

## The Secrets of Healthy Longevity

Gamma Sigma Delta Fall Lecture Series

December 7, 2007; Baton Rouge, LA

Eric Ravussin  
 Don Williamson  
 Steven R Smith  
 Frank Greenway  
 Leonie Heilbronn  
 Corby Martin  
 Leanne Redman  
 Anthony Civitarese

and the Pennington  
 CALERIE, LHAS  
 Teams

Supported by NIA

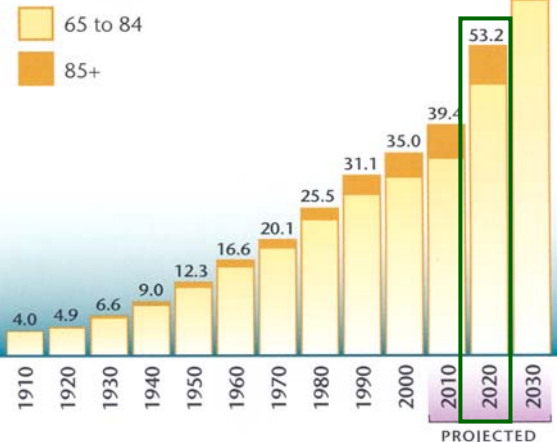


Ravusse@pbrc.edu

- By 2020, there will be 10 million Americans above the age of 85 years.
- Assistance is required by 45% of those over 85 years of age.

### Older Population by Age

1910 to 2030 (In Millions)



**THE OBESITY SOCIETY 25th ANNUAL SCIENTIFIC MEETING 2007**

**THE OBESITY SOCIETY**

**THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF PUBLIC HEALTH AND HEALTH SERVICES**

# The Obesity Challenge:

## What the Next President Should Do

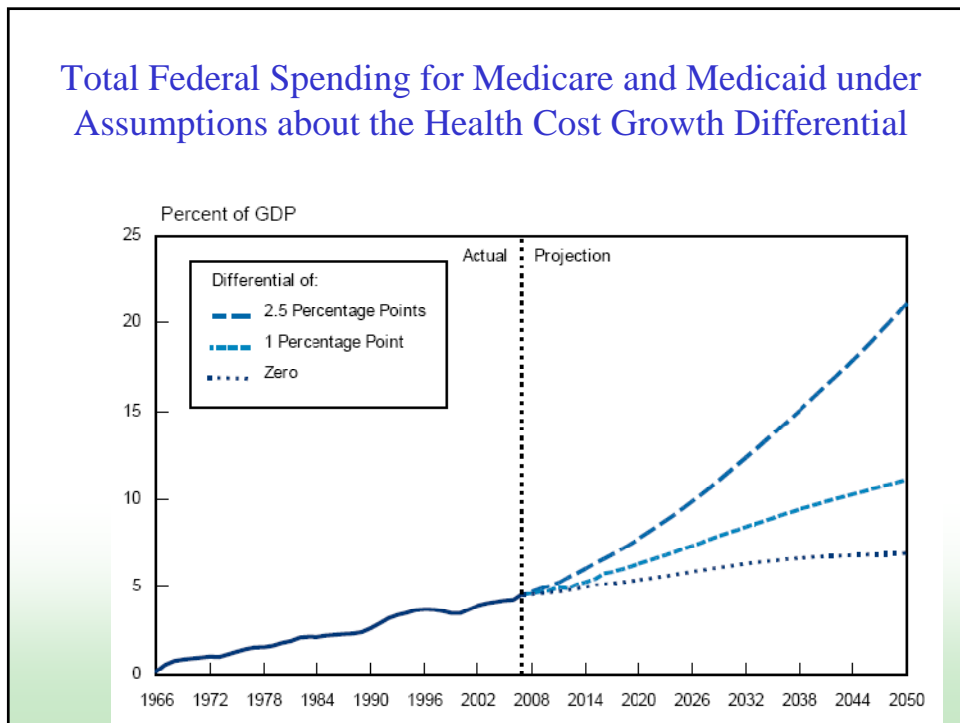
Wednesday, September 19th, 2007

The Jack Morton Auditorium, George Washington University

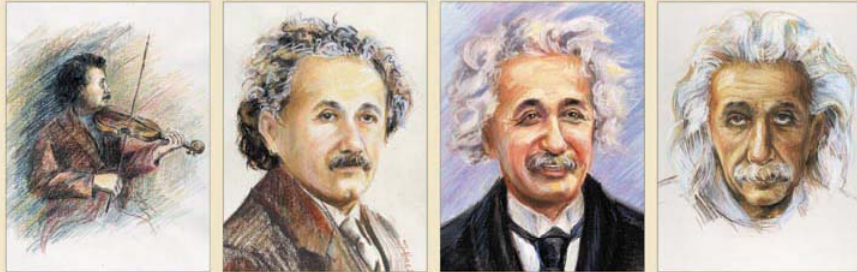
Hosted by:  
The Obesity Society and the GW School of Public Health

## Presidential Public Policy Meeting



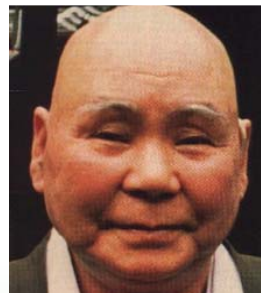



On the surface, aging is obvious.



The Aging of Albert  
Aging is a hypothetical construct.

**Individuals of the Same Chronological Age Can Appear To be of Very Different Biological Age**



**But is this appearance a real biological phenomenon or merely superficial?**



Significant factors in the ability to maintain health and independence in old age include:

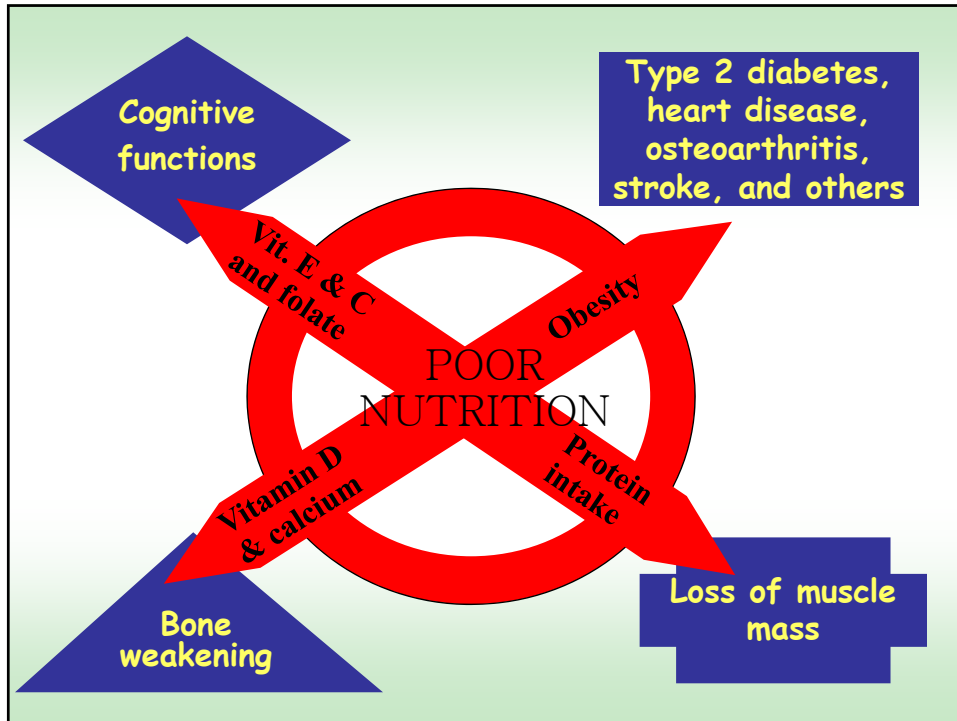
- Genetic predisposition
- Diet
- Physical activity
- Healthy weight



## A COMMENT ON NUTRITION

- A decrease in total energy intake is commonly observed with aging.
- *However*, some nutrients are required in higher amounts to compensate for the reduced metabolic efficiency associated with aging.
- Hence, the paradox: lower caloric requirements but higher nutrient needs.



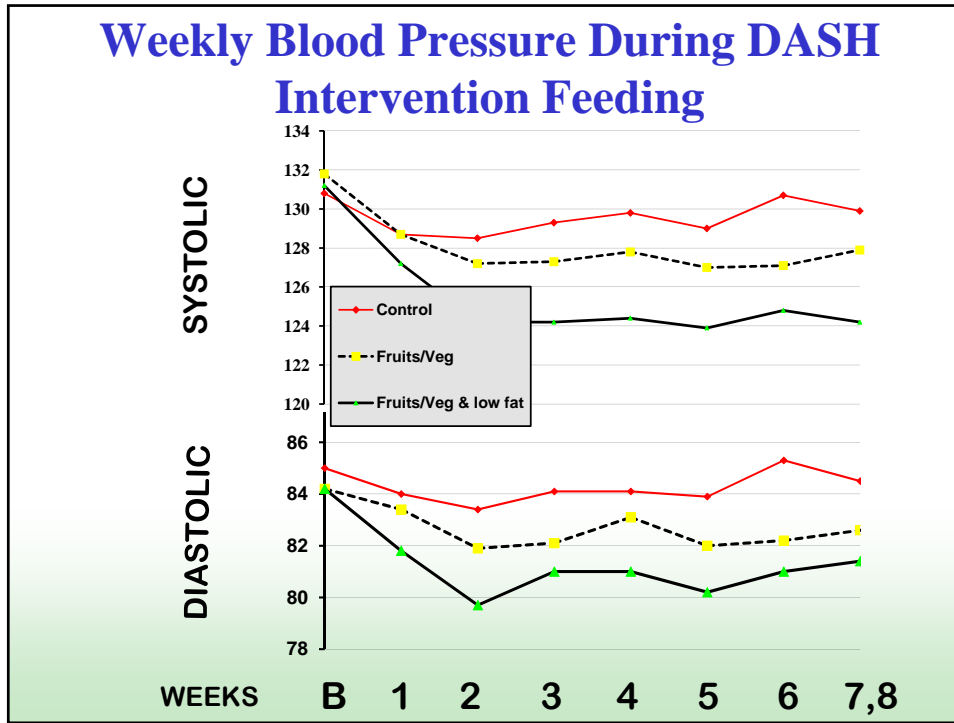


### **PENNINGTON BIOMEDICAL RESEARCH CENTER**

- Established in 1988, the Center has grown steadily and comprises 600,000 square feet of research space by mid 2003
- At present, PBRC employs 85 faculty scientists, with 650 staff and support personnel
- The center has a yearly operational budget of \$65 M
- The Center has performed more than 280 clinical research projects

