Aging and Metabolism

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In childhood we are "perfect."

- Everything works as we would wish.
- Life-sustaining processes are optimized.
- Skin is smooth, muscles strong, vision clear, minds sharp and ready to learn.
- We look upon our parents and grandparents with pity. Surely we will not meet THEIR fate ... in bed before midnight? Glasses to see? Unable to leap steps three at a time? Horrors!
But then .... entropy.

- Entropy is a measure of disorder.
- Entropy increases in any *closed* system.
- The good news: living systems are *not* closed systems.
  - Even ecosystems are not closed systems.
    - With energy, bouncing balls can be collected and put in a box.
    - With energy, bouncing atoms can be forced to form cells.
    - With energy, cells can be forced to fuse to form organisms and ecosystems.
  - Energy input to the biosphere is continuous ....
    - ... on Earth, from the sun, and thence into our bodies, from food.
  - Take-home: local entropy can be reversed. .... but it requires energy input from outside the system.
- The bad news: individuals are not the "end goal" - Mother Nature cares about species, not individuals.
Entropy and an Old House (example):

• Energy must be invested to maintain order.
  – BUT: How much order is worth maintaining?
• It's all about the allocation of energy: a house is not a closed system.
Entropy and an Old House (example):

- Energy must be invested to maintain order.
  - The roof will be damaged by weather.
  - Paint will discolor.
  - The floor will wear down in areas of frequent use.
  - Useful items get misplaced.

- How much order is worth maintaining? (When should we abandon the old house and build a new one?)
  - New roof?
  - Remove all old paint before repainting?
  - Resurface the floor? Replace it?
  - Find the hammer?

- It's all about the *allocation* of energy: a house is not a closed system.
Entropy and Organisms

- Energy must be invested to maintain order.
- How much order is worth maintaining? How carefully?
- Mom (Mother Nature) only cares about one thing: reproductive success.
  - Reproductive success is the ONLY thing that makes maintenance worthwhile to Mom.
  - Her answer is: repair the old house UNTIL we build a new one.
Entropy and Organisms

• Energy must be invested to maintain order.
  – External structures get damaged.
  – UV light, oxygen, and other reactive species cause chemical alterations in macromolecules.
    • Gene and protein activity must be maintained at the optimum level.
    • Damaged DNA must be accurately repaired.
  – Teeth and other permanent structures wear out.
  – Molecules drift due to random molecular motion.

• How much order is worth maintaining? How carefully?
Entropy and Organisms

- Energy must be invested to maintain order.
- How much order is worth maintaining? How carefully?
  - Replace integument? If so, which parts? Epidermis? Dermis?
  - Remove damaged intracellular components? Extracellular ones?
    - Should we precisely and accurately maintain controls (methylation, acetylation, phosphorylation, etc.)? HOW precisely and accurately?
      - Enough to last 1000 years, when wars or famines will kill us in 100?
    - Should we repair damaged DNA sequences with high fidelity?
      - How much fidelity? What is the cost/benefit to "perfection?"
    - Should we replace/repair extracellular structures?
      - Hint - Mom usually says "no" to this one!
  - Should we replace worn items .... teeth? lenses? intestinal lining?
    - We don't, we don't, and we do, by the way, respectively.
  - Should we put things back when they move?
    - Molecular transport. (Mom says, "sometimes.")
Hypermaturetion

• Seldom discussed, but potentially important.
• What is hypermaturenation?
  – Growth or developmental processes which are gradual and yet continue after an optimum is reached.
    • The eye's lens
    • Cartilage in the nose and ears
      – Individuals vary. For some, growth stops. For others - not.
    • Molecular level: gradual changes in a gene's expression or a protein's activity.
      – "Delayed developmental events"
        » e.g. puberty, male pattern baldness ...
  – Mom's view: why put on the brakes when the kids have left the car?
  – There may also be consequences in seemingly unrelated systems.... an entropic effect.
    • Gratuitous example: lens overdevelopment > bad vision > crick in neck from poor reading posture > cervical arthritis
Growth of the lens: *in vitro* observations
Wear and Tear and (Sometimes) Repair

