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
Leonic 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](chart.png)

Source: U.S. Census Bureau
Total Federal Spending for Medicare and Medicaid under Assumptions about the Health Cost Growth Differential
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?
No! But, maybe we can slow it down a bit.

HEALTHY AGING DEPENDS ON A MULTITUDE OF FACTORS
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.
Type 2 diabetes, heart disease, osteoarthritis, stroke, and others

Cognitive functions

POOR NUTRITION

Vit E & C and folate

Vitamin D & calcium

Bone weakening

Obesity

Protein intake

Loss of muscle mass

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

The mission of the Pennington Biomedical Research Center is “to promote healthier lives through research and education in nutrition and preventive medicine.”
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)
Weekly Blood Pressure During DASH Intervention Feeding

Effect of the DASH Diet in Hypertensive

<table>
<thead>
<tr>
<th></th>
<th>Fruits/Veg</th>
<th>Fruits/Veg/ Low Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>-0.8/-0.3</td>
<td>-3.5/-2.1</td>
</tr>
<tr>
<td>n=326</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>-7.2/-2.8</td>
<td>-11.4/-5.5</td>
</tr>
<tr>
<td>n=133</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
Incidence of Diabetes

Risk reduction:
- 31% by metformin
- 58% by lifestyle

Cumulative incidence (%)

Years from randomization

Placebo (n=1082)
Metformin (n=1073)
Lifestyle (n=1079)

Physical Activity and Health

Health Benefits

Light  Moderate  High  Very high

Physical Activity Level
Decrease in Physical Working Capacity with Age

**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.
The HERITAGE Family Study

Distribution of the VO$_2$max training responses

- 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 = 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 = 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
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.

Subjects and Interventions

48 healthy men and women
   - Age 25 - 50y (45y for women)
   - BMI 25-30 kg/m²
   - 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)
**Study Design**

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Healthy Diet Control (Control)</th>
<th>25% CR (CR)</th>
<th>12.5% CR + 12.5% EX (CR+EX)</th>
<th>15% Wt. loss + Maintenance (LCD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BL</td>
<td>TDEE by DLW</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Food Provided**
  - M3
  - M6
  - Food at Home

- **Weight**
  - DEXA
    - % fat, FFM, FM
    - BMC, BMD

- **Energy Expenditure**
  - RMR (ventilated hood)
  - 24-h Energy Expenditure (chamber)
  - TDEE (Doubly labeled water)

- **Oxidative Stress** (DNA, Prot, Lipids)

- **Biomarkers of Longevity**
  - body temperature, Insulin, DHEAS

- **Insulin Sensitivity (FSIGTT)**

- **CVD risk factors**

- **Muscle and adipose biopsies**

- **QOL, Psychological Assessment**

- **Body Weight and Composition**

**Body Mass Changes**

- **Changes at week 24**
  - FM
  - FFM

- **Weight change (kg)**
  - Control
  - LCD
  - CR+EX
  - CR

- **Weeks**
  - 2 4 6 8 10 12 14 16 18 20 22 24
Biomarkers of Aging & Longevity

- Fasting Insulin
- Wrinkles
- ?

- DHEAS
- GH?

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
IHL but not IMCL is Reduced in Response to Caloric Restriction

A. IMCL

B. IHL

CR and CREX decreased LDL-C, increased HDL-C and decreased TG

Lefevre et al, in press, 2007
Conclusions

- CR with or without exercise improved insulin sensitivity and decreased IHL

- CR with or without exercise improved the cardiovascular 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

- No change in pulse frequency
- No change in half-life
- Increased amplitude & mass
- Increased GH concentrations
- Reduced GH concentrations
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
Metabolic measurements, risk factor assessments, dietary evaluation, and the oxidative stress

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 5 (331): Cognitive Function in Aging. K. Cherry
Resting Metabolic Rate Decreased with Aging but is not Correlated to Oxidative Stress

Although nonagenarians appear to be protected from the age-related increase in oxidative damage to DNA, reduced RMR could not be implicated in the mechanism.

Physical Activity Level is Correlated to Physical Functionality

PAL (TEE/RMR)
A HaPE Laboratory (Human Physiology)
Multi-site Study

Sponsor
National Institute on Aging

Clinical Sites
- Tufts University
  PI: Susan Roberts
- PI: Eric Ravussin
- Washington University in St. Louis
  PI: John Holloszy
- Coordinating Center
  Duke University
  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-α (TNF-α).
  - 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/m²
- 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
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.
Resveratrol as a Candidate CR Mimetic

<table>
<thead>
<tr>
<th>Bakers Yeast</th>
<th>Roundworms</th>
<th>Fruit flies</th>
<th>Mice</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

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

*Nature. 444: 337-342, 2006*


**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 Biologia del Desarrollo, Universidad Pablo de Olavide
- Sirtris Pharmaceuticals, Inc.
- Molecular and Cell Biology Laboratory, The Salk Institute

**Graph a:**
- **Y-axis:** Body weight (g)
- **X-axis:** Time (hours)
- Lines represent:
  - Standard diet
  - High Calorie
  - High Calorie + Resveratrol

**Graph b:**
- **Y-axis:** Proportion surviving
- **X-axis:** Time (hours)
- Lines represent:
  - Standard diet
  - High Calorie
  - High Calorie + Resveratrol

**Bar Chart 1:**
- **Y-axis:** Plasma Glucose (mg/dl)
- **X-axis:** Diet Group
- Groups:
  - Standard
  - Hi Cal
  - Hi Cal + Res

**Bar Chart 2:**
- **Y-axis:** Plasma Insulin (ng/ml)
- **X-axis:** Diet Group
- Groups:
  - Standard
  - Hi Cal
  - Hi Cal + Res

* indicates a significant difference.
Glucose Tolerance Test

Liver Morphology

Heart Morphology
Exercise Performance

![Graph showing exercise performance](image)

**Latency to fall from rotarod (s)**

- **SD**: Standard diet
- **HC**: High cal
- **HCR**: High cal + resv

Diet Group:
- 15 months
- 18 months
- 21 months
- 24 months

Note: * indicates statistical significance.
Proanthocyanidin fraction was most effective for lifespan and thermotolerance.
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
Calorie Restriction in Biosphere 2: Alterations in Physiologic, Hematologic, Hormonal, and Biochemical Parameters in Humans Restricted for a 2-Year Period

Roy L. Walford, Dennis Mock, Roy Verdery and Taber MacCallum

* Department of Pathology, Center for Health Sciences, University of California, Los Angeles
* San Diego Supercomputer Center, University of California, San Diego
* D.W. Reynolds Department of Geriatrics, The University of Arkansas for Medical Sciences, Little Rock
* Paragon Development Co., Tucson, Arizona