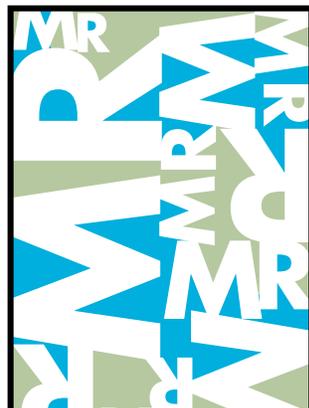


REPORT OF THE DIRECTORS

January 2013

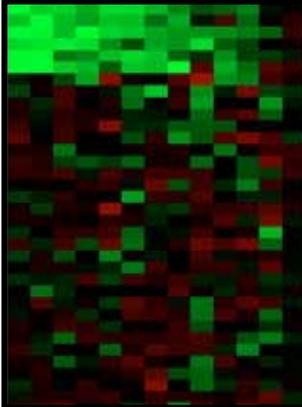


Metabolism

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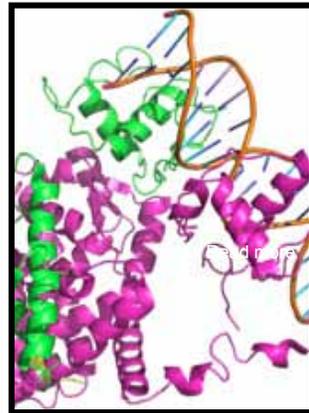
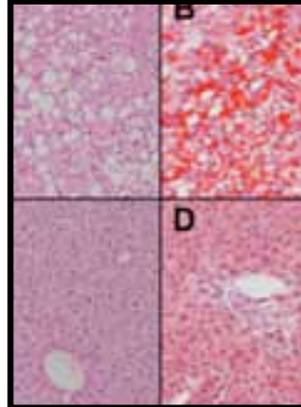


Cysteine

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Bone Density

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Ppar γ

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Message from the Co-Directors



Advances in medical technology and improvements in public health have extended average human lifespan dramatically over the past century. We see the work of this century as being the improvement of those extra years, which are now all too often marred by age-related disorders such as metabolic syndrome X, diabetes, and cardiovascular disease. Over the past two decades, we have investigated dietary restriction of the amino acid methionine as a means not only of extending lifespan but also of preventing or delaying the onset of debilitating conditions so often associated with advancing age.

Genomic and metabolic studies to elucidate the mechanisms by which methionine restriction achieves its effects have constituted a good portion of our most recent studies. We have also examined methionine restriction's effects on specific systems and organs, such as the liver and bones, and its potential utility in breast cancer prevention. Published results of our latest work are summarized below.

2013 stands to be a very exciting year for us. As we enter into our third decade of research on methionine restriction, we will, in collaboration with Penn State University, study the metabolic effects of methionine restriction in humans. We will also collaborate with the National Cheng Kung University (Taiwan) on methionine restriction's effects on bone mineral status, fragility, and remodeling. Also on the horizon are studies to determine the level of immunoprotection conferred by a methionine-restricted diet and investigations designed to selectively deliver its favorable effects.