- Some of the changes that occur with aging are due to prolonged exposure to harmful environmental conditions (as opposed to internal, unavoidable conditions)
  - UV light on skin
  - Physical Activity/Inactivity (there is an optimum)
  - Dietary excesses or deficiencies
    - The latter two combine with other factors to accelerate many changes that we think of as "aging," via the development of "metabolic syndrome" - which will be discussed shortly.
Metabolism

• Metabolism = the use of chemical energy to perform biological processes = catabolism + anabolism
  – Catabolism - breakdown of food or unused internal resources
  – Anabolism - use of energy and materials supplied by catabolism for action or construction
• The study of metabolism is a specialized field with many sub-fields.
  – Cellular Metabolism
  – Gross Physiology
    • Organ Metabolism
    • Organ-system Metabolism
    • Organismic Metabolism
Age-related Changes in Metabolism

- Altered Catabolism (variations in fuel usage)
  - Malfunction
    - Inappropriate Catabolism (destruction of useful items).
    - Damage to or down-regulation of youthful pathways.
  - Incidental
    - Consequent to altered diet, lifestyle, etc.
  - Adaptive
    - to adjust for malfunctions or incidental changes (see above!)
- Altered Anabolism
  - Changes in macronutrient storage location or type.
  - Decreased repair or replacement.
    - Examples: cartilage, bone, muscle
    - NOTE: some structures were not repaired in the first place (eg lens) - that's a different lecture.
Preferential fat vs lean tissue production and maintenance. Computed tomography (CT) scan of the upper leg (mid-thigh level) in a young and old subject, matched for body mass and height.


Note also: fat infiltration into and between muscles, enlarged femoral medullary cavity due to bone thinning.

©2009 by American Physiological Society
Sarcopenia - loss of muscle due to aging.

- Exercise can postpone but not prevent sarcopenia.
- Protein turnover in skeletal muscle is responsive to protein intake, but the response is blunted with age. Larger "spikes" of amino acids are required to trigger muscle hypertrophy.
  - Consequence: while protein synthesis is greatest after consumption of slowly digested proteins during youth, the higher initial levels achieved with rapidly digested proteins are more effective in promoting protein synthesis in the elderly
- mTOR activation following amino acid ingestion is attenuated with age
  - (more on mTOR later)
- Impairments may be partially due to digestive/absorptive declines

Review: Koopman and van Loon; JAP 106:2040-2049; 2009
Jack Lalanne, Master Athlete

In his youth ...

In his 70s ... and 80s ...

... and in his 90s ...
Public Health Note

• Muscle function is lost during even short term disuse. (atrophy)
  – Young individuals rapidly regain lost muscle mass.
  – The elderly rapidly regain lost weight, but not as muscle: lean tissue is replaced by fat.
    • Result: frailty.
  – This is immensely important: the elderly are the most likely to experience repeated bouts of disuse, due to age-related illnesses, injuries, and hospitalizations.
    • Several studies have suggested that appropriate nutritional supplementation during and following the period of disuse can greatly ameliorate this problem, but such practices have not been widely implemented.
      – Other interventions - anabolic steroids (short term), etc. - have been suggested.
    • "Primum non nocere" - but there is strong evidence that our accepted practices are harming more than helping. In our hospitals, we're turning the healthy elderly into the frail and dying elderly.
Changes in basal metabolic rate (BMR) with age are not fully explained by changes in body composition.

Categories of total energy expenditure.

Resting metabolic rate (RMR) accounts for 60–80% of the total, thermic effect of food (TEF) metabolism uses 10% of the total, activity energy expenditure (AEE) is the most variable component and can be divided into volitional exercise and non-exercise activity thermogenesis (NEAT). Exercise and NEAT can comprise 20–50% of total.

Age-related changes in categories of energy expenditure.

Body mass index is also plotted as a function of age to evaluate the tracking association between energy expenditure and body mass with age. Data reproduced from Table 3 in Black et al. (1996) demonstrates a decrease in all components of energy expenditure with increasing age. (B) Summarized changes in daily resting metabolic rate (RMR), activity energy expenditure (AEE) and the thermic effect of food (TEF) in men and women per decade after onset of adulthood (data reproduced from Elia et al., 2000).

Schematic of biological control processes for age-related decrease in resting metabolic rate.