### **RECENT RESEARCH RELEVANT TO AGING PERFORMED AT THE PENNINGTON BIOMEDICAL RESEARCH CENTER**

- Dietary Approaches to Stop Hypertension (DASH)
- Diabetes Prevention Program
- HERITAGE Family Study (Physical Activity)
- Metabolic Adaptations to Two-Year Caloric Restriction (CALERIE)



### Effect of the DASH Diet in Hypertensive

	Fruits/Veg	Fruits/Veg/ Low Fat
Normotensive n=326	-0.8/-0.3	<u>-3.5/-2.1</u>
Hypertensive n=133	<u>-7.2/-2.8</u>	<u>-11.4/-5.5</u>

Changes in Systolic/diastolic pressure, adjusted for controls



## DASH Summary

A diet high in fruits and vegetables and low in fat was found to:

- Significantly lower both systolic and diastolic blood pressure
- Benefit a wide variety of people:
  - women and men,
  - ethnic groups,
  - normotensives and hypertensives,
  - younger and older.



## Diabetes Prevention

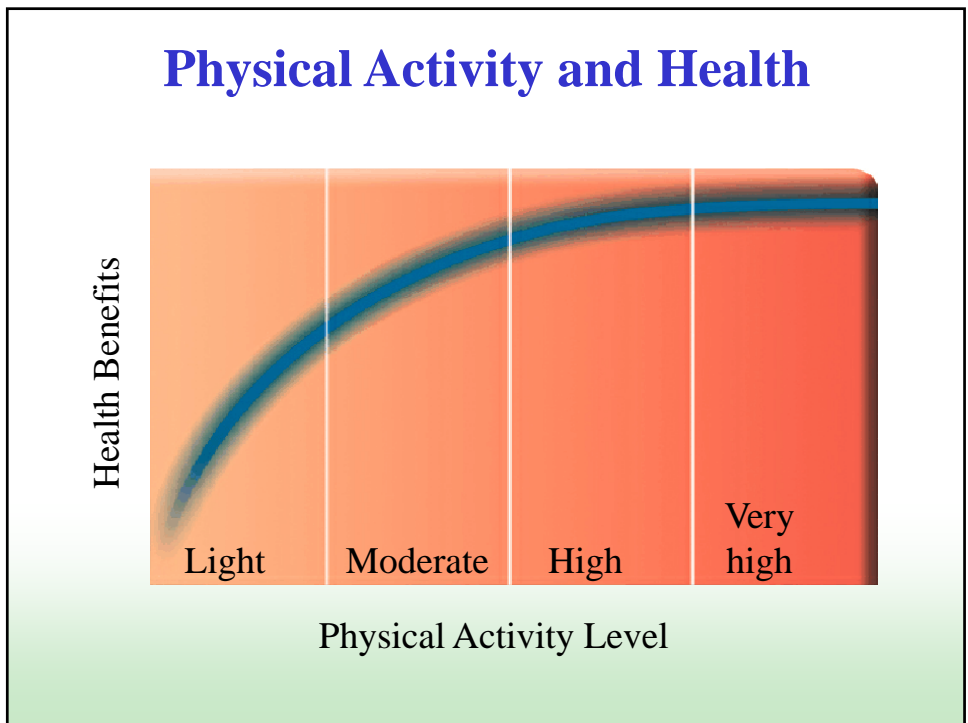
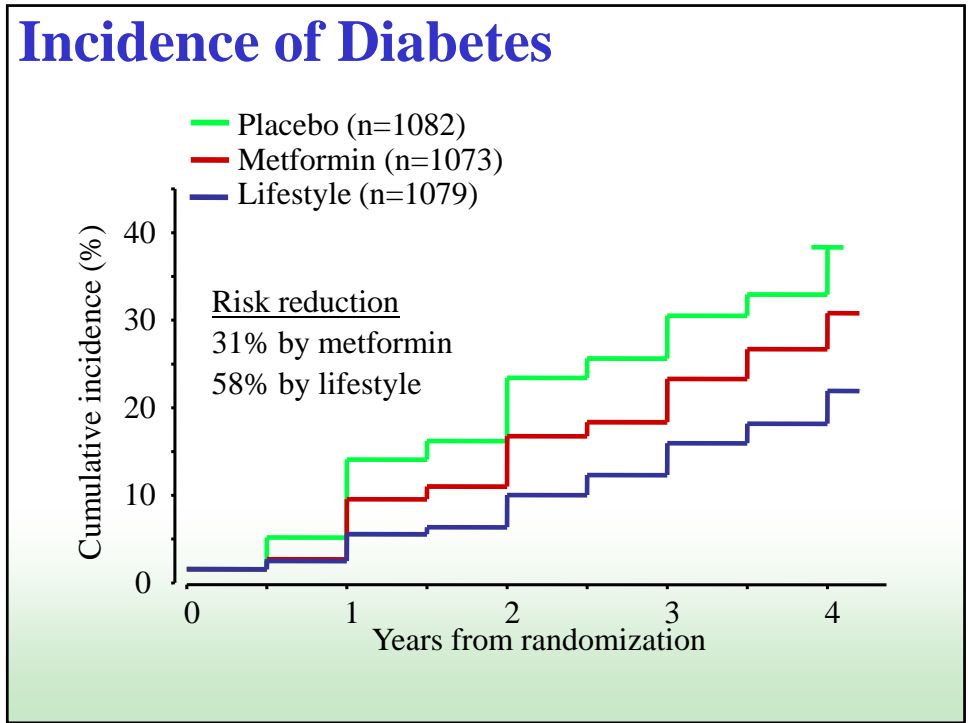
Over 3,200 volunteers aged 21 to over 85 were tested in 27 centers, including the Pennington Center.

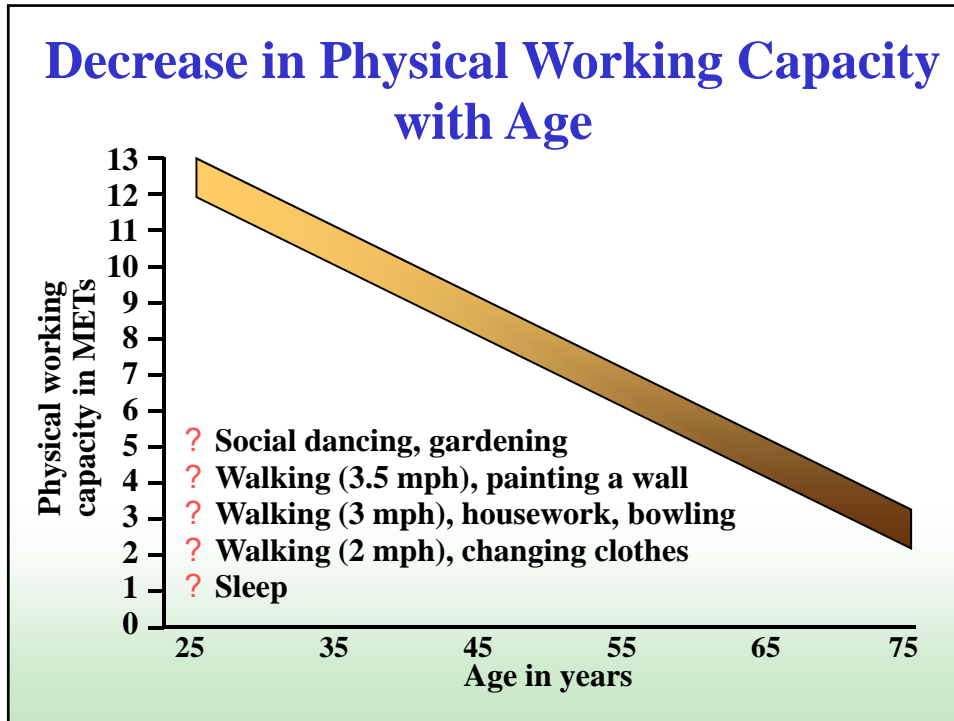
There were 3 arms: lifestyle, placebo, and pharmaceutical (metformin).

The Intensive Lifestyle was so effective that the first phase of the trial terminated early.