Norman Orentreich, MD, FACP
David S. Orentreich, MD

Metabolic Adaptations to Methionine Restriction

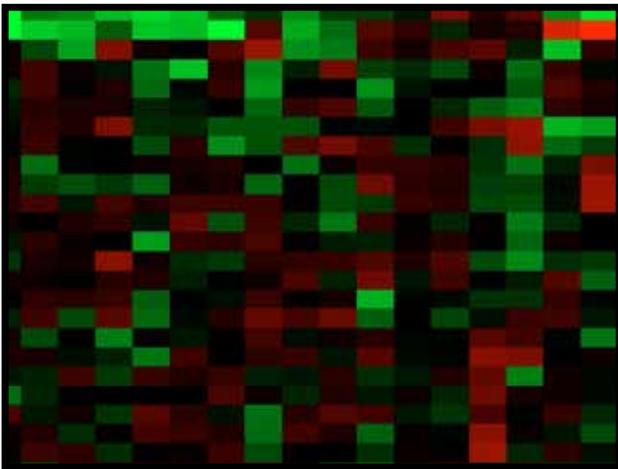


Restriction of dietary methionine by ~80% slows the progression of age-related diseases and prolongs lifespan in rodents. A salient feature of the methionine restriction (MR) phenotype is the significant reduction of adipose tissue mass, which is associated with improvement of insulin sensitivity. MR's beneficial effects involve a host of metabolic adaptations leading to increased mitochondrial biogenesis and function, elevated energy expenditure, changes in lipid and carbohydrate homeostasis, and decreased oxidative damage and inflammation. This review summarizes observations from MR studies and provides insight about potential mediators of tissue-specific responses associated with MR's favorable metabolic effects that contribute to health and lifespan extension.

Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents

Perrone CE, Malloy VL, Orentreich DS, Orentreich N. Proceedings of the 11th International Symposium on Neurobiology and Neuroendocrinology of Aging, *Experimental Gerontology*, in press

Omics, Methionine Restriction & Lifespan



MR increases lifespan, reduces adiposity, and improves insulin sensitivity; however, these effects are reversed by supplementation of the MR diet with cysteine. Genomic and metabolomic studies were conducted to identify potential mechanisms by which these effects occur. This study suggested that increased lipid metabolism in inguinal adipose tissue and quadriceps muscle, decreased triglyceride synthesis in liver, and the downregulation of inflammation-associated genes are among the factors that could favor the lean phenotype and increased insulin sensitivity observed in MR rats.

Genomic and metabolic responses to methionine-restricted and methionine-restricted, cysteine-supplemented diets in Fischer 344 rat inguinal adipose tissue, liver and quadriceps muscle

Perrone CE, Mattocks DAL, Plummer JD, Chittur SV, Mohney R, Vignola K, Orentreich DS, Orentreich N. *Journal of Nutrigenetics & Nutrigenomics* 2012;5:132-157

Cysteine Metabolism & the Methionine-Restricted Diet

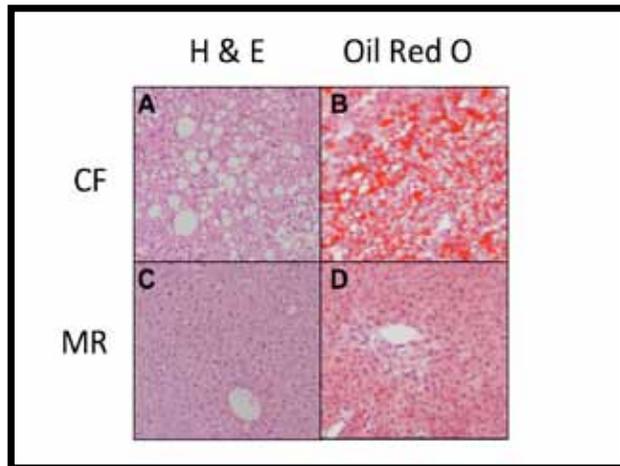


MR rats have low serum total cysteine (tCys) and taurine and decreased hepatic expression and activity indices of stearoyl-coenzyme A desaturase-1. These effects are partly or completely reversed by cysteine supplementation. We investigated whether reversal of MR phenotype could be achieved by other sulfur compounds, namely taurine or N-acetylcysteine (NAC). Taurine supplementation of MR did not affect adiposity but lowered serum triglycerides. NAC supplementation of MR raised tCys and reversed MR effects on weight and body fat. Our data rule out taurine as a mediator of increased adiposity produced by cysteine supplementation in MR and shows that NAC, similar to L-cysteine, blocks anti-adiposity effects of MR.