Volitional physical activity levels across the lifespan in a nationally representative sample of Americans

Data from the (National Health and Nutrition Examination Survey—NHANES 2003–2004) over 7 days. Physical activity was measured by accelerometry as (A) mean counts per minute and (B) time spent in moderate or vigorous physical activity according to an activity count threshold.

Low BMR - good.
Low AEE - bad!

Fig. 9. (A–C) Kaplan–Meier survival plots adjusted for body mass along with mortality rates. Each component of energy expenditure was divided into tertiles of (A) total energy expenditure, (B) resting metabolic rate and (C) activity energy expenditure. Trend tests, which adjusted for the effect of body mass on both energy expenditure and mortality, were calculated with Cox regression analysis and used to determine the equality of survivor functions between the tertiles.

Accelerating Aging?

Physiological changes which occur with age are often thought to cause or to accelerate aging.

– However: did aging cause the changes, or did the changes cause the aging?
  
  • "Although it is well established that many metabolic pathways ... decline with age, it often remains uncertain if these [changes] are a cause or consequence of the aging process."

– Example: BMR declines with age ... so is maintaining a high BMR "youthful?"
Disease states generally require energy to combat, thus elevating BMR.

"We confirm previous findings of an age-related decline of BMR. In our study, a blunted age-related decline in BMR was associated with higher mortality, suggesting that such condition reflects poor health status."

What is aging?

- Aging is a cumulative, progressive, intrinsic and deleterious alteration in physiological state which increases vulnerability and culminates in death.
  - Note: it does not refer to chronological time-since-birth! Mice "age" in less than a decade, humans in roughly a century.

How long is 12 years?

For a hummingbird, time for twelve 2000-mile migrations from Central America to Alaska.

For mice, time for several generations to die of old age.

★ The tiny rufous hummingbird, the size of your thumb, its wings a blur, zips its way happily through twelve years or more of life. A mouse, not much larger and much less energetic, barely dodders along for three. What causes the difference?

★ A child given a kitten will still be a youth when the kitten dies of old age. Why does the cat age so quickly?
Fed or Fasted: Shifting Gears

• Absorptive State
  – The state in which the body is absorbing nutrients.
  – Lasts for several hours after each meal.
  – Energy and raw materials are supplied by nutrients being absorbed by the intestines.

• Post-absorptive State
  – Literally, "after absorption" – the GI tract contains no nutrients
  – Energy needs are met by drawing on stored fuels.
  – Raw materials are obtained by recycling existing molecules
    • Existing molecules are catabolized and their component parts used to build new molecules that may be needed.
Resource Allocation

**Caloric Surplus**
- Maintenance, Repair, Survival
- Growth, Development, Reproduction
  ... and harmful side-reactions?

**Caloric Deficit**
- Maintenance, Repair, Survival

Growth, Development, Reproduction
... and harmful side-reactions?
Feeding Paradigm

<table>
<thead>
<tr>
<th></th>
<th>Bodyweight (grams; 17.5 months)</th>
<th>MLSP (days; 80% mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AL</td>
<td>CR</td>
</tr>
<tr>
<td>LD-fed (NIH31)</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>EOD-fed (NIH07)</td>
<td>36</td>
<td>31</td>
</tr>
</tbody>
</table>

Data for C57 BL/6 mice: adapted from Goodrich et al (EOD-fed); Turturro et al (LD-fed)

Key: LD-fed, Limited Daily Feeding (60% of AL level)
EOD-fed, Every Other Day Feeding
Anson et al. PNAS 100(10), 6216-6220, 2003. (IF = Intermittent Fasting; LDF = Limited Daily Feeding)

**Venn Diagram**

- **IF**
  - Weekly food intake near *ad libitum* level
  - Bodyweight high
  - Body fat high
  - Fasting beta-hydroxybutyrate high
  - Total IGF1 high*

- **LDF**
  - *Longevity higher than ad libitum fed*
  - Large time blocks are spent in a post-absorptive state
  - Insulin sensitivity higher than *ad libitum* fed
  - Bodyweight low
  - Body fat low
  - Fasting beta-hydroxybutyrate low
  - Total IGF1 low