- 58% reduction in development of diabetes
- Higher weight loss in older subjects



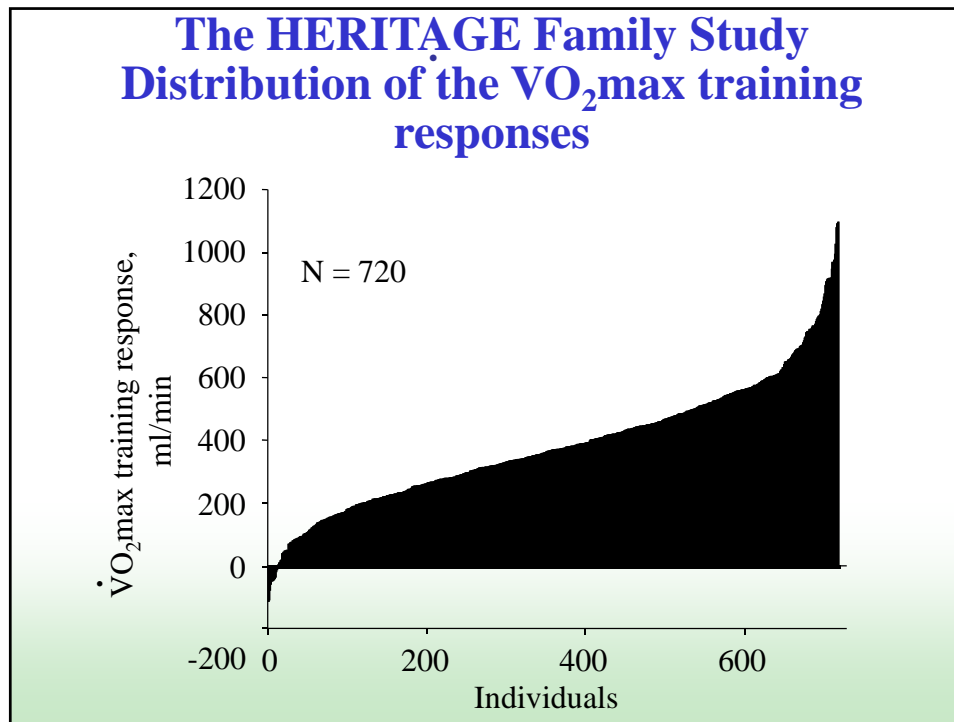




## HERITAGE Family Study

- 800 subjects from 200 families exercised at 4 clinical centers for 5 months with no dietary changes.
- Large inter-individual differences in the response to regular exercise were observed.





## HERITAGE Family Study

- Strong aggregation with high responders or low responders clustering in some families.
- An understanding of the effects of nutrition will be achieved only if the role of physical activity and the interactions with biological individuality are taken into account.

## calerie

### CALERIE = Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

- Pennington was 1 of 3 centers selected by the National Institute on Aging to study caloric restriction (\$15M/7yrs).
  - Caloric restriction in rodents prolongs life, as well as causing weight loss.
  - One hypothesis is that metabolic rate is decreased, and the production of free radicals is reduced.
- PBRC scientists are investigating in controlled human trials the role of caloric restriction in:
  - Metabolic rates
  - Gene expression
  - Risk factors for chronic diseases
  - Oxidative stress in tissues

## calerie

### CALERIE = Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

- NIA sponsored studies of caloric restriction in non obese humans
- Study the feasibility and safety of caloric restriction in non obese humans
- Biomarkers of longevity
- DM risk factors: insulin sensitivity
- Cardiovascular risk factors
- GH secretion
- Metabolic adaptation and oxidative stress
- Physical activity during CR
- Muscle mitochondrial biogenesis

## **calerie**

- Aging is thought to bring deterioration of specific cell components resulting in increased release of free radicals, which attack DNA, lipids and proteins causing further damage.
- One method of coping with free radicals is use of nutritional antioxidants.
- PBRC has one of the most progressive laboratories in the US to measure specific DNA alterations associated with aging, as well as study of reparative enzymes.

## **calerie**

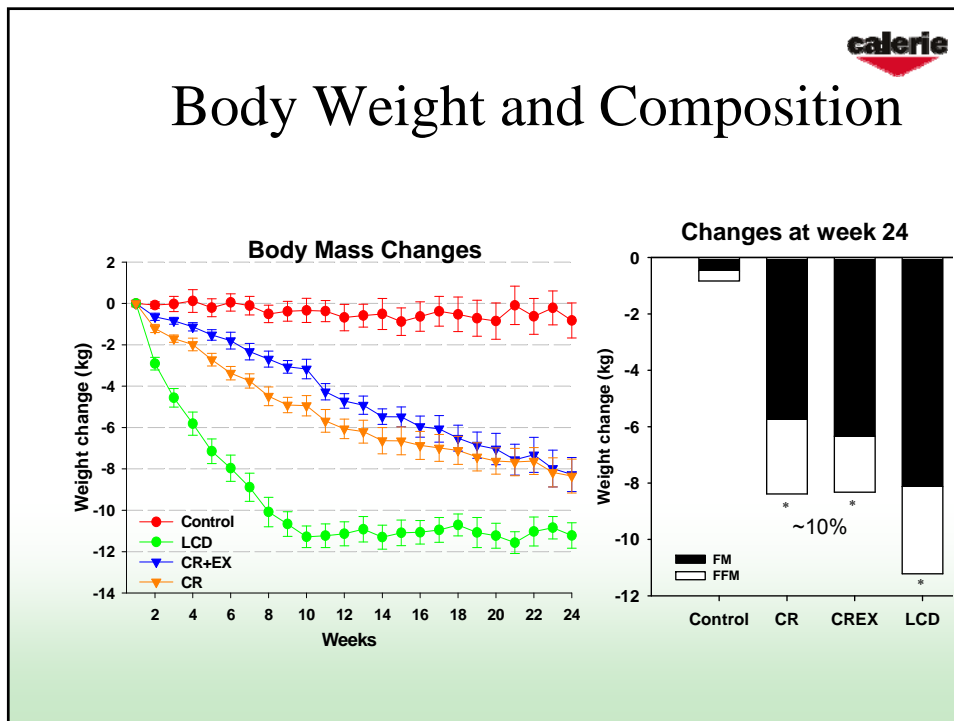
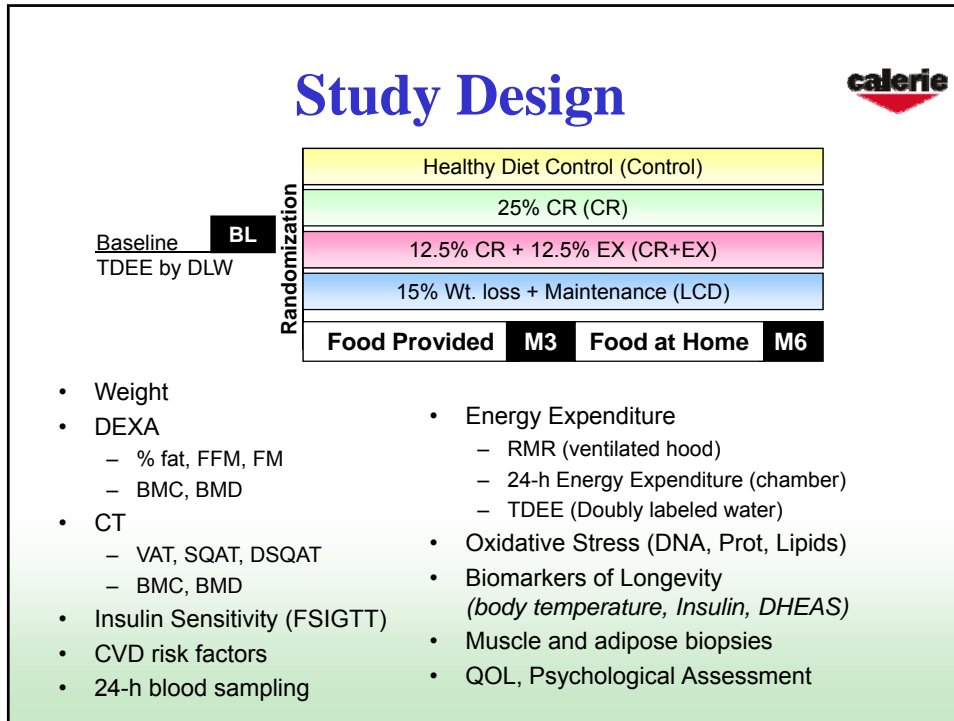
### **Subjects and Interventions**

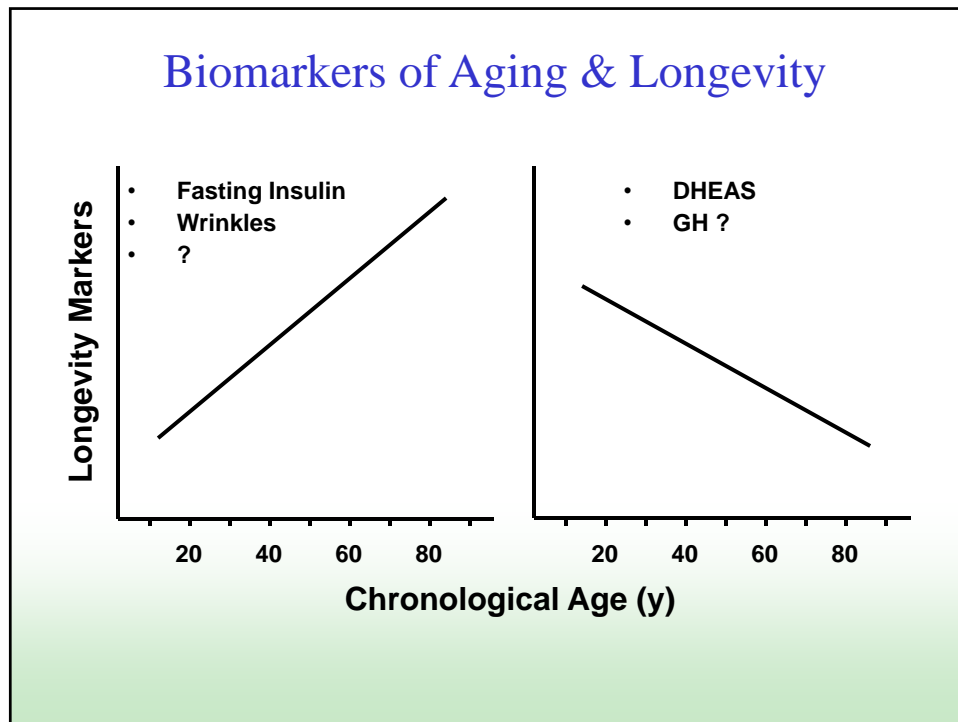
48 healthy men and women

- Age 25 - 50y (45y for women)
- BMI 25-30 kg/m<sup>2</sup>
- Exercise < 3 times per week.

