Orientation, "Fatiguability"

Taffet & Alexander
9/3/2008
6:00-6:15PM

Speaker Information
George E. Taffet, MD serves as Chief of Geriatrics Section at Baylor College of Medicine. Neil Alexander, MD serves as a Professor & Director at Ann Arbor VA GRECC & the University of Michigan. Both Drs. Taffet & Alexander served on the Planning Committee for *Idiopathic Fatigue of Aging*. Dr. Taffet is a member of the AGS Research Committee.

Talk Summary
This talk will welcome all participants to the conference and give a brief orientation on "Fatiguability".

Highlights of Previous Exploratory Conf, Challenges of Research in the Field, Domains of Study, Why Focus on Energy Balance

Nayfield & Eldadah
9/3/2008
6:15-6:35PM

Speaker Information
Susan Nayfield, MD, MSc if Chief of the Geriatrics Branch at the Division of Geriatrics and Clinical Gerontology at the NIA. Basil Eldadah, MD, PhD is a program officer at the NIA. Both Drs. Nayfield & Eldadah served on the Planning Committee for *Idiopathic Fatigue of Aging*.

Key Presentation Slides attached – See page 24.

Talk Summary
Unexplained Fatigue in the Elderly: A summary from the NIA exploratory workshop

Fatigue is a significant complaint among older adults associated with diminished activity, increased co-morbidity, and greater mortality. In recognition of the need for further research on this topic, the National Institute on Aging sponsored an exploratory workshop in June, 2007, in Bethesda, Maryland, entitled, "Unexplained Fatigue in the Elderly." This 2-day meeting drew over 70 scientists from a broad range of basic and clinical backgrounds at academic institutions, the NIH, and the FDA. The purpose of the workshop was to explore the current state of understanding of fatigue epidemiology, measurement, mechanisms, and interventions, and to identify knowledge gaps and opportunities for further research of fatigue in older adults. This presentation will give an overview of the workshop, highlighting key data and relevant discussion points.

Key References
A summary of the NIA exploratory workshop can be found on the NIA website at: http://www.nia.nih.gov/ResearchInformation/ConferencesAndMeetings/UnexplainedFatigue.htm

Dynamics of Energy Balance and Use and Relation to Fatigue

Ferrucci
9/3/2008
6:35-6:55PM

&

Gender, Body Comp, Diet, PA and Energy Balance

Ferrucci
9/4/2008
9:00-9:30AM

Speaker Information
Luigi Ferrucci, MD, PhD is Chief of Longitudinal Studies Section at CRB/NIA/NIH. Dr. Ferrucci served on the Planning Committee for *Idiopathic Fatigue of Aging*. He is currently a member of the AGS Research Committee.

Thyroid and Energy Expenditure

Celi
9/4/2008
9:30-10:00AM

Speaker Information
Francesco S. Celi, M.D. serves as Staff Clinician at the NIDDK, NIH in Bethesda, MD.

Key Presentation Slides attached – See page 30.

Talk Summary
Thyroid hormone action plays an important role in the modulation of energy expenditure and substrate utilization. This is particularly evident in case of overt pathological conditions such as florid hypo- or hyperthyroidism. While small studies indicate that the subclinical thyroid dysfunction (either hypo- or hyperthyroidism) is associated with measurable changes in energy metabolism parameters, large studies do not corroborate these findings. This presentation will be focused on the role of the local, tissue-specific thyroid hormone metabolism in the modulation of energy and substrate metabolism. The presentation will also address some of the technical aspects of clinical research as they apply to the study of thyroid hormone axis pathophysiology.

Key References
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GLUT1 and GLUT4 glucose transporter proteins. J Endocrinol 164:187–195.

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Relationship Between Maximal and Submaximal Oxygen Use and Self-Reported Fatigue

Alexander
9/4/2008
10:00AM-10:30AM

Speaker Information
Neil Alexander, MD serves as a Professor & Director at Ann Arbor VA GRECC & the University of Michigan. Dr. Alexander served on the Planning Committee for *Idiopathic Fatigue of Aging*.

Key Presentation Slides attached – See page 34.