**C57Bl/6 mice**

* IGF1 levels have not been independently verified. Other measures have.
Model

1) A food shortage is sensed *at the organismic level*.
2) A centrally controlled signal is sent.
3) Responses to ensure survival during the shortage are initiated, including:
   - Up-regulated stress resistance (prevention)
   - Enhanced maintenance (repair)
   - Increased resource recycling (turnover)
   - Food seeking or ingestive behavior

Note on model:
   - Dietary effects on aging are due to positive pleiotropy: survive the shortage. "Slow aging" is not the selected phenotype.
More on recycling: Autophagy

• Macroautophagy
  – phagophore (a double-membraned, temporary organelle) forms to digest other organelles and long-lived proteins
  – phagophores fragment to form autophagosomes which fuse with lysosomes, so that cellular components can be recycled or discarded
  – Declines with age!

• Microautophagy
  – During periods of starvation, the cellular membrane invaginates and engulfs near-by cellular components, all of which are then degraded for recycling.

• Chaperone-mediated Autophagy
  – Some proteins in the cell are specifically degraded by chaperones which recognize a specific amino-acid sequence which they contain. These are degraded/recycled on a preset and not-fully-understood schedule. This pathway declines with age.
### An Overfed World
Life in the Land Of MetS and PMetS

**Table 1: The new International Diabetes Federation (IDF) definition**

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

- **Central obesity** (defined as waist circumference* with ethnicity specific values)

Plus any two of the following four factors:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised triglycerides</td>
<td>$\geq 150$ mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>$&lt; 40$ mg/dL (1.03 mmol/L) in males, $&lt; 50$ mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Systolic BP $\geq 130$ or diastolic BP $\geq 85$ mm Hg or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Raised fasting plasma glucose</td>
<td>(FPG) $\geq 100$ mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dL, OGGT is strongly recommended but is not necessary to define presence of the syndrome.</td>
</tr>
</tbody>
</table>

*If BMI is $>30$kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

**International Diabetes Federation (IDF)**

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www.idf.org • communications@idf.org
An Overfed World
Life in the Land Of MetS and PMetS (cont.)

"This is the first generation where children may die before their parents."
Paul Zimmern

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Obesity* (WC)</th>
<th>Triglycerides</th>
<th>HDL-C</th>
<th>Blood pressure</th>
<th>Glucose (mmol/L) or known T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–10</td>
<td>≥90&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.</td>
<td>1.7 mmol/L (≥150 mg/dL)</td>
<td>&lt;1.03 mmol/L (≤40 mg/dL)</td>
<td>≥5.6 mmol/L (100 mg/dL) or known T2DM</td>
</tr>
<tr>
<td>10–16 Metabolic syndrome</td>
<td>≥90&lt;sup&gt;th&lt;/sup&gt; percentile or adult cut-off if lower</td>
<td>1.7 mmol/L (≥150 mg/dL)</td>
<td>&lt;1.03 mmol/L (≤40 mg/dL)</td>
<td>Systolic ≥130/ diastolic ≥85 mm Hg</td>
<td>≥5.6 mmol/L (100 mg/dL) or known T2DM</td>
</tr>
<tr>
<td>16+ Metabolic syndrome</td>
<td>Use existing IDF criteria for adults, ie: Central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups*) plus any two of the following four factors:</td>
<td>Raised triglycerides: ≥ 1.7 mmol/L</td>
<td>Raised HDL-cholesterol: &lt;1.03 mmol/L (≤40 mg/dL) in males and &lt;1.29 mmol/L (≤50 mg/dL) in females, or specific treatment for these lipid abnormalities</td>
<td>Raised blood pressure: systolic ≥130 or diastolic ≥85 mm Hg, or treatment of previously diagnosed hypertension</td>
<td>Impaired fasting glycemia (IFG): fasting plasma glucose (FPG) &gt;5.6 mmol/L (≥100 mg/dL), or previously diagnosed type 2 diabetes</td>
</tr>
</tbody>
</table>

*The IDF Consensus group recognises that there are ethnic, gender and age differences but research is still needed on outcomes to establish risk.

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MetS and Risk

"It is estimated that around 20-25 per cent of the world’s adult population have the metabolic syndrome and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome."

