fluorescence techniques. RT-PCR data revealed that the adult EDs expressed AQP 1, 7, and 9, while the epididymis expressed AQP 1, 3, 5, 7, and 9. In the EDs, by light microscope immunocytochemistry, AQP 1 was localized to microvilli and basolateral plasma membranes of epithelial nonciliated cells and cilia of ciliated cells, while AQP 9 localized to microvilli of nonciliated cells only. AQP 7 was present on sperm and myoid cells. In the epididymis, AQP 9 stained microvilli of principal cells of all regions, with highest intensity in the initial segment and cauda regions, while AQP 11 localized mainly on microvilli of principal cells of more distal regions. AQP 7 was expressed primarily to lateral plasma membranes of principal cells of the caput region, while a basal reaction was noted in more distal regions. AQP 5 was also expressed in distal regions but was associated with endosomes of principal cells, while AQP 3 was present in basal cells of all epididymal regions. Additionally, AQP 7 and 11 were expressed by some basal cells, AQP 7 and 9 in some clear cells and AQP 7 and 11 in some halo cells. Functional experiments revealed that AQP 1 and 9 in epithelial cells of the EDs were not regulated by testosterone, while principal cells of the initial segment were dependent in part on testosterone and a lumicrine testicular factor for AQP 9 expression, as was AQP 3 expression in basal cells. These findings indicate unique associations of AQPs with specific membrane domains in a cell type and region specific manner within the EDs and epididymis of adult animals, in addition to complex regulation patterns.