Talk Summary
How does self-reported fatigue change through the day and how does it relate to specific tasks that require varying amounts of aerobic demand? How does daily fatigue relate to important confounders such as pain, and important outcomes such as physical activity and functional mobility? In Part I of this presentation, older women with leg osteoarthritis (OA) have greater increases in momentary fatigue throughout the day than pain, and this fatigue associates with decreased physical activity. In a subsequent four week controlled intervention and compared to controls, women with OA participating in a group exercise plus activity strategy training designed to reduce individual barriers to PA and improve symptom control had greater improvements in pain, fatigue, and physical activity. In Part II of this presentation, measures of submaximal oxygen kinetics correlate as highly with functional mobility performance as peak oxygen uptake (VO2) measures, particularly for impaired old during post-exercise recovery. This suggests that submaximal test VO2 kinetics may be more useful than maximal test VO2 in estimating the contribution of aerobic function to mobility impairment. In a subsequent group of relatively functional older adult Type 2 diabetics undergoing maximal and submaximal tests: 1) peak VO2 and post-task fatigue increase with task demand; 2) self-reported task-specific fatigue is not related to general fatigue; 3) submaximal task-related fatigue may better relate to usual mobility function; and 4) task specific self-reported fatigue relates more to submaximal VO2 kinetics than peak VO2.

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What Does Evidence About Energy Consumption and Mitochondrial Function With Exercise Have to Do With Fatigue of Aging

Taffet & Hadley
9/4/2008
10:30AM-11:30AM

Speaker Information
George E. Taffet, MD serves as Chief of Geriatrics Section at Baylor College of Medicine. Dr. Taffet served on the Planning Committee for *Idiopathic Fatigue of Aging*, and is a member of the AGS Research Committee. Evan Hadley, MD is Director of Geriatrics & Clinical Gerontology at the NIA. Dr. Hadley is currently serving as the NIA liaison to the AGS Research Committee.

Key Presentation Slides attached – See page 40.

Talk Summary
This talk will briefly examine four issues important to considering idiopathic fatigue in the elderly; definitions, ergoreceptors, AMP-activated kinase, and mitochondrial diseases. The broad range of definitions including questionably associated symptoms and lack of integration of effort will be discussed. If the definition of fatigue requires work to be done, then the ergoreceptors are critical to an appreciation of what muscle is doing and how it is signaling back to the CNS. In heart failure, where fatigue is frequently seen, the mechanosensitive ergoreceptors may be oversensitive, perhaps increasing the patient's perception of effort. If the fatigue definition does not require external work, then the entire energy requirements of the patient are important. AMP-activated protein kinase functions as the cellular energy sensor and stimulates changes that can provide more substrate for energy production. The role of this pivotal protein in fatigue is uncertain, but agents that stimulate it may be therapeutic.

Finally, most of the energy available to a muscle is produced in the mitochondria. In mitochondrial mutation diseases, exercise intolerance is frequently, but not uniformly seen. Nevertheless, one potential barrier to energy production in the absence of such mutations is inability to use fatty acids due to levo-carnitine deficiency. The role of carnitine supplementation will be mentioned. Older people may sense fatigue as a final common pathway manifestation of many underlying processes, however progress will be hampered by a lack of uniformity in its definition.

The concept of fatigability (the degree of fatigue resulting from given amount of activity) is useful for understanding relationships between fatigue, function, and quality of life. Increased fatigability with age may contribute to retirement, decreased physical activity and disabilities, because individuals seek to limit their degree of fatigue to tolerable levels. Fatigability can contribute both to increases in fatigue over the course of the day, and to slowing of activities at any time of the day, both of which cause limitations in activity. Tools such as ecological momentary assessment can increase understanding of such relationships. Instruments that assess persons' capacities for doing all the activities that they need and wish to do over the course of a day could be useful for assessing the benefits of interventions to decrease fatigability.

Key References

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A Mitochondrial Paradigm for Metabolic and Degenerative Disease, Cancer and Aging: Why Do We Still Have a Mitochondrial DNA?

Wallace

9/4/2008

1:00PM-1:30PM

Speaker Information

Douglas C. Wallace, PhD is a Donal Bren Professor of Molecular Medicine and Director at the Center for Molecular and Mitochondrial Medicine and Genetics (MAMMAG) at the University of California, Urvine.