"... people with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes."

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Type 2 Diabetes

**No Longer Just ‘Adult-Onset’**
A study of diabetes in overweight and obese youngsters bears an ominous warning about future health care trends in this country. It found that Type 2 diabetes, a new scourge among young people, progresses faster and is harder to treat in youngsters than in adults. The toll on their health as they grow older could be devastating.

These findings provide more evidence of why the country must get the obesity epidemic under control — to improve health and to curb soaring health care costs.

Only two decades ago Type 2 diabetes was called “adult-onset diabetes” because it was seldom found in young people, who suffered primarily from Type 1, in which the patient’s immune system destroys cells that make insulin, a hormone needed to control blood sugar levels. Type 2 — thought to be brought on by obesity and inactivity in many people — has increased alarmingly and accounts for almost a fifth of newly diagnosed cases in young people.

Obesity increases the risk of many chronic diseases. And some 17 percent of American children from age 2 to 19 are now considered obese, roughly half the rate of obesity among adults.
MetS and Risk (continued)

<table>
<thead>
<tr>
<th>List of recent meta-analysis references</th>
<th>Observations</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito K, Chiodini P et al. [48]^a</td>
<td>Breast cancer (postmenopausal)</td>
<td>MS was associated with a 52% increase in cancer risk ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Jinjuvadia R, Patel S et al. [49]^a</td>
<td>Hepatocellular carcinoma (HCC)</td>
<td>Overall 81% increased risk of HCC in cases with MS (95% CI, 1.37-2.41)</td>
</tr>
<tr>
<td>Esposito K, Chiodini P et al. [1]^a</td>
<td>Colorectal cancer (CRC)</td>
<td>MS was associated with an increased risk of colorectal cancer incidence in both men (RR: 1.33, 95% CI 1.18-1.50) and women (RR: 1.41, 1.18-1.70)</td>
</tr>
<tr>
<td>Esposito K, Chiodini P et al. [50]^a</td>
<td>Endometrial cancer</td>
<td>MS was associated with an increased risk of cancer (RR: 1.89, 95% CI 1.34-2.67, $P &lt; 0.001$)</td>
</tr>
<tr>
<td>Xiang YZ, Xiong H et al. [51]^a</td>
<td>Prostate cancer</td>
<td>The overall analyses revealed no association between MS and prostate cancer risk</td>
</tr>
<tr>
<td>Rosato V, Tavani A et al. [52]^a</td>
<td>Pancreatic cancer</td>
<td>Summary 55% increased cancer risk (95% CI, 1.19-2.01) in subjects with MS</td>
</tr>
</tbody>
</table>

^a Numbers in brackets are references cited in Reference list.
Age-Specific Prevalence of the Metabolic Syndrome (N=8814)

The Obesity Epidemic: Prevention and Treatment of the Metabolic Syndrome
Authors: George L. Blackburn, MD, PhD; Laura C. Bevis, MSN, ARNP, FNP-C, ACNP-C
Obesity Trends Among U.S. Adults Between 1985 and 2010

**Definitions:**

- Obesity: Body Mass Index (BMI) of 30 or higher.

- Body Mass Index (BMI): A measure of an adult’s weight in relation to his or her height, specifically the adult’s weight in kilograms divided by the square of his or her height in meters.
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990

2000

2010

Source: Behavioral Risk Factor Surveillance System, CDC.
If we knew what it was we were doing, it would not be called research, would it?

(Albert Einstein)
Be wary of the news.

- A warning about "news" - "dog nips shoe" will be reported as "Crazed Canine Tries For Throat"
  - New results get sensationalized. Real life example (of mice and men):

Potential players

• The metabolic pathways controlling the effects of macronutrient intake on the rate of aging are still being actively investigated.
  – Keep Einstein's quote in mind!
• Remember that new results get sensationalized, whether correct or not, by an over-eager press.
  • mTORC1
  • AMPK
  • Sirtuins and NAD+/NADH
  • BDNF?
mTORC1

• activated in the absorptive state
• promotes anabolism, esp. protein synthesis
• inhibited by rapamycin - now famous for its putative anti-aging effects
• Inhibits macroautophagy.
  – (Why recycle in a time of plenty?)
Rapamycin Trials for Pets

Dog Aging Project

Who We Are
The University of Washington’s Dog Aging Project is dedicated to promoting healthy aging in people and their companion animals. The Dog Aging Project is led by Dr. Daniel Promislow and Dr. Matt Kaeberlein. Dr. Kate Creedy is our Chief Veterinary Officer.

