Interventions that modify aging and longevity

- Environmental manipulation.
- Caloric restriction.
  - Also called dietary restriction.
- Genetic manipulations.
- Drugs

Discovery of Calorie Restriction

- Environmental manipulations (temperature, feeding) of small, cold-blooded animals (fruit flies, water fleas) were known to alter lifespan.
  – Thought trivial, not relevant to aging in mammals.
- McKay was interested in the effect of the rate of growth on lifespan.
  – Late puberty → long lifespan and vice versa.
  – Known that reducing food intake slowed growth and development in mice, cows, rats, other mammals.
  – Also observed in humans, on subsistence diet women reach menarche at 18-19, in US at 12-13.

McKay thought that other studies had confounded a reduced calorie diet with malnutrition and starvation, and thus given unreliable results.

McKay’s experiment:
Feed rats a reduced diet rich in vitamins and minerals.

Results:
Caloric restricted male rats lived 75% longer than controls. Maximum lifespan +1 yr., 35% longer.
No difference for female rats.

In later experiments using a reformulated diet, found lifespan extension in both male and female rats.
Survival of Calorie Restricted Rats


CR in mouse

Feeding level: 1, 0.75, 0.44 times ad libitum

Caloric restriction extends life span

Data: Weindruch et al, 1986

Van Leeuwen et al 2002 A mathematical model that accounts for the caloric restriction on body weight and longevity. Bioenergetics 3: 373-381

CR phenotype

- Maintain youthful activity levels longer.
- Maintain immune function longer.
- Better performance in memory tests (water maze), retain memory abilities longer.
- Fewer tumors.
- More resistant to carcinogens.
- Less oxidative damage
  - Collagen crosslinks form slower (less AGEs).
  - Fewer free radicals.
- Lower mean blood glucose.

CR phenotype

- Body temperature lower in mice but not in rats.
- If extreme CR started in juveniles, get reduced rate of reproduction in rats, cessation of reproduction in mice.
- Metabolic rate per cell falls initially, then recovers (More efficient use of oxygen?).
CR variations in rodents that produce extended lifespans

• Start CR at weaning.
  • Small size, longer development time.
• Start CR in young adults.
• Start CR in adults.
  • Generally, lifespan extension proportional to time on CR.
• Fast and ad libitum diet on alternate days.
• Different diet compositions work:
  • Fats, proteins, or carbohydrates can be cut.
Different levels of CR, 10% - 70%, all work, generally more CR gives longer lifespan extension.

CR in mouse

Weindruch, et al., 1986

CR extends lifespan in every animal tested

<table>
<thead>
<tr>
<th>Species</th>
<th>Mean lifespan</th>
<th>Max. lifespan</th>
<th>CR mean ls.</th>
<th>CR max. ls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>23 months</td>
<td>33 months</td>
<td>33 months</td>
<td>47 months</td>
</tr>
<tr>
<td>Guppy</td>
<td>33 months</td>
<td>54 months</td>
<td>46 months</td>
<td>59 months</td>
</tr>
<tr>
<td>Bowl and doily spider</td>
<td>50 days</td>
<td>100 days</td>
<td>90 days</td>
<td>139 days</td>
</tr>
<tr>
<td>Protozoan</td>
<td>7 days</td>
<td>14 days</td>
<td>13 days</td>
<td>25 days</td>
</tr>
<tr>
<td>Yeast</td>
<td>21 generations</td>
<td>40 generations</td>
<td>26 generations</td>
<td>49 generations</td>
</tr>
<tr>
<td>Fly</td>
<td>25 days</td>
<td>47 days</td>
<td>46 days</td>
<td>78 days</td>
</tr>
</tbody>
</table>

Primate CR trials

• NIA
  - Juvenile (1 yr) and adult (3–5 yr) male rhesus monkeys (*Macaca mulatta*) and juvenile (1–4 yr) and adult (5–10 yr) male squirrel monkeys (*Saimiri sciureus*).
  - Fed a diet at or near ad libitum levels based on recommended caloric intake for age and body weight or fed 30% less of the same diet with this restriction gradually introduced over a 3-month period.
  - Actual food intake of CR groups 22–24% below control levels.
Primate NIA experiment

<table>
<thead>
<tr>
<th>Findings in NIA Primate CR Study</th>
<th>Matches Rodent Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) Body weight</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) Fat and lean mass</td>
<td>Yes</td>
</tr>
<tr>
<td>(-) Time to sexual maturation</td>
<td>Yes</td>
</tr>
<tr>
<td>(-) Time to skeletal maturation</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) Fasting glucose/insulin</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) Metabolic rate (short-term)</td>
<td>Yes</td>
</tr>
<tr>
<td>(*) Metabolic rate (long-term)</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) Body temperature</td>
<td>Yes</td>
</tr>
<tr>
<td>(*) or (+) Locomotion</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) Triglycerides</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) IGF-1/growth hormone</td>
<td>Yes</td>
</tr>
<tr>
<td>(+) 8-6</td>
<td>Yes</td>
</tr>
<tr>
<td>(*) Wound closure rate</td>
<td>Yes</td>
</tr>
<tr>
<td>(*) Clonal proliferation</td>
<td>Yes</td>
</tr>
<tr>
<td>(*) B-gal senescent cells</td>
<td>Yes</td>
</tr>
<tr>
<td>(-) Lymphocyte number</td>
<td>No</td>
</tr>
<tr>
<td>(*) Lymphocyte calcium response</td>
<td>Lane et al., 1999</td>
</tr>
</tbody>
</table>

Primate CR trials: UW experiment

- 30 adults (8–14 years old) male rhesus monkeys.
- Adult–onset DR
- Started with a 3–6 month period of baseline data collection.