Talk Summary

The human cell is assembled from two different organisms: the nucleo-cytosol organism which specializes in cellular and tissue structure and whose genes are Mendelian and the mitochondrial organism which specializes in energy and whose genes are maternal and stochastic. Inherited pathogenic mitochondrial DNA (mtDNA) mutations have been linked to a wide range of metabolic and degenerative diseases. Somatic mtDNA mutations accumulate with age in a broad spectrum of organisms, introduction of catalase into the mouse mitochondrial matrix reduces the mtDNA somatic mutation rate and extends life span, increasing *Drosophila* cAMP levels reduces mitochondrial reactive oxygen species (ROS) and extends life span, and treating short-lived *Drosophila* mutants with mitochondrially-targeted antioxidants can restore the life span. Ancient adaptive mtDNA polymorphisms have been associated with altered risk for metabolic and neurodegenerative diseases, such as Parkinson disease, and somatic mtDNA mutations are elevated in the brains of Alzheimer Disease patients. Finally, both germline and somatic mtDNA mutations are associated with various cancers including prostate cancer. Therefore, diseases which appear "complex" when viewed exclusively from the nucleo-cytosol perspective might be more readily understood if the contribution of the mitochondrial organism were also considered.

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Mitochondrial Dysfunction and Muscle

Goodpaster
9/4/2008
1:30PM-2:00PM

Speaker Information
Bret H. Goodpaster, PhD is an Associate Professor of Medicine at the University of Pittsburgh.

Key Presentation Slides attached – See page 49.

Talk Summary
Aging is associated with higher rates of mitochondrial DNA mutations, diminished mitochondrial content or function within skeletal muscle. Diminished skeletal muscle function and higher prevalence of metabolic disturbances are also characteristic of aging. However, it is unclear whether or not defects in muscle mitochondria are mechanistically linked with poor muscle function, and in particular the fatigability of muscle, in aging. Physical activity and calorie restriction have been demonstrated to improve mitochondrial content and function, improve metabolic regulation and enhance muscle function. The degree to which diminished physical activity and excess adiposity contribute to these so-called 'aging' effects has not been firmly established. Several key questions remain that, if addressed, could shed important light on the role of mitochondria in age-related fatigue. For example, is there a mechanistic link between skeletal muscle mitochondria and fatigue? If so, can the known responsiveness of mitochondria to interventions be related to improve functional outcomes in older men and women, including greater resistance to fatigue?

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Neural and Muscular Factors in Muscle Fatigue of Older Adults

Kent-Braun
9/4/2008
2:00PM-2:30PM

Speaker Information
Jane Kent-Braun, PhD is a Professor of Kinesiology at the University of Massachusetts, Amherst.

Key Presentation Slides attached – See page 56.

Talk Summary
The decrease in force or power production that occurs during muscular contractions is referred to as muscle fatigue. This form of fatigue is readily quantifiable in humans, and its causes can be neural or intramuscular. Many studies have shown that older adults fatigue relatively less than young adults, although this is not always the case. Recent work indicates that the primary mechanism of this age-related fatigue resistance is a difference in intramuscular energy metabolism. We hypothesize that chronic changes in neural activation and contractile function combine to confer an advantage on the part of older muscle in terms of fatigue resistance under some conditions. The implications of this age-related fatigue resistance and the conditions under which it may be lost will be discussed.

Key References
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McNeil & Rice, J Gerontol 2007

Central Fatigue – the Serotonin Hypothesis and Beyond

Meeusen
9/4/2008
3:30PM-4:00PM

Speaker Information
Romain Meeusen, PhD is a Professor at Vrije Universiteit Brussel Dept. Human Physiology & Sports Medicine is Brussels, Belgium.

Key Presentation Slides attached – See page 57.

Talk Summary
The original central fatigue hypothesis suggested that an exercise-induced increase in extracellular serotonin (5-HT) concentrations in several brain regions contributed to the development of fatigue during prolonged exercise. Serotonin has been linked to fatigue because of its well-known effects on sleep, lethargy and drowsiness and loss of motivation. Several nutritional and pharmacological studies have attempted to manipulate central serotonergic activity during exercise, but this work has yet to provide robust evidence for a significant role of 5-HT in the fatigue process.

However, it is important to note that brain function is not determined by a single neurotransmitter system and the interaction between brain 5-HT and dopamine during prolonged exercise has also been explored as having a regulative role in the development of fatigue. This revised central fatigue hypothesis suggests that an increase in central ratio of 5-HT to DA is associated with feelings of tiredness and lethargy, accelerating the onset of fatigue, whereas a low ratio favors improved performance through the maintenance of motivation and arousal.

Convincing evidence for a role of dopamine in the development of fatigue comes from work investigating the physiological responses to amphetamine use, but other strategies to manipulate central catecholamines have yet to influence exercise capacity during exercise in temperate conditions. Recent findings have, however, provided support for a significant role of dopamine and noradrenaline in performance during exercise in the heat. As serotonergic and catecholaminergic projections innervate areas of the hypothalamus, the thermoregulatory centre, a change in the activity of these neurons may be expected to contribute to the control of body temperature whilst at rest and during exercise. Fatigue during prolonged exercise clearly is influenced by a complex interaction between peripheral and central factors.