Learn more

LONGER, HEALTHIER LIVES FOR ALL DOGS
The Dog Aging Project is a unique opportunity to advance scientific discovery while simultaneously providing enormous benefit for people and their pets. We believe that enhancing the longevity and healthspan – the healthy period of life – in peoples’ pets will have a major impact on our lives. To accomplish this goal, we are creating a network of pet owners, veterinarians, and scientific partners that will facilitate enrolling and monitoring pets in the Project. The Dog Aging Project has two major aims, described further below: a longitudinal study of aging in dogs and an intervention trial to prevent disease and extend healthy longevity in middle-aged dogs.
In the dog world, humans are elves that routinely live to be 500+ years old.

"They live so long... but the good ones still bond with us for our entire lives."

"These immortals are so kind we must be good friends to them"

My heart wtf

Not gonna lie, this f***ed me up a bit.

POV Fantasy slice of life book when?

"Now I am old. The fur around my muzzle is grey and my joints ache when we walk together. Yet she remains unchanged, her hair still glossy, her skin still fresh, her step still sprightly. Time doesn't touch her and yet I love her still."

"For generations, he has guarded over my family. Since the days of my great-great-great-great-great-grandfather he has kept us safe. For so long we thought him immortal. But now I see differently, for just as my fur grows gray and my joints grow stiff, so too do his. He did not take in my children, but gave them away to his. I will be the last that he cares for. My only hope is that I am able to last until his final moments. The death of one of his kind is so rare. The ending of a life so long is such a tragedy. He has seen so much, he knows so much. I know he takes comfort in my presence. I only wish that I will be able to give him this comfort until the end."
AMPK

- Activated in the post-absorptive state.
- Promotes catabolism
  - Indirectly promotes breakdown of potentially damaged macromolecules, even in the absence of damage detection.
- Activated by metformin
  - common diabetes medication
  - CR mimetic (triggers post-absorptive response)
- Suppresses mTORC1
Metformin in Longevity Study (MILES)

This study is ongoing, but not recruiting participants.

Sponsor:
Albert Einstein College of Medicine of Yeshiva University

Information provided by (Responsible Party):
Albert Einstein College of Medicine of Yeshiva University

ClinicalTrials.gov Identifier:
NCT02432287

First received: February 24, 2015
Last updated: December 8, 2015
Last verified: December 2015

Purpose
Metformin, an FDA approved first-line drug for the treatment of type 2 diabetes, has known beneficial effects on glucose metabolism. Evidence from animal models and in vitro studies suggest that in addition to its effects on glucose metabolism, metformin may influence metabolic and cellular processes associated with the development of age-related conditions, such as inflammation, oxidative damage, diminished autophagy, cell senescence and apoptosis. As such, metformin is of particular interest in clinical translational research in aging since it may influence fundamental aging factors that underlie multiple age-related conditions. The investigators therefore propose a pilot study to examine the effect of metformin treatment on the biology of aging in humans. Namely, whether treatment with metformin will restore the gene expression profile of older adults with impaired glucose tolerance (IGT) to that of young healthy subjects.
Sirtuins and NAD+/NADH

- Sirtuins require NAD$^+$ as a substrate.
- Implicated (still controversial) in age-delay.
BDNF

- "Plasma BDNF significantly correlates with multiple risk factors for metabolic syndrome and cardiovascular dysfunction. Whether BDNF contributes to the pathogenesis of these disorders or functions in adaptive responses to cellular stress (as occurs in the brain) remains to be determined."
- "[BDNF] is the most prominent neurotrophic factor in the brain, [and] regulates differentiation, maturation, and synaptic plasticity throughout life."
- "... BDNF exerts an anorexigenic function in the brain."
- It is one of the signals used to coordinate the switch from fasting to fed.
- [By activating mTOR] in the hypothalamus, [BDNF indirectly] is thought to reduce food intake.