Effect of taurine and N-acetylcysteine on methionine restriction-mediated adiposity resistance

Elshorbagy A, Valdivia-Garcia M, Mattocks DAL, Plummer JD, Orentreich DS, Orentreich N, Refsum H, Perrone CE. *Metabolism: Clinical and Experimental*, in press

Methionine Restriction & Bone Density

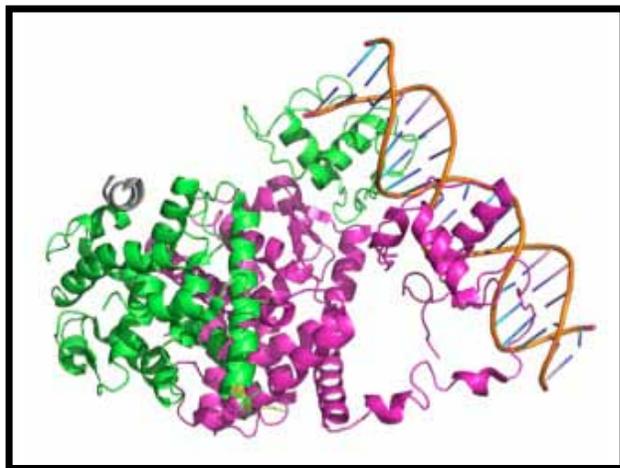


MR extends lifespan, an effect associated with reduction of body weight gain and improvement of insulin sensitivity, in mice and rats as a result of metabolic adaptations in liver, adipose tissue, and skeletal muscle. To test whether MR confers resistance to adiposity and insulin resistance, mice were fed a high fat diet (HFD) containing either 0.86% methionine or 0.12% methionine. MR mice on HFD had lower body weight gain despite increased food intake and absorption efficiency compared to controls. MR mice on HFD were more glucose tolerant and insulin sensitive and had reduced accumulation of hepatic triglycerides. However, restriction of growth rate in MR mice on HFD was also associated with lower bone mass. It is concluded that MR mice on HFD are metabolically healthy compared to controls on HFD but have decreased bone mass.

Methionine-restricted C57BL/6J mice are resistant to diet-induced obesity and insulin resistance but have low bone density

Ables GP, Perrone CE, Orentreich D, Orentreich N. *PLoS ONE* 2012, 7(12): e51357. doi:10.1371/journal.pone.0051357

Ppar γ & Nonalcoholic Fatty Liver Disease



Nonalcoholic fatty liver disease (NAFLD) is the most common initial presentation of obesity and insulin resistance. Uninterrupted progression of hepatic lipid accumulation often leads to fatty liver disease and, eventually, cirrhosis. Insulin resistance is one characteristic of type 2 diabetes. Some treatments employed against type 2 diabetes ameliorate NAFLD. Thiazolidinediones (TZDs), which activate the nuclear receptor peroxisome proliferator activated receptor gamma (Ppar γ), are frequently used to improve insulin sensitivity. Although TZDs are proven to be very effective in this, their actions on Ppar γ have been complicated, specifically on NAFLD. According to studies in different models, Ppar γ manifests both beneficial and undesirable effects on NAFLD. This paper reviews the current knowledge in this area.

Update on Ppar γ and nonalcoholic fatty liver disease

Ables GP. *PPAR Research*, vol. 2012, Article ID 912351, 5 pages. doi:10.1155/2012/912351

New Consultants

Two new consultants have joined our extended family this year. Both are currently faculty members at New York Medical College in Valhalla, NY. Drs. Cooper and Popilskis will take part in guiding future investigations and developing research projects. Dr. Popilskis also serves as our consulting veterinarian and is a member of the Institutional Animal Care & Use Committee.

Sulli J. Popilskis, DVM, DACLAM

Director of Comparative Medicine
New York Medical College

Arthur J.L. Cooper, PhD

Professor of Biochemistry & Molecular Biology
New York Medical College

Joseph H. Vogelman, DEE



1920 - 2012

Dr. Vogelman joined our extended family 50 years ago. He served as Technical Director of the Advanced Clinical Blood Laboratory, which performed routine and special research assays. He designed the computer system and software for cataloguing, locating, retrieving, and indexing of frozen serum samples in the Kaiser Permanente-OFAS Serum Repository; and was OFAS's principal investigator for all collaborations that used the Repository for medical research. He was an author on 56 OFAS publications.

He is greatly missed.

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For collaborations, contact Dr. Carmen Perrone at ofas@orentreich.org.

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