Reference:
Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF. Central Fatigue – the serotonin hypothesis and beyond. Sports Med. 36(10): 881-909, 2006

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Hasegawa H, Meeusen R, Takatsu S, Yamasaki M. Exercise Performance in the heat – possible brain mechanisms and thermoregulatory strategies. *Adv. Exerc. Sports Physiol.* 13(4): 81-92, 2008

Hasegawa H, Piacentini M, Sarre S, Michotte Y, Ishiwata T, Meeusen R. Effect of a dopamine/ noradrenaline reuptake inhibitior on exercise performance and thermoregulation of the rat in a warm environment. J Physiol 586: 141-149, 2008

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From Inflammation to Sickness, Depression and Fatigue

Dantzer
9/4/2008
4:00PM-4:30PM

Speaker Information
Dr. Robert Dantzer is a Professor of Psychoneuroimmunology in the Integrative Immunology and Behavior Program at the University of Illinois at Urbana-Champaign.

Key Presentation Slides attached – See page 58.

Talk Summary
Activation of the peripheral innate immune system by microbial pathogens induces a normally reversible synthesis and release of proinflammatory cytokines by microglia and brain macrophages. This takes place via several immune-to-brain communication pathways including the sensory innervation of the site of the body in which the inflammation takes place. This local production of cytokines leads to a reorganization of the organism priorities so as to fight more efficiently microbial pathogens. The behavioral component of this response is termed “sickness behavior” and includes components of fatigue and loss of energy.

Intense and/or prolonged activation of the innate immune system induces depression in vulnerable individuals. Inflammation-associated depression is characterized by a predominance of neurovegetative symptoms including fatigue and loss of energy over psychological symptoms. Inflammation-associated depression is caused at least in part by immune activation of the tryptophan degrading enzyme indoleamine 2,3 dioxygenase. This results in the decreased availability of tryptophan for the synthesis of serotonin and the production of tryptophan metabolites acting on NMDA receptors. Fatigue induced by interferon-alpha in humans is associated with hypermetabolism of basal ganglia that probably reflects decreased dopaminergic neurotransmission.

Sensitization or “priming” of microglia can occur under several conditions including aging. Macrophages and microglia of aged subjects produce more proinflammatory cytokines and less anti-inflammatory cytokines both spontaneously and in response to immune stimulation. This makes aged subjects more at risk for developing more intense symptoms of depression and fatigue.

Supported by NIH grants to RD (R01 MH 71349 and R01 MH 079829), KWK (R01 AG 029573) and post-doctoral training grant to JCO (T32 DK59802-01).

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Oxidative Stress and Muscle Fatigue

Andrade
9/4/2008
4:30PM-5:00PM

Speaker Information
Francisco H Andrade, PhD is an Associate Professor of Physiology at the University of Kentucky.

Key Presentation Slides attached – See page 60.

Talk Summary
Intrinsic muscle fatigue is the reversible decline in muscle performance not explained by changes in neural drive or neuromuscular transmission. Intense muscle activity is associated with increased production of reactive oxygen species and oxidative stress. In turn, the cellular targets of reactive oxygen generated during exercise are key factors that limit muscle performance. While the link between oxidative stress and fatigue is robust, we still have significant gaps in our understanding of the cellular sources of reactive oxygen species, the mechanisms by which they influence muscle function, and their potential role in muscle adaptation.

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Congestive Heart Failure, Oxygen Utilization, and Muscle NMR

Mancini
9/5/2008
8:00AM-8:30 AM

Speaker Information
Donna Mancini, MD is a Professor of Medicine at Columbia University in New York, NY.

HIV

Gerschenson
9/5/2008
8:30AM-9:00AM

Speaker Information
Mariana Gerschenson, PhD is Associate Professor, Department of Medicine and Director of the Molecular Medicine and Infectious Diseases Laboratory at Hawaii AIDS Clinical Research Program at the University of Hawaii at Manoa.

Fatigue and Cancer Treatment: A Model for Studying Fatigue

Cleeland
9/5/2008
9:00AM–9:30AM

Speaker Information
Charles S. Cleeland, PhD, is Chair of the Department of Symptom Research at U.T. M.D. Anderson Cancer Center, in Houston, TX.

Key Presentation Slides attached – See page 61.

