

CR VI at GSA

Atlanta Marriott Marquis and Hilton Atlanta • November 20-21 2009



The Calorie Restriction Society is a nonprofit organization committed to supporting the science and practice of calorie restriction to promote health and longevity.

Visit us at www.calorierestriction.org.

CR VI organized and produced by Robert Krikorian and David Stern



62nd ANNUAL SCIENTIFIC MEETING

Hilton Atlanta and Atlanta Marriott Marquis

LETTER FROM THE PRESIDENT

Dear Colleagues,

CR VI, the sixth meeting of the CR Society, is upon us. Our conference program for this meeting is integrated with the 62nd Annual Scientific Meeting of the Gerontological Society of America. The theme of this year's GSA meeting is "Creative Approaches to Healthy Aging."

We are extremely pleased and excited about the partnership with GSA. We believe this will be a mutually beneficial arrangement that offers CR Society members access to the latest science on aging, and provides GSA members with a view of the science and human practice of calorie restriction that is not available anywhere else in the world. There will be numerous symposia that focus on the latest research into the mechanisms underlying the processes of aging and age-associated diseases. The work that will be discussed provides the foundation on which to build strategies for maintaining the health and vitality of people as they age. In addition to the CR-specific program, topics to be covered include the pathobiology of Alzheimer-type dementias; comparative perspectives on aging and life history evolution; nutrition intervention, aging, and cancer; anti-aging medicines; evolutionary biogerontology of slow aging and negligible senescence; genome and epigenome instability in aging; immune deficiency in aging; protein alterations in aging and aging disease; and contemporary approaches to biogerontology.

The meeting will also feature the increasingly popular Late Breaker Poster session, which allows for rapid dissemination of the latest research findings. These posters reflect abstracts submitted as recently as one month prior to the conference. They will be on display in the Exhibit Hall.

Please enjoy your time at the conference and in Atlanta.

Sincerely,



Brian Manning Delaney
President, CR Society

Friday, November 20

CR Session I
1:30 pm – 3:00 pm
Grand Salon A (Hilton)

Richard Miller

Professor of Pathology, University of Michigan School of Medicine

Associate Director for Research, Geriatrics Center, University of Michigan

Two new systems for lifespan extension by dietary manipulation in mice

Caloric restriction (CR) is the most famous nutritional intervention that extends lifespan in mammals, but it is not the only one that works. In 1993 Zimmerman, Orentreich and their colleagues discovered that rats on low methionine diets showed a lifespan increase of about 40%, which could not be attributed to diminished caloric intake. Like rats, mice on low methionine diets also show significant extension of maximum lifespan, and new data show that this effect can be seen even if the low-methionine diet is initiated at 12 months of age. These "Meth-R" mice are similar to CR mice in some ways (smaller size, low glucose and low insulin, low levels of IGF-I and thyroid hormones, postponement of many aspects of aging, and liver resistance to acetaminophen damage), but differ in many respects. For example, CR mice, but not Meth-R mice, are very lean, show many changes in liver gene expression not seen in Meth-R animals, have high levels of activation of the stress kinases p38 and Erk, and have low levels of activation of the TOR pathway in liver. The time is ripe to explore a range of explanatory models for lifespan extension in Meth-R rodents, including those that emphasize (a) alterations in glutathione metabolism; (b) effects on DNA methylation; (c) changes in translation initiation; and (d) augmentation, by hormesis, of multiple forms of stress resistance.

We have documented a significant effect on maximal lifespan of a brief, but very early, period of nutritional deprivation. In the "crowded litter" (CL) protocol, control mice were members of litters of size 8, and CL pups were raised in litters of size 12, from birth until 3 weeks of age. After weaning, each mouse was housed under standard conditions at the same caging density; thus, the only experimental manipulation was the crowded condition in the first three weeks of life. CL pups, at weaning, were significantly smaller, and had significantly lower IGF-I levels, compared to control animals, but these differences became minimal by 12 weeks of age. Mice of the CL group had an 18% increase in median survival and a significant increase in maximal (i.e. 90th percentile) survival. Thus a brief, very early intervention that reduces food availability leads to lifelong changes in mortality risk. Further work will be needed to determine to what extent the lifespan effects are caused by altered nutrition or instead by other aspects of the CL situation such as psychological responses to stress of crowding or delay in food availability.