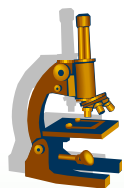
Randomized to 4 treatment groups

- 25% CR
- LCD to -15% Body weight
- 12.5% CR + 12.5% ↑ EE (exercise)
- Control healthy diet (AHA – STEP1)





### Possible Molecular Biomarkers of Aging



- Telomere shortening
- DNA damage and repair
- Glycation of protein
- Oxidation of proteins



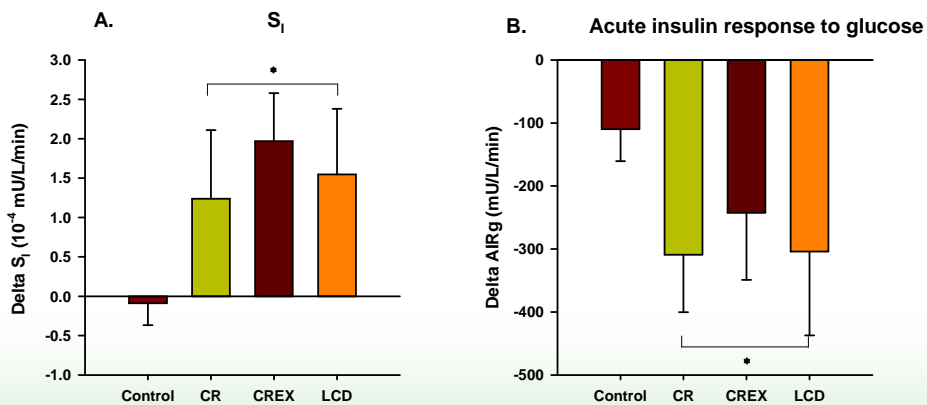
## Hypothesis: Biomarkers of “Longevity” are improved



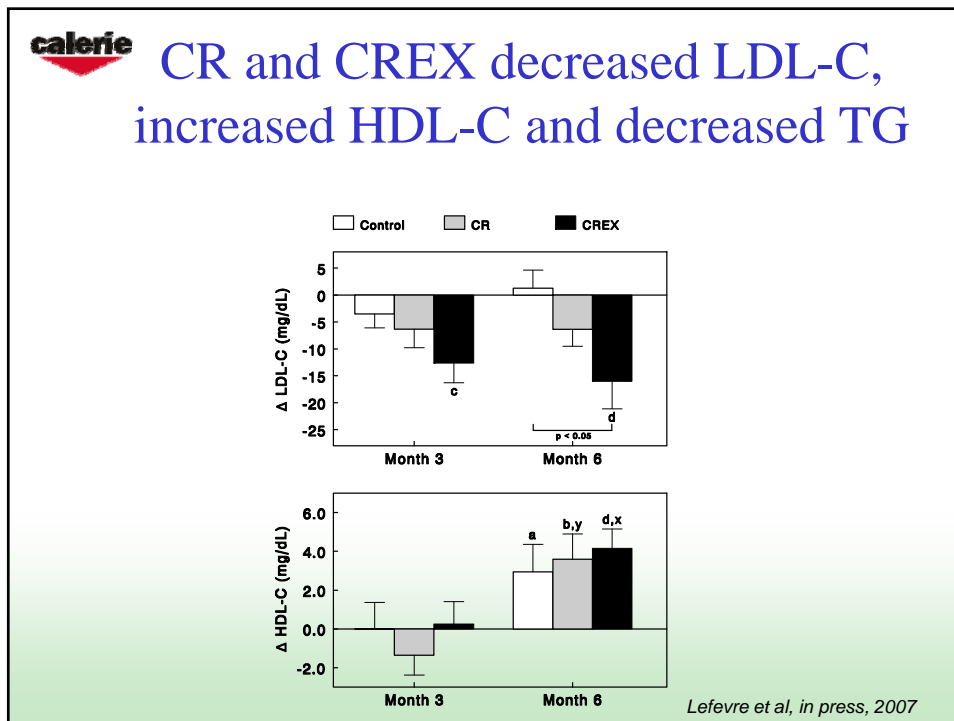
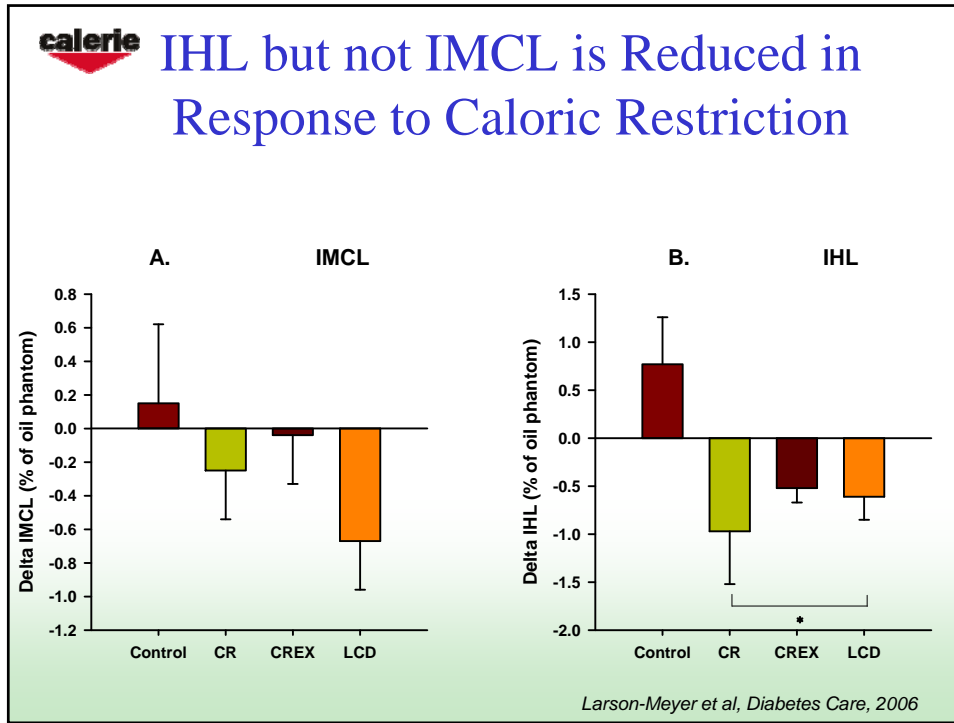
- CR decreased core temperature
- CR decreased fasting insulin ( IS ↑)
- CR did not influence DHEAS

Two out of 3 biomarkers of longevity were improved from baseline following 6-mo of CR intervention in non-obese humans

## Caloric Restriction Improved Insulin Sensitivity and Decreased Insulin Secretion



Larson-Meyer et al, Diabetes Care, 2006



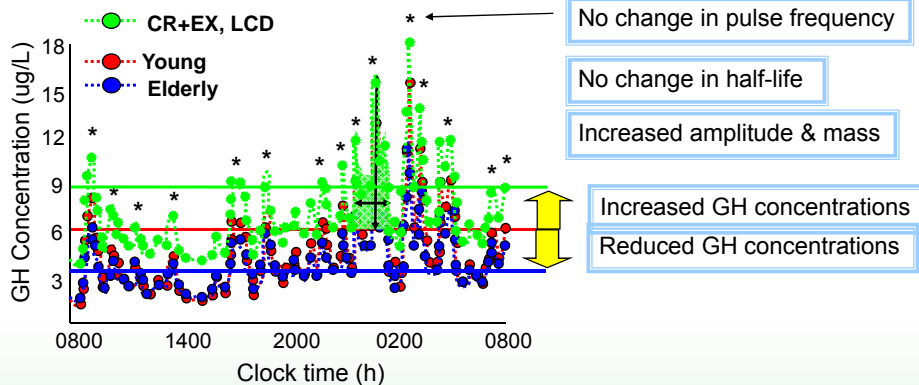
## Conclusions



- CR with or without exercise improved insulin sensitivity and decreased IHL
- CR with or without exercise improved the cardio vascular risk profile (lowers LDL\* and TG and increases HDL)
- Together, these factors improved the estimated CVD risks by 30-40%

\* CR alone did not significantly lower LDL or raise HDL

## CR may reverse the impaired GH axis in aging



## Program Project on Aging

- In 2002, there were 35.6 million people over the age of 65y in the US, a 10.2% increase since 1992
- In 1997, more than half of this older population (55%) reported having at least one disability of some type with over a third (38%) reported having at least one severe disability