Talk Summary
Fatigue is endemic in patients with cancer. For many, it is the first sign of cancer leading to diagnosis. Fatigue is one of the most distressing symptoms of late stage cancer. Fatigue is also associated with the treatment of cancer, due to the toxicities of cancer therapy. Treatment-related fatigue can become so severe that patients may choose to discontinue therapy, or therapy may be delayed, reducing the total dose of therapy administered. Depending on the type of cancer and the treatment used, the trajectory of fatigue related to treatment is relatively predictable. This presents the opportunity to explore the mechanistic basis of fatigue as well as the effectiveness of potential fatigue interventions. For example, there is increasing evidence that deregulation of inflammation produced by cancer treatment may play a role in the development of fatigue. Longitudinal studies of changes in fatigue level and in underlying biology produced by cancer treatment may provide information on this and other hypotheses about the development of fatigue. The use of newer investigational techniques, such as neuroimmaging, would enhance these investigations. It would also worth the effort to develop animal models of treatment-related fatigue as a pre-clinical framework for exploring fatigue mechanisms and potential methods of reducing fatigue.

Sleep and Energy Balance

Zee
9/5/2008
9:30AM-10:00AM

Speaker Information
Phyllis C Zee, MD, PhD is Professor of Neurology & Director of the Sleep Center at Northwestern University Feinberg School of Medicine.

Key Presentation Slides attached – See page 67.

Talk Summary
Sleep disturbances, whether due to voluntary sleep curtailment, sleep disorders, or medical illnesses are pervasive throughout our modern society. Recent research demonstrates that sleep, like feeding and physical activity plays an important role in regulating energy balance. Experimental sleep deprivation results in alterations in the neuroendocrine regulation of appetite, glucose metabolism, autonomic function and inflammation. Furthermore, epidemiological studies have consistently demonstrated an association between short sleep duration and increased risk of obesity and diabetes. Interestingly, this trend towards shorter sleep duration has occurred in parallel with the dramatic increase in the prevalence of obesity.

Older adults are at particular risk for sleep loss and sleep disorders which likely contribute to the high prevalence of symptoms of fatigue and sleepiness. One of the hallmarks of sleep in older adults is the increase in sleep fragmentation and decline in slow wave sleep. Studies have shown that physical higher physical activity levels are associated with better sleep quality. Our data indicate that increasing physical activity in older adults improves objective and subjective sleep quality, ratings of vigor and affect, as well as overall vitality. Together, the available evidence indicates that sleep is integrally involved in metabolism and energy conservation.

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Fatigue measurement approaches, NIH PROMIS initiative

Butt
9/5/2008
11:30AM-12:00PM

Speaker Information
Zeeshan Butt, PhD is a Research Scientist at the Center on Outcomes, Research, and Education (CORE) and a Research Assistant Professor at Northwestern University Feinberg School of Medicine.

Key Presentation Slides attached – See page 69.

Talk Summary
Fatigue is a clinically important, but non-specific symptom present across a number of chronic illnesses and health conditions. Patients may describe their experience of fatigue in terms of being exhausted, tired, weak, or slowed. Given the subjective nature of fatigue, self-report may be the best assessment method, and while there are a number of validated instruments available to assess fatigue, there is no gold-standard. Many existing instruments assess fatigue as a multi-dimensional concept, parsing the symptom in terms of its temporal characteristics, severity, and impact, for example. However, from a measurement perspective, data suggests that fatigue is sufficiently unidimensional for the application modern measurement theory, such as item response theory (IRT). The NIH Patient-Reported Outcomes Measurement Information System (PROMIS; http://www.nihpromis.org) Roadmap initiative is a 5-year cooperative group program designed to develop, validate, and standardize IRT-informed item banks to measure patient-reported outcomes that are relevant across common medical conditions. PROMIS allows for flexible assessment of fatigue with use of psychometrically robust short forms and computerized adaptive testing, while allowing cross-walk to legacy instruments.

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Performance measures related to energy expenditure and physical activity

Chen
9/5/2008
12:00PM-12:30PM

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Key Presentation Slides attached – See page 74.

Talk Summary
Energy expenditure and physical activity are increasing being used as clinical outcome and/or exposure measures in nutritional studies. It is important to ascertain these measurements accurately because there is individual variability which may be clinically relevant. This presentation intends to discuss the current technologies in assessing energy expenditure and physical activity measurements in humans, both under laboratory and free-living environments. Indirect calorimeters (carts, portable units, and whole-room respiratory chambers), doubly-labeled water, and portable activity monitors will be presented.

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