A Hypothesis on Biological Protection from Space Radiation Through the Use of New Therapeutic Gases

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Abstract. Radiation exposure to astronauts could be a significant obstacle for long duration manned space exploration because of current uncertainties regarding the extent of biological effects. Furthermore, concepts for protective shielding also pose a technically challenging issue due to the nature of cosmic radiation and current mass and power constraints with modern exploration technology. The concern regarding exposure to cosmic radiation is the biological damage it induces. As damage is associated with increased oxidative stress, it is important and would be enabling to mitigate and/or prevent oxidative stress prior to the development of clinical symptoms and disease. This paper hypothesizes a “systems biology” approach in which a combination of chemical and biological mitigation techniques are used conjunctively. It proposes using new, therapeutic, medical gases as both chemical radioprotectors for radical scavenging and biological signaling molecules for management of the body’s response to exposure. From reviewing radiochemistry of water, biological effects of CO, H₂, NO, and H₂S gas, and mechanisms of radiation biology, it is concluded that this approach may have great therapeutic potential for radiation exposure. Furthermore, it also appears to have similar potential for curtailing the pathogenesis of other diseases in which oxidative stress has been implicated including cardiovascular disease, cancer, chronic inflammatory disease, hypertension, ischemia/reperfusion injury, acute respiratory distress syndrome, Parkinson’s and Alzheimer’s disease, cataracts, and aging.
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1. Define the Problem
   - What is space radiation?
   - Why is it a challenge?
   - What is radiation damage?

2. Introduce the Hypothesis by Describing its Evolution
   - Is radiolysis of water related to radiation damage?
   - Could mitigation techniques in radiation chemistry of water be applied biologically to mitigate radiation damage?

3. Provide Overview of Some Medical Gas Research
   - Is the idea reasonable & feasible?
Highly energetic, light to heavy nuclei (high nuclear charge) (HZE) from stars (solar wind or galactic cosmic rays)

**NATURE**
- highly ionizing & penetrating
- capable of generating 2\textsuperscript{nd} radiation by nuclear fragmentation
- causes biological damage that is more difficult to repair

**CHALLENGES**
- difficult to shield (mass attenuation or force deflection (magnetic or electrostatic))
- unpredictability of true exposure & uncertainty in biological risk (currently)
- \(w/\) faster speeds from advanced propulsion; could relative velocity change the effective energy & thus dose?
What is Radiation Damage?

How Exposure Causes Disease
Disease is Macroscopic Effects of Molecular Modifications Initiated by Radiation Induced Chemical Reactions

**Chemical Changes**
- Ionizes & breaks bonds of molecules
- Makes organic molecules chemically reactive

**Molecular Transformation**
- Reactions cause structural modifications of molecule

**Molecular Changes**
- Structural changes alter molecular properties
- Changes biochemical functionality

**Cellular Changes**
- Increased membrane permeability
- Chromosome aberrations

**Tissue, Organ & System Changes**
- Tissue necrosis
- Bone marrow damage
- Decrease red & white blood cell counts
- Etc.

**Medical Symptoms**
- Cancer
- Ulcers
- Potentiating infection
- Nausea
- Anorexia
- Infection
- Etc.

**Radiation Induced Damage & Propagation**
- $\leq 10^{-15}$ sec

**Effects Propagate into Symptoms**
- $\leq 10^{-3}$ sec
- Minutes
- Days - Weeks
- Days - Years
Types of Molecular Damage

• **Indirect damage is mostly caused by ROS radiolysis byproducts**
  - "ions will probably have little effect as the DNA contains numerous ionizable positions at the phosphate group."
  - "Excited hydrolysis products may transfer the excitation energy to the DNA, leading to a localized break in the sugar-phosphate chain."
  - "Free radicals like OH and oxidizing products like H₂O₂ are highly reactive and can add to unsaturated bonds which upsets the sensitive hydrogen-π-bonding and may break the bonding between two helices."

• **Indirect damage is due to ‘poisoning’ of cell w/ decomposition products**
  - "The matrix effect considers the particle-water interaction in which ions, radicals and excited atoms are produced. This is the dominating effect at large radiation doses and dose rates…Free radicals and oxidizing products interact directly with cell DNA, causing the DNA-strands to break. One can state that at such high doses the cell is simply poisoned by decomposition products and the whole organ may be destroyed."
  - "Cross linking process is thought to be primarily a direct effect of the radiation, while double-chain breaks are largely indirect."

• **Direct damage is non-negligible in a biological systems where there are large molecules**
  - "… an excess of water in dilute solutions of DNA, however, the indirect effect predominates and double chain breaks are produced....."
  - "when aqueous organic solution is irradiated, the usual “indirect” reaction on the organic molecule is the removal of either a H atom or an entire radical group (such as the –CH₃)"
  - "Normally, in dilute solutions of small molecules, the radiation dose that will cause a considerable proportion of the solute to react with free radicals will only suffice to ionize directly a negligible proportion of the solute molecules. Thus, the direct action of the radiation on the solute molecules is small."
  - "However, the fraction of the total reactions which are related to the direct effect can be increased in several ways. If material is irradiated dry, the water molecules have been removed so that there will be only direct interactions with the molecules of the material. If a solution is frozen, the mobility of the radicals which are produced in the water molecules is decreased. This will decrease the possibility of indirect action and result in a greater proportion of the interactions being of the direct type."
  - "The dose required to produce a chemical change in a given proportion of the molecules of a substance, by direct action, is inversely proportional to the molecular weight of the substance assuming that the ionic yield is constant. (the larger molecules are more likely to be in the path of the radiation)...."
  - "The direct effect is not very important in consideration of simple chemical systems, but is of importance in macromolecular and biological systems because of the presence of many large molecules."

• **Damage among types of biological molecules appears to largely involve loss of H atoms**
  - "when aqueous organic solution is irradiated, the usual “indirect” reaction on the organic molecule is the removal of either a H atom or an entire radical group (such as the –CH₃ “methyl” group) from the molecule"
  - "saturated hydrocarbons probably undergo a hydrogen extraction & are converted into alcohols in a two step process"
  - "acetic acid most frequently loses a hydrogen atom...."
  - "energy which is absorbed any place in the molecule can be transmitted down the molecular chain to the weakest bond….They hydrogen bonds are among the weakest in the molecule and thus, are the first to be broken by radiation."

80% (water), 5% (DNA), 10-20% (RNA), remainder (protein)
Could radiochemical methods in inhibiting the radiolysis of water be applied biologically to mitigate damage?

Comparing Trends in Radiolysis of Water & Biological Factors of Radiosensitivity
Radiolysis Process
Dissociation of Water by Ionizing Radiation

**Energy Deposition**
- **Mechanisms**
  - ionization
  - excitation
- **Yields**
  - ions (H₂O⁺, sub-excitation electrons (e⁻)
  - excited molecules (H₂O*)

**Free Radical Formation**
- **Mechanisms**
  1. ionization $\text{H}_2\text{O}^+ + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{OH}$
     - charge neutralization $\text{H}_3\text{O}^+ + e^- \rightarrow 2\text{H} + \text{OH}$
  2. decomposition $\text{H}_2\text{O}^* \rightarrow \text{H} + \text{OH} \ (10^{-14} \text{ sec})$
     - ionization $\text{H}_2\text{O}^* \rightarrow \text{H}_2\text{O}^+ + e^-$
  3. thermalization $e^- \rightarrow e^-_{\text{aq}} \ (10^{-12} \text{ sec})$

**Chemical Reactions**
- **radical-radical rx.**
  - like—like $\