Holly Brown-Borg

Department of Pharmacology, Physiology, and Therapeutics
University of North Dakota School of Medicine and Health Sciences

GH status affects metabolic adaptation to short-term calorie restriction

Ames dwarf mice live 49 and 68% longer than their wild type siblings (males and females, respectively). Calorie restriction (CR) further extends the lifespan of both Ames dwarf and wild type mice. We have shown that a deficiency of circulating growth hormone (GH) and reduced insulin-like growth factor 1 (IGF-1) signaling leads to enhanced oxidative defense and stress resistance in dwarf mice in several tissues across the lifespan when compared to age-matched wild type mice. With regard to longevity, reduced GH/IGF-1 signaling is thought to differ mechanistically from calorie restriction. To delineate the potential mechanisms involved, we examined the effects of calorie restriction on specific aspects of metabolism to identify adaptational differences between dwarf and wild type mice. Dwarf and age-matched wild type mice were subjected to every-other-day feeding for six weeks. The restricted animals lost 6 and 10% of their body weight (wild type and dwarf, respectively). Components of antioxidative defense tended to differentially change in wild type as compared with dwarf mice following every other day feeding. For example, liver glutathione peroxidase increased following CR in dwarf mice but decreased in wild type mice. The liver glutathione/glutathione disulfide ratios were lower in both genotypes following CR. In general, mitochondrial enzyme activities were decreased while gene expression was increased following the six-week diet regimen. Expression of PGC-1 α was higher in dwarf versus wild type mice under both fed (43%) and CR (190%) conditions. We have previously shown that methionine metabolism was significantly altered by GH status. Further changes in the expression of this metabolic pathway were also observed following CR in dwarf and wild type animals. Overall, decreasing caloric intake altered a variety of metabolic components in a manner different from a growth hormone –dependent mechanism, suggesting independent mechanisms involved in lifespan extension.

CR Session II

3:30 – 5:00 pm

Grand Salon A (Hilton)

James F. Nelson

Barshop Institute for Longevity and Aging Studies
University of Texas Health Sciences Center

Genetic variation in the longevity response to calorie restriction: From life extension to life shortening

Published but often overlooked data indicate that calorie restriction (CR) does not always extend lifespan in rodents. A systematic, unbiased screen to determine the efficacy of CR across a range of genotypes is lacking. We therefore undertook such a study in 41 recombinant inbred strains of mice. The major finding was that CR

shortened lifespan in some strains, and that the number of strains with shortened lifespans under CR was similar to the number with lengthened life. Strains in which CR shortened lifespan were neither under- nor overweight, nor at extremes of food intake or reproductive potential (i.e., none of these traits correlated with CR survival). CR extended lifespan more frequently in shorter-lived strains than in longer-lived strains, and the maximum lifespan achieved by any strain under CR did not exceed that of the longest lived strains under AL feeding. These results suggest that the mechanisms responsible for long life under CR may be similar to those genetically specified to confer long life in AL fed mice. The observation that CR shortened lifespan more frequently in long-lived strains indicates that traits that raise risk of negative effects of CR are more frequent in long-lived strains. These results reveal that CR can have negative as well as positive effects on lifespan, dependant on genotype. They also raise a cautionary note concerning the application of CR to humans and a critical need for predictors of efficacy.

Donald K. Ingram

Professor, Nutritional Neuroscience and Aging Laboratory
Pennington Biomedical Research Center, Louisiana State University

A convergence of concepts: Diet restriction and diet selection

Diet restriction (DR) has proven to be the most robust means to retard aging as demonstrated in numerous animal models. Reducing intake of a nutritious diet by 20-50% can increase lifespan, reduce incidence and retard onset of chronic diseases, enhance stress protection, and maintain youthful function. Reports of persons who practice DR and clinical studies indicate that such regimens can positively impact indices of health and risk factors for disease. Nonetheless, if evidence existed that DR could produce beneficial effects in humans, implementation would be problematic due to difficulties with compliance and quality of life issues. Diets rich in fruits and vegetables have also been related to enhanced health and longevity in human studies, while animal studies demonstrate anti-aging effects of such diets paralleling those observed in DR. Emerging research on the mechanisms of DR points to “hormesis” which enhances stress protection. An exciting concept creating convergence between DR and diet selection is that plant polyphenols produced in response to stress act as hormetic signals when consumed by animals and activate stress protection through mechanisms similar to DR.