### Louisiana Healthy Aging Study

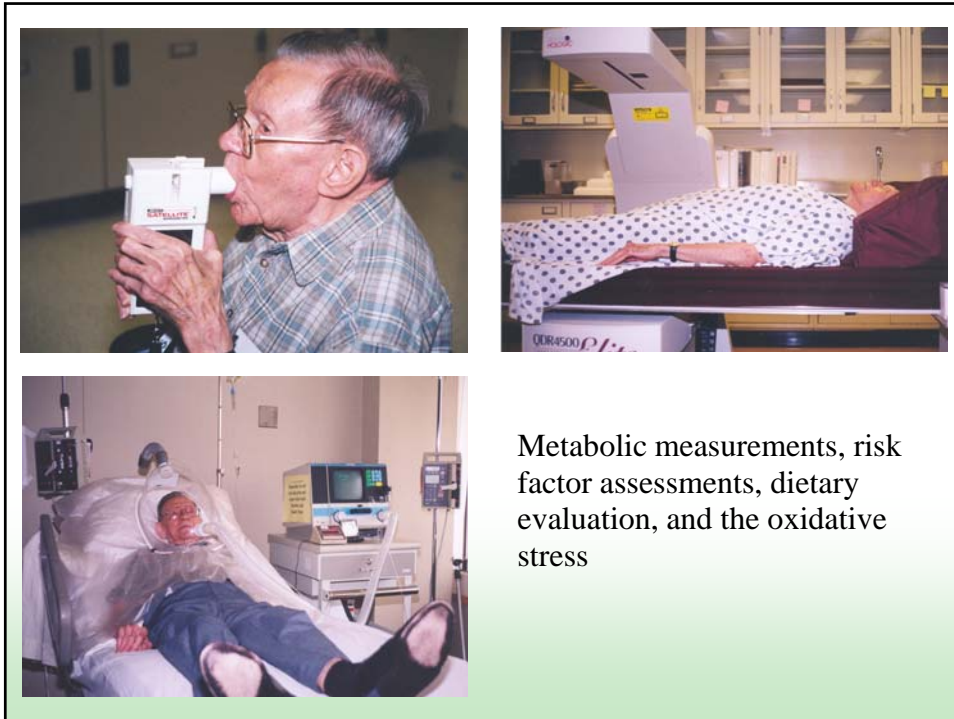
- Population based study
- Genetics, Physiology, Physical function, Cognitive function
- “Successful agers”
- Assess biological age

## Louisiana Healthy Aging Study

One comprehensive research project is being conducted by scientists from the Louisiana State University Health Sciences Center in New Orleans, LSU in BTR and the Pennington Center with the aim of defining metabolic factors in the aging process, in subjects aged 90 yrs and older.



Aging, Metabolism,  
Oxidative Stress,  
Physical and Cognitive  
Functionality



## Determinants of Human Longevity and Healthy Aging (P01)

Program project PI: M. Jazwinski

Core A: Administrative. M. Jazwinski; D. Welsh

Core B: Sampling and Data Management. J. Su

**Core C: Recruitment and Clinical Testing.** E. Ravussin (C Traylor)

Project 1 (877): Genetics & Genomics. M. Jazwinski; M. Batzer

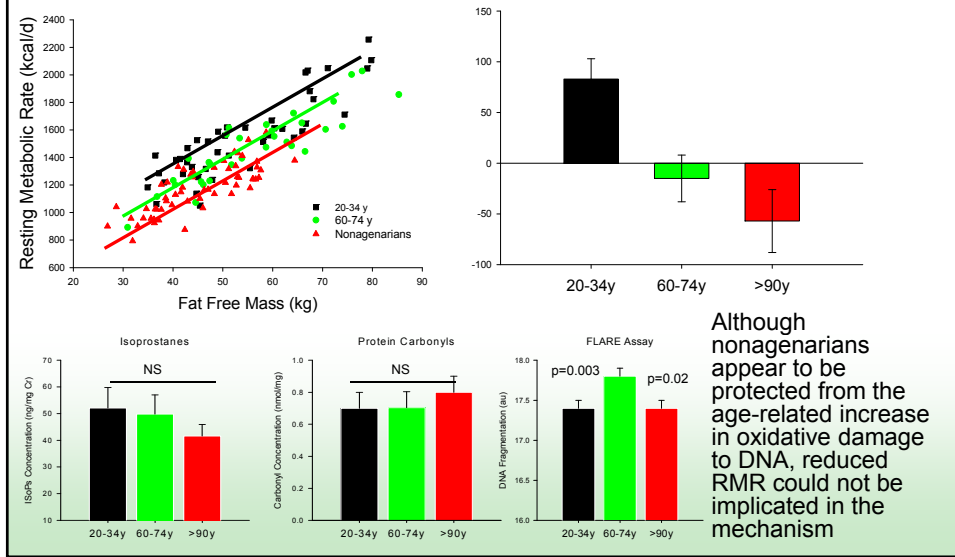
Project 2 (207): Glucose Metabolism and T Cell Function in Aging  
D. Scott, J. Mountz

**Project 3 (207): Energy Metabolism and Oxidative Stress in Aging**  
E. Ravussin

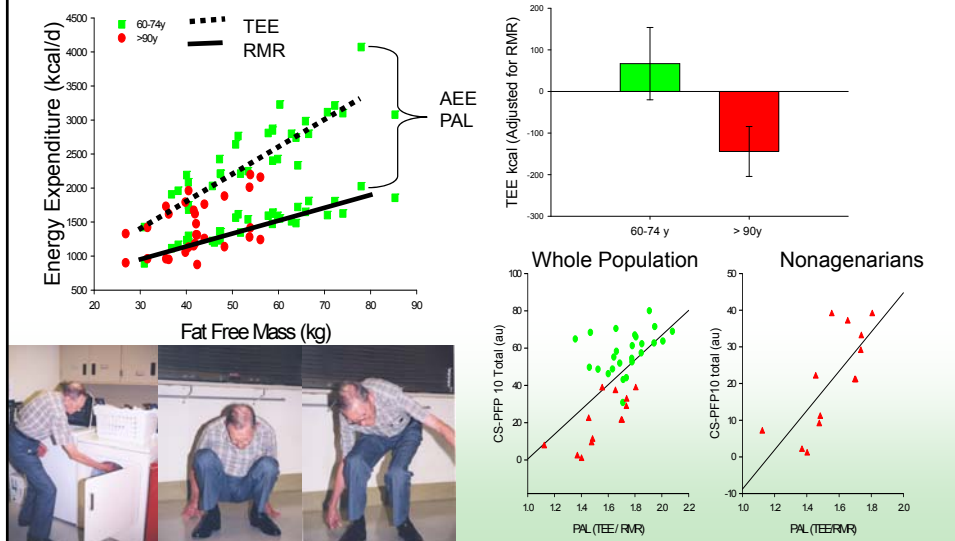
Project 4 (303): Vascular Status and Physical Function in Aging. M. Welsh

Project 5 (331): Cognitive Function in Aging. K. Cherry

## Resting Metabolic Rate Decreased with Aging but is not Correlated to Oxidative Stress




## Physical Activity Level is Correlated to Physical Functionality



## A HaPE Laboratory (Human Physiology)







## Multi-site Study

Sponsor  
National Institute  
on Aging ■ ◆ ★ ✨


Clinical Sites



PI: Susan Roberts




PI: Eric Ravussin




PI: John Holloszy

Coordinating Center



PI: Jim Rochon



## Hypotheses & Aims

**Primary specific aim**

- As in rodents, CR in humans causes sustained (over two years) metabolic adaptation as defined by:
  - a reduction in core body temperature and
  - reduced resting metabolic rate (RMR) corrected for changes in body composition.
  - PBRC Ancillary R01s - 24h EE in metabolic chamber and MRS/mitochondria

**Secondary aims**

- CR in humans:
  - Reduces serum T3.
  - Reduces inflammation as reflected in plasma concentrations of Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ).
  - To determine whether CR has adverse effects in humans and to evaluate their seriousness.



## Design



- Multi-center, parallel group RCT
- Enroll 250 participants (80 per site)
  - CR (sustained 25% CR)
  - Control
- 24 month study
- No dietary restrictions. Controlled feeding for first 4 weeks. No ramping of CR

## Subjects



- Healthy men & women
- Age 25-45 years (inclusive)
- BMI 22.0 - <28.0 kg/m<sup>2</sup>
- Exclusion criteria
  - Medical
  - Laboratory
  - Psychiatric/behavioral
  - Medication
  - Other

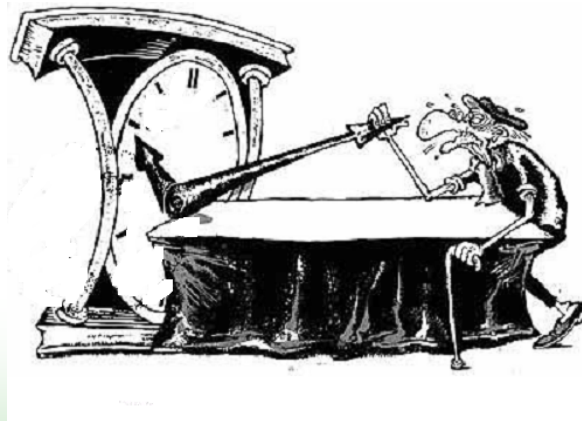
# Healthy Aging?

What is healthy aging?