BDNF (continued)

• NOTE: early assumptions regarding food restriction revolved around true intake reductions, and appetite suppressants were proposed as potential anti-aging drugs.

• It is now believed that it is the relative, rather than absolute, level of restriction which matters; and further, that the nature of the ingested macronutrients and their ratios influence the response.
  – The neuroendocrine response to a perceived shortage leads to the "fasted" response of interest, not the actual energy available.
  – The response is complex and is influenced by the composition of the diet.
    • Excessive supplies of any macronutrient must be stored or used and deficiencies corrected by de novo synthesis, all while maintaining organismal homeostasis. Defects in any of the involved metabolic pathways disrupt homeostasis.
  – BDNF seems to be one of the sensors that allows switching from fasted to fed (but while it has attained great attention it is far from the only sensor).
The role of medical science in reversing entropy

  – Mom (Nature) only cares about one thing: reproductive success. That's the ONLY thing that makes maintenance worthwhile, to her.
  – **We** care about a great deal more!
  – Energy must be invested to maintain order.
    • External structures get damaged.
    • UV and oxygen cause chemical alterations in macromolecules.
    • Teeth wear out.
    • Molecules drift due to random molecular motion.

• Geroscience.
The role of medical science in reversing entropy


• Geroscience.
  – Replace integument? If so, which parts? Epidermis? Dermis?
    • All of it if necessary.
    • Use retinoic acid.
    • Dermal abrasion.
  – Remove damaged intracellular components? Extracellular ones?
    • It’s being studied.
  – Replace worn items .... teeth? lens? intestinal lining?
    • Dentures.
    • Man-made lenses (cataract surgery).
  – Molecular transport.
    • Improve glucose transport into cells (diabetes).
    • Etc. ....
  – This is a later lecture in the course, and could be a course in itself.
GeroScience

• Age is the biggest risk factor for CVD, cancer, and many other diseases
  – The various NIH institutes have formed a united "Geroscience Special Interest Group" based on that insight.
  – Viewpoint: aging and disease are integrated processes.
• An additional, unintended outcome of advancing treatments for age-related diseases: longevity.
  – Our efforts to extend healthspan will inevitably extend lifespan
  – Impacts policy and society in many ways.
GeroScience (GSIG at NIH)

The trans-NIH
GeroScience Interest Group
(GSIG)

Improving health span through interdisciplinary collaboration.

https://gsig.irp.nia.nih.gov/
The role of medical science in reversing entropy.

• Videos ...
  – https://www.youtube.com/watch?v=UFt73AvOk90
  – https://www.youtube.com/watch?v=xI38YRz1bbQ
Major Take-Home Messages

1) Entropy creates disorder; living systems combat entropy by devoting externally-obtained energy to the task.
2) Metabolic (catabolic and anabolic) homeostasis is optimized for species continuity rather than individual survival.
3) In humans, catabolic processes gradually predominate in terms of lean tissue and extracellular structures. Anabolic processes shift toward fat storage over time.
4) Food consumption controls sweeping metabolic shifts. In the fed state de novo synthesis and storage predominate; in the fasted state recycling is favored.
5) Recycling of resources has an incidental effect: removal of old and damaged items.
6) Major nexuses for the fed/fasted shift seem to be mTOR (which activates the "fed" pathways) and AMPK (which activates the "fasted" pathways.) However, this is new research and will be enhanced or modified by future work.
7) Optimizing diet and exercise decreases damage and enhances recycling and repair, extending healthspan and to a lesser extent, lifespan.
8) There is a worldwide obesity epidemic, which is the foundation for Metabolic Syndrome. The causes are multifactorial, as are the consequences. Major increases in age-related diseases including cardiovascular disease, type II diabetes, and cancer are resulting.
9) Illness- and hospitalization-induced inactivity in the elderly leads to frailty and accelerated health declines due to an inability to regain lost lean tissue, and is a major "action-item" for those interested in gerontology and public health.
10) Efforts to combat aging-related illnesses by medical science are growing more focused; "geroscience" is now one of the hottest topics throughout the NIH and the world. Efforts to defeat age-related illnesses have as an inevitable if unintended consequence: the eventual retardation of aging itself.