CR Society Dinner

6:30 pm – 8:30 pm

Crystal Ballroom F (Hilton)

Fee: \$60

Join CR Society members for a delicious and nutritious dinner. Tickets are available at the on-site registration desk in the Hilton Atlanta.



Saturday, November 21

CR Session III

10:00 am – 11:30 am

Grand Salon A (Hilton)

Luigi Fontana

Division of Geriatrics and Nutritional Science and Center for Human Nutrition
Washington University School of Medicine

Division of Food Science, Human Nutrition and Health
Istituto Superiore di Sanità

Calorie restriction, endurance exercise, and successful aging

The worldwide prevalence of overweight/obesity and type 2 diabetes has increased markedly over the last several decades. Excessive consumption of nutrient-poor, energy-dense foods, sedentary lifestyle, and subsequent abdominal obesity are associated with impaired function of most organ systems, serious medical diseases, and premature mortality. Weight loss, induced by negative energy balance, simultaneously improves multiple metabolic and hormonal risk factors and decreases mortality rate in obese patients. Furthermore, a reduction in calorie intake below usual ad libitum intake with adequate nutrition has been shown to prevent/delay cardiovascular and cancer mortality and morbidity in rodents and monkeys. Whether or not calorie restriction (CR) increases maximal longevity in humans remains an unanswered question. However, in young and middle-aged healthy individuals CR causes many of the same cardiometabolic adaptations that occur in long-lived CR rodents, including decreased metabolic, hormonal, and inflammatory risk factors for diabetes, hypertension, cardiovascular disease and cancer. Unravelling the mechanisms that link calorie intake and body composition with metabolism and aging will be a major step in understanding the age-dependency of a wide range of human diseases and will contribute to improved quality of life with aging.

Richard D. Feinman

Department of Biochemistry and Family Practice
State University of New York Downstate Medical Center

Restricting calories by restricting carbohydrate

The benefits of carbohydrate-restricted diets (CHORD) derive from the metabolic effects of better glycemic and insulin control as well as from a behavioral component, a spontaneous reduction in consumption. From the metabolic standpoint, CHORDs reliably

reduce all of the markers of metabolic syndrome, many of which are associated with the aging process. Behaviorally, by removing the sense of deprivation that accompanies explicitly low-calorie diets, popular implementations of CHORDs lead to reduced consumption, analogous to the psychological strategy of paradoxical therapy. Several other fail-safe mechanisms are in place that may make CHORD the preferred road to reduction in calories. A common approach to CR is the recommendation of portion control. Rarely accompanied by practical advice, portion control usually means nothing more than self-control, a strategy with a mixed record at best. Low carbohydrate diets allow the option of multiple small portions reducing hunger and allowing some distinction between poor satiety and mindless eating. The convergence of behavioral and metabolic effects is seen in the energy inefficiency described popularly as metabolic advantage providing improved weight loss, calorie-for-calorie. Reduction in energy intake by any method is difficult and, in the worst case scenario, CHORD provides improvements in lipid profile and glycemic control even if no weight is lost. Finally, in an elderly population, adequate protein need not be compromised in obtaining the benefit of reduced calories.

CR Society Lunch

11: 45 am – 1:15 pm

Crystal Ballroom A (Hilton)

Fee: \$40

Join CR Society members for a delicious and nutritious lunch. Tickets are available at the on-site registration desk in the Hilton Atlanta.

CR Session – Scientific Panel: Questions and Discussion

2:30 – 4:00 pm

Grand Salon A (Hilton)

Speakers:

Holly Brown-Borg
Richard Feinman
Luigi Fontana
Donald Ingram
James Nelson

Scientists participating in research pertinent to calorie restriction will take questions from the audience and from each other in an interesting, extended discussion of the mechanisms of CR and its application in humans.