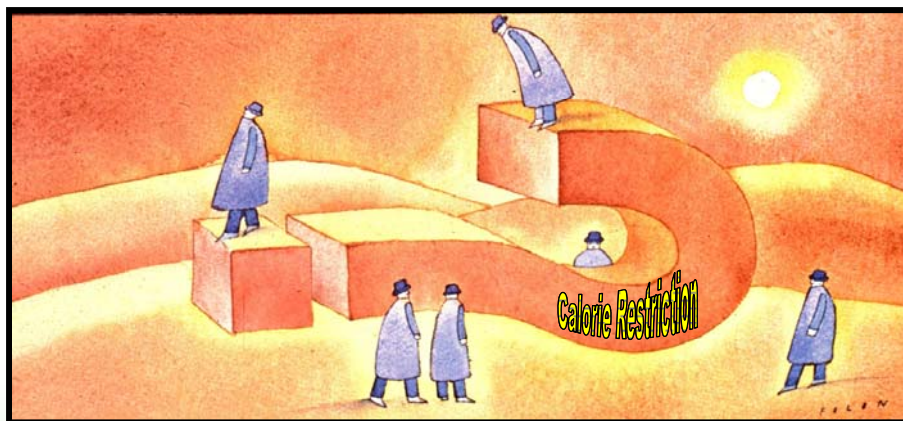
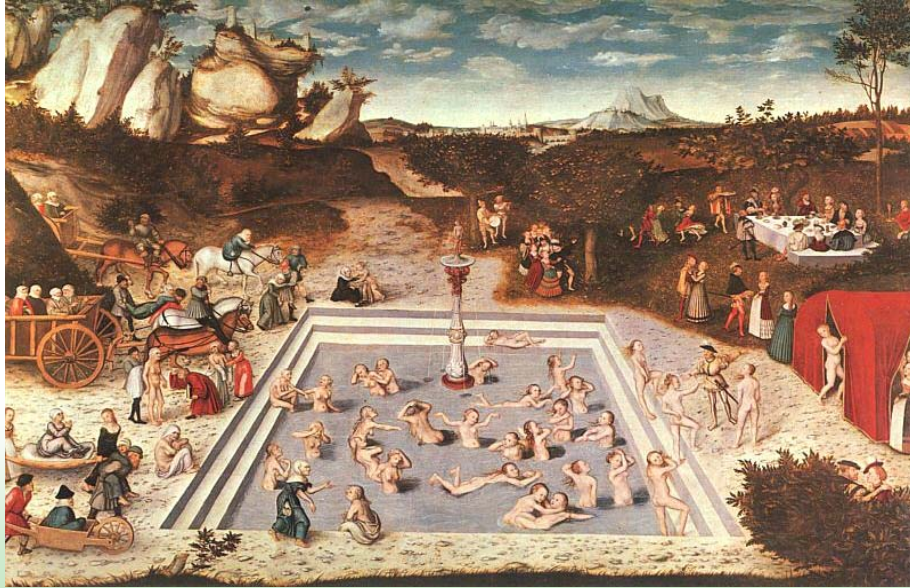
- Retention of:
- Quality of life
  - Cognitive function
  - Physical function



## The Challenge



Lucas Cranach the Elder, 1546  
The Fountain of Youth



## Calorie Restriction in Humans: Lessons from Mice and Rats

- 1) How much calorie restriction?  
**The more the better**
- 2) When should calorie restriction start?  
**The earlier the better**
- 3) Does long-term restriction cause adaptation with decreased hunger?  
**Not sure!!!**



Eric and Jacqueline  
Ravussin  
on July 4, 1975

CR of 15% for  
next 52 years

**Benefit:**  
**4.7 years**



32 years later

30% CR for 20 years

Benefit?

Two Months!



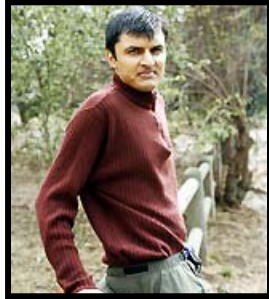
I prefer that...



... or take resveratrol possibly in a wine bottle



10/24/05



### Bare-minimum diet: Is long life the payoff?

By Kathleen Fackelmann

Khurram Hashmi has drastically cut the calories he consumes — eating mostly salads and raw vegetables — in the hopes of living a longer, better life.

At 5-11, Khurram Hashmi has adopted a bare-minimum diet that has reduced his weight from about 180 pounds to 129.

But he's hungry almost all the time. "That's something for me that has never gone away, but it is easier to accept now," says Hashmi, 37. He says he used to cheat, but not anymore. The hunger tells him that the diet's working, he says.

The diet is not for everyone: Hunger and low libido are facts of life for Hashmi and other followers. But they put up with what amounts to a near-starvation diet because a slew of studies has shown that mice and other lab animals that eat a very low-calorie diet live about 30% longer than they otherwise would. These studies also suggest that the diet protects the body from age-related diseases such as diabetes.

"It is the only nutritional regimen thought to retard aging," says Richard Weindruch at the University of Wisconsin-Madison. His studies have suggested that middle-aged mice can start the diet and still get the longevity benefit.

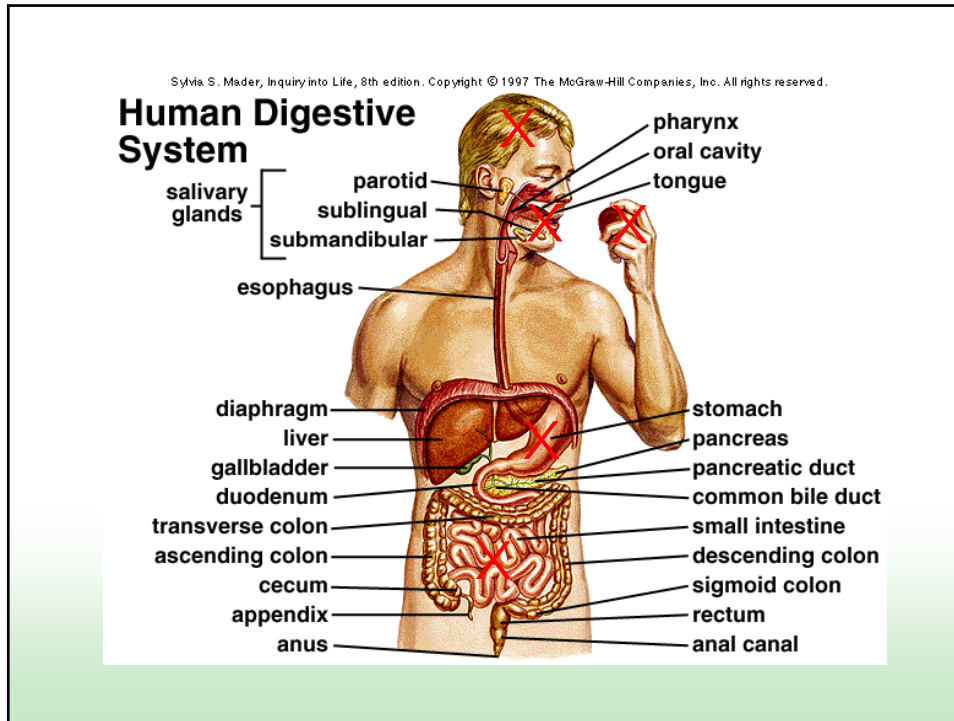
## A 30% Calorie Restriction a tough diet!

3000 calories → 2000 calories

2400 calories → 1600 calories

2100 calories → 1400 calories

**So this diet should be stressful.**





## Caloric Restriction Mimetics



What are they and will they work?

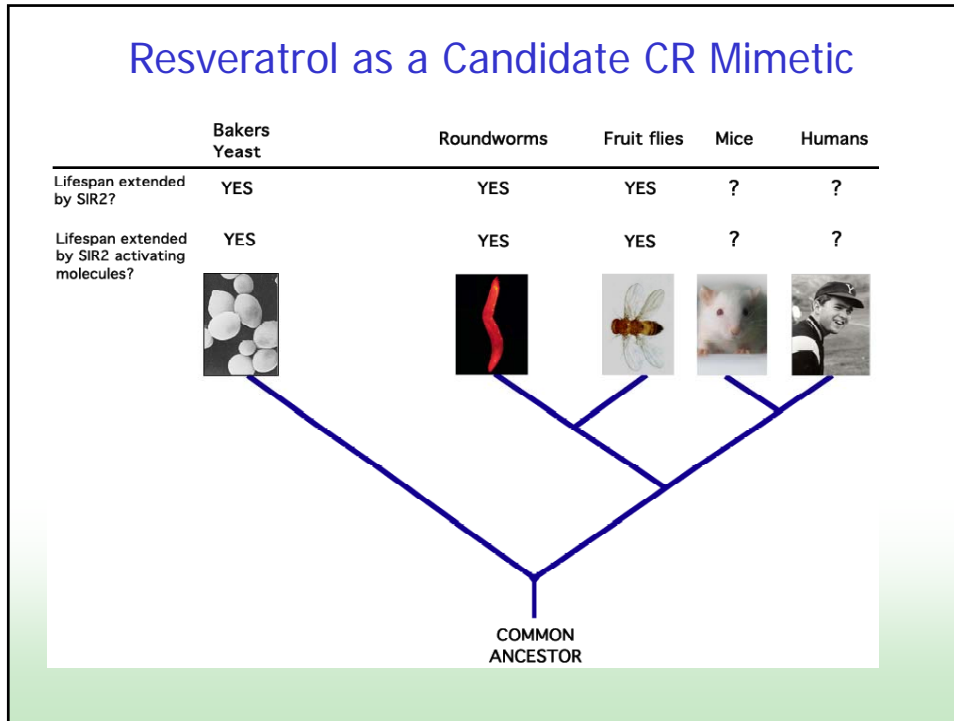


## Resveratrol is a polyphenolic phytoalexin.

Oc1ccc(cc1)/C=C/c2cc(O)c(O)cc2

The chemical structure of Resveratrol is shown, featuring a stilbenoid core with a hydroxyl group at the 4' position and hydroxyl groups at the 3 and 5 positions of the phenolic ring.