- 15 animals were assigned to a control group and given free access to a semipurified diet for 6–8 hours per day.
- 15 monkeys were fed the same diet but at 70% of their baseline intake levels predetermined individually.

Results after 1 year:
- All monkeys appear to be in excellent health.
- Average body weights for controls increased by 9% while monkeys on DR did not gain weight.
- DR monkeys have less body fat than do control monkeys, whereas the amount of lean body mass has not been significantly influenced by DR.
- Reduction in physical activity for monkeys on DR relative to controls.
- Control monkeys gradually reduced their voluntary levels of food intake during the first year of study, and DR monkeys food reduced to maintain 30% difference.

Why does caloric restriction extend lifespan?

- There is evolutionary competition to successfully reproduce.
- Which drives life history strategies to maximize reproductive success.
Relationship between reproduction and lifespan

Adaptable life history strategies:
- Semelparity is an extreme case (Salmon, Antechinus stuartii, annual plants).
- Many other organisms alter their breeding time or rate to maximize reproductive success.

The caloric restriction response is an example of this.

- Low food availability -> postpone reproduction, wait for better conditions.
  - Animal puts energy into maintenance rather than reproduction, lives longer.
  - High food availability -> reproduce quickly.

How does caloric restriction extend lifespan?

- What cellular processes are altered?
- Is the life span extension an inherent consequence of CR, directly due to low metabolism?
- Or is the organism’s response a regulated response to the signal of CR?

Important characteristics of calorie restricted animals

- Maintenance of mitochondrial energy production
- Maintenance of a better daily balance of insulin and growth hormone that mirrors shifts in glucose vs fatty acid usage.
- Elevated sensitivity to hormonal stimulation, especially to insulin.
- Higher protein synthetic rates especially in old age
  - Ad Lib fed animals have a 40-70% decline over youthful levels

Insulin Receptor Down Regulation

- Constant food
- Constant glucose -> high insulin production
- Less receptors less sensitivity
- More insulin leads to a greater chance of getting adult onset diabetes (Type II).
  - Why? Mechanism not understood in detail.
Receptor Down Regulation
Lower Insulin Sensitivity

Hormone Levels
CR rats Vs Ad Lib Fed

Caloric restriction: Will it work in humans?

Caloric restriction is being tried by a number of individuals.

Calorie Restriction with Optimum Nutrition web site: http://www.cron-web.org

Article describing the experience of a college student on a caloric restricted diet:
http://health.ivillage.com/eating/estyles/0,,7559kd1h,00.html?ice=iv%7Cwb%7Ccrfasting1
Caloric restriction in humans

Effects of CR in humans:

Some biological parameters improve:
- Blood pressure reduced
- Blood sugar lowered
- Immune response improved

Some do not:
- Wrinkles
- Hair greying, loss.
- Progression slows

Studies of CR in humans

Big question: Does it extend lifespan?
Can’t be answered yet.

Studies look at biological variables in CR humans.

Compare the findings to CR in animals to get a provisional answer. Does CR in humans appear to be having similar effects?

Studies of CR in humans

Comparing people on CR voluntarily to matched controls:

CR group:
21 men and four women
1,400 to 2,000 calories per day for three to 15 years
Mean age 53±12 years, range 35 to 82 years

Controls:
25 age- and gender-matched controls
Typical Western diets
2,000 to 3,000 calories per day
Meyer et al., 2006

Meyer et al., 2006

Examined normal aging-associated impairments in diastolic function.

- Diastolic function indexes of the CR group were similar to those of younger individuals (average 15 yrs “younger”)
- Viscoelasticity and stiffness, were significantly lower than in control subjects.

Also improved in the CR group (measures of inflammation):
- Blood pressure
- Serum CRP levels
- TNF-alpha and TGF-beta(1) levels
Fontana et al., 2004

- 18 individuals who had been on CR
  - average of 6 years and
- 18 age-matched healthy individuals on typical American diets.

- CR group was leaner:
  - Body mass index (BMI)
    - 19.6 +/- 1.9 vs. 25.9 +/- 3.2 kg/m(2);
  - Percent body fat
    - 8.7 +/- 7% vs. 24 +/- 8%

- Lower in CR group:
  - Serum total cholesterol
  - Low-density lipoprotein cholesterol
  - Ratio of total chol. to high-density lipoprotein cholesterol
  - Triglycerides
  - Fasting glucose
  - Fasting insulin
  - Systolic and diastolic BP were all markedly lower
  - HDL-C was higher

Fontana et al., 2004

CR in humans and other animals

Only short term changes can be compared at this time.

<table>
<thead>
<tr>
<th>Human studies</th>
<th>Matches NIA primate study</th>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(-) Body temperature</td>
<td>Yes</td>
<td>Yes(mouse)/No(rat)</td>
</tr>
</tbody>
</table>