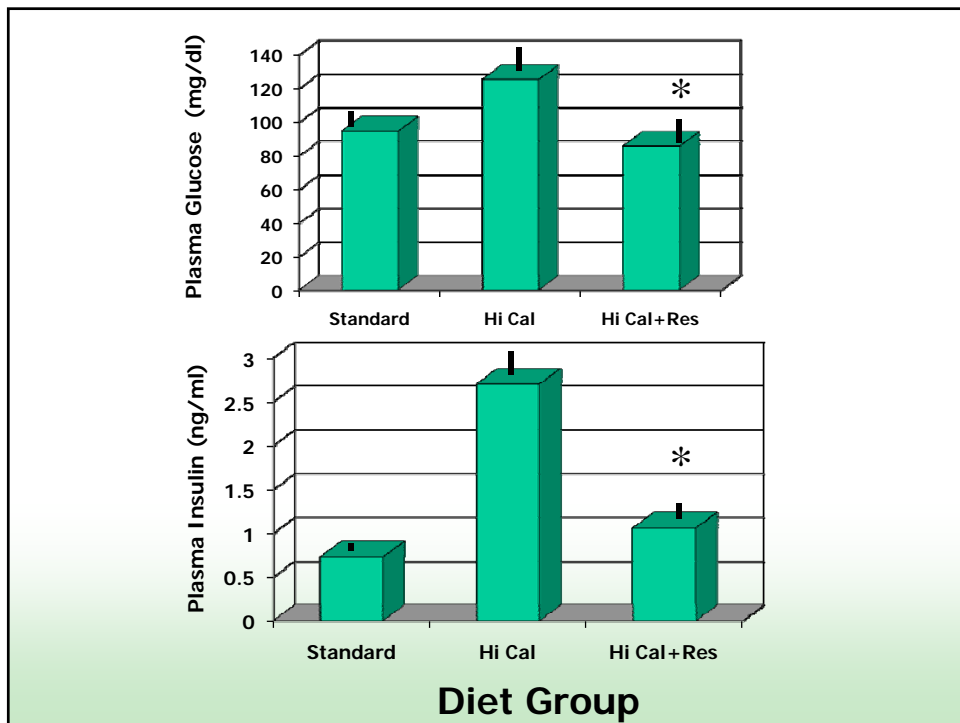
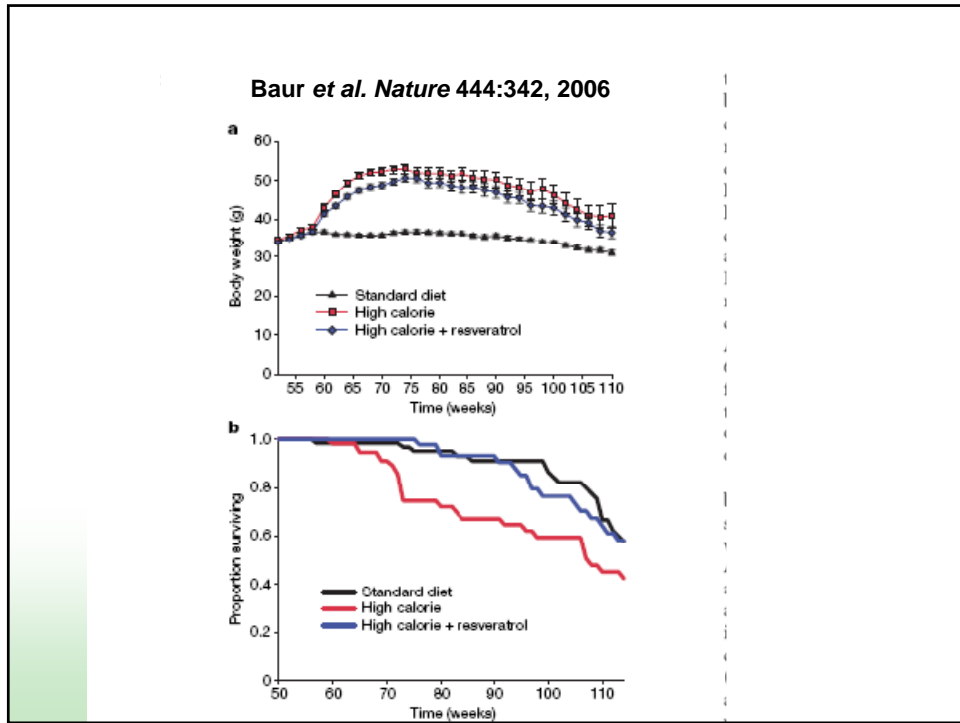
## Resveratrol improves health and increases survival of mice on a high-calorie diet

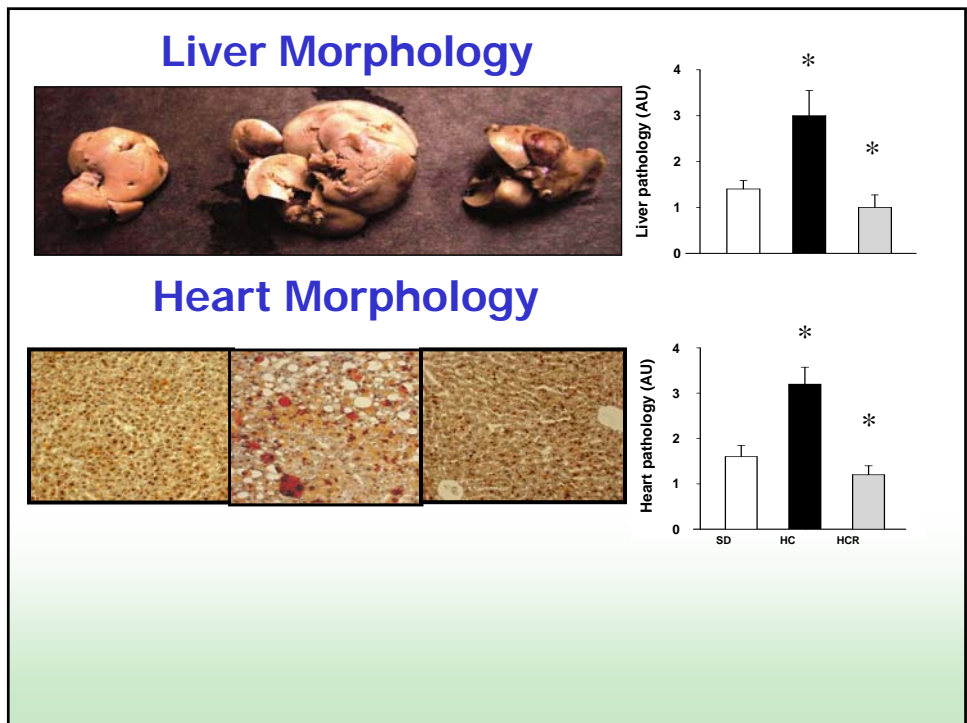
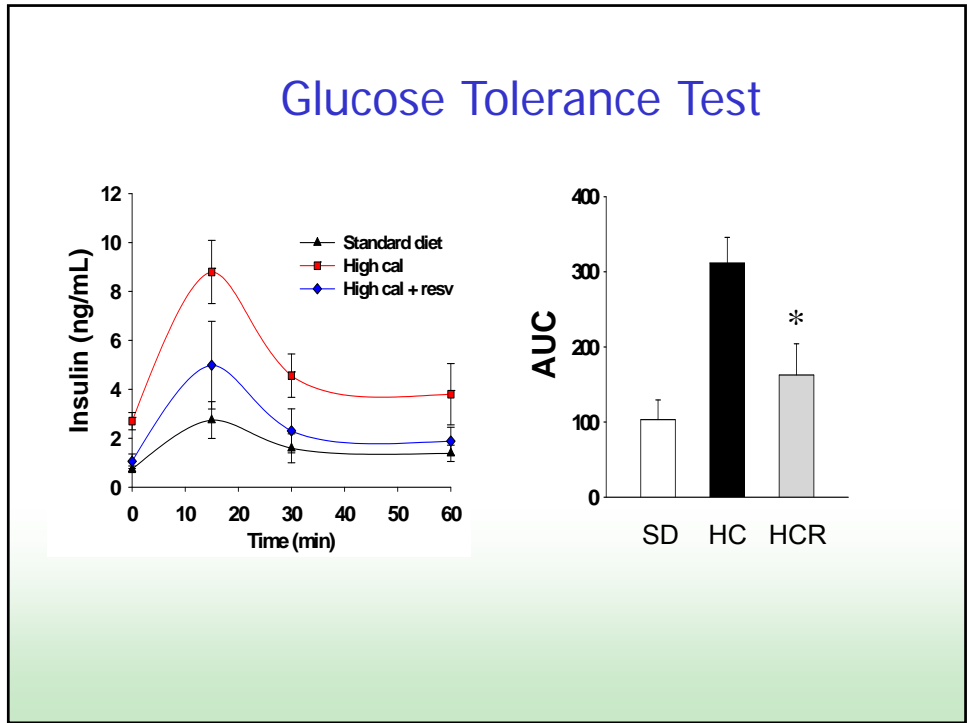
***Nature*. 444: 337-342, 2006**

Joseph A. Baur, Kevin J. Pearson, Nathan L. Price, Hamish A. Jamieson, Carles Lerin, Avash Kalra, Vinayakumar V. Prabhu, Joanne S. Allard, Guillermo Lopez-Lluch, Kaitlyn Lewis, Paul J. Pistell, Suresh Poosala, Kevin G. Becker, Olivier Boss, Dana Gwinn, Mingyi Wang, Sharan Ramaswamy, Kenneth W. Fishbein, Richard G. Spencer, Edward G. Lakatta, David Le Couteur, Reuben J. Shaw, Placido Navas, Pere Puigserver, Donald K. Ingram, Rafael de Cabo, and David A. Sinclair

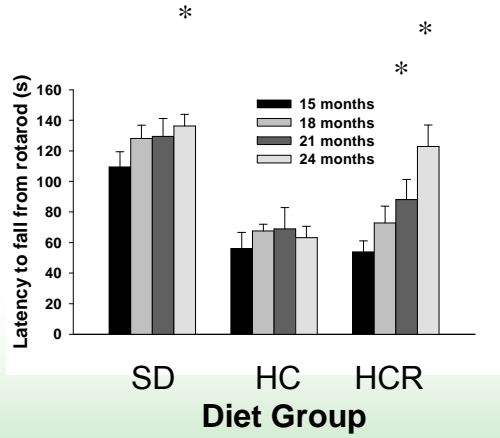
### ***Cooperating Units***

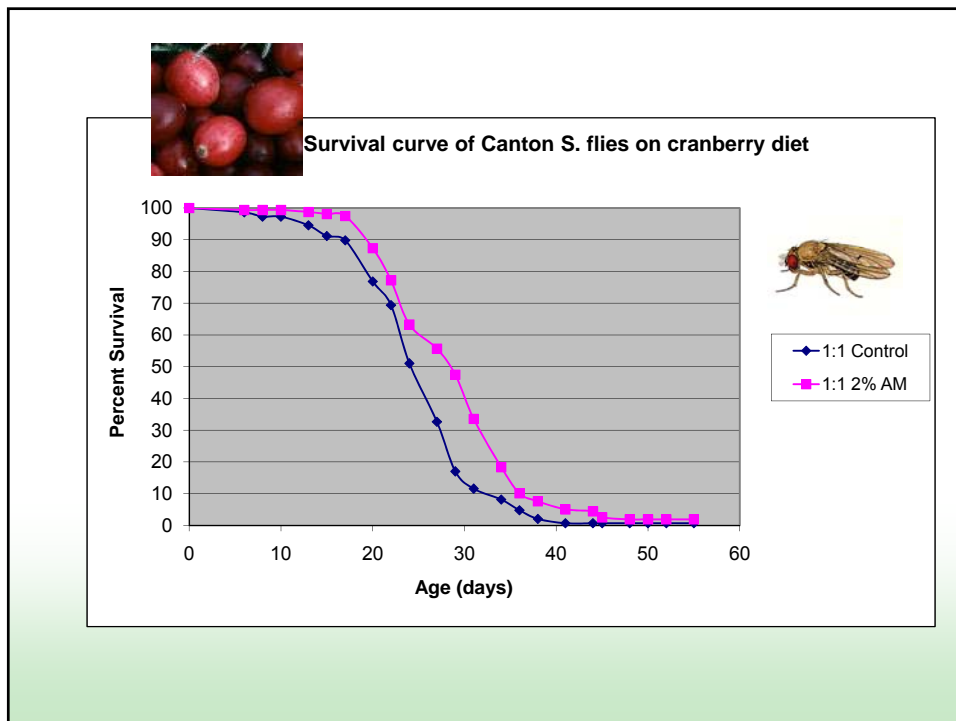
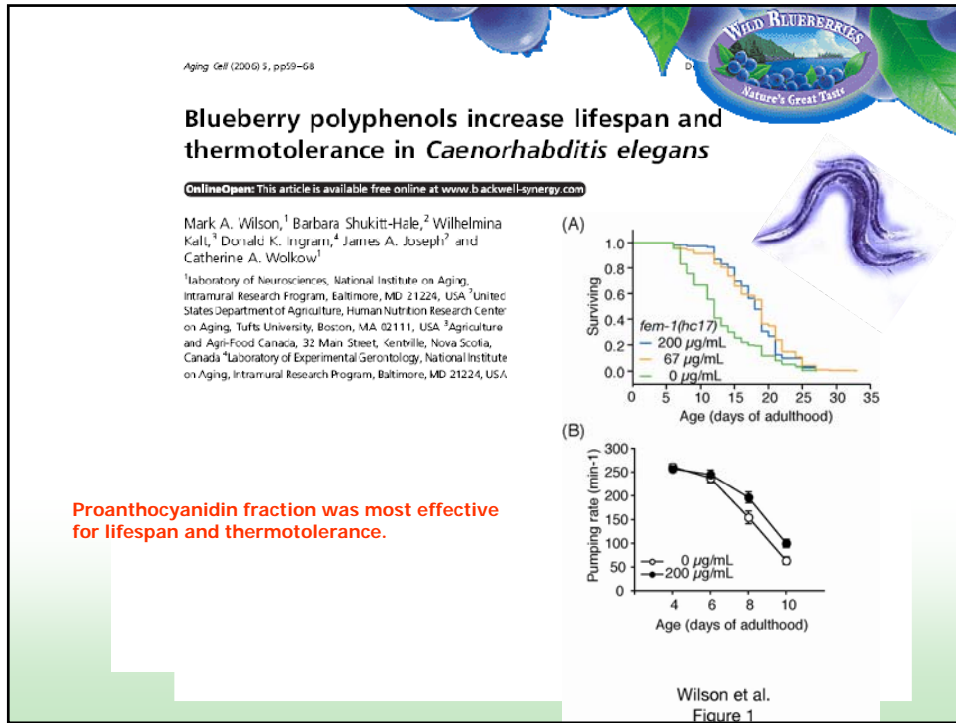
- *National Institute on Aging*
- *Department of Pathology, Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, Harvard Medical School*
- *Centre for Education and Research on Ageing, and the ANZAC Research Institute University of Sydney*
- *Department of Cell Biology, Johns Hopkins University School of Medicine*
- *Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide*
- *Sirtris Pharmaceuticals, Inc.*
- *Molecular and Cell Biology Laboratory, The Salk Institute*





# Exercise Performance

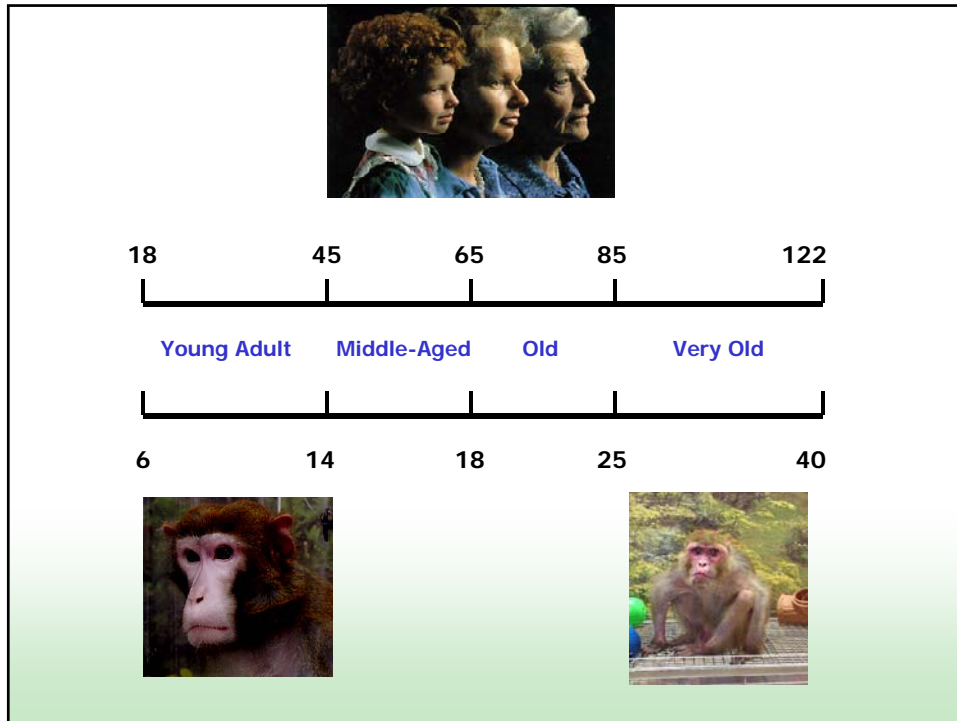




**CR MIMETICS WANNABES**

**Hypothesized Mechanisms of the Anti-Aging Effects of Calorie Restriction**

Reduced oxidative stress  
 Reduced glycation of proteins  
 Reduced DNA damage and increased repair  
 Reduced inflammation and autoimmunity  
 Increased metabolic efficiency  
 Maintain control over gene expression (chromatin?)  
**Improved stress responses--hormesis**



**Will CR mimetics allow us to have our cake  
and eat it, too?**



**So I wish you many happy birthdays!!!**

## Cocktails, anyone?

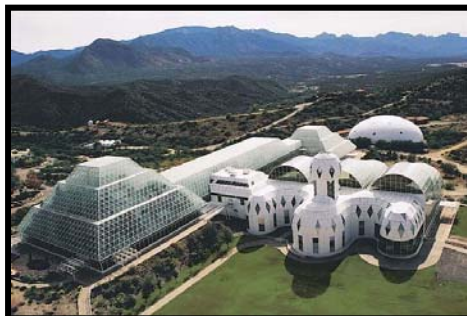


## The Ultimate CR Mimetic "Cocktail"

- Anti-glycolytic
- Insulin sensitizer
- PPAR agonist
- Antioxidant
- Mitochondrial efficiency enhancer
- Sirtuin activator
- Autophagy enhancer
- Lipid regulator







*The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 57:B211-B224 (2002)

**Calorie Restriction in Biosphere 2: Alterations in Physiologic, Hematologic, Hormonal, and Biochemical Parameters in Humans Restricted for a 2-Year Period**

**Roy L. Walford<sup>a</sup>, Dennis Mock<sup>b</sup>, Roy Verdery<sup>c</sup> and Taber MacCallum<sup>d</sup>**

<sup>a</sup> Department of Pathology, Center for Health Sciences, University of California, Los Angeles

<sup>b</sup> San Diego Supercomputer Center, University of California, San Diego

<sup>c</sup> D.W. Reynolds Department of Geriatrics, The University of Arkansas for Medical Sciences, Little Rock

<sup>d</sup> Paragon Development Co., Tucson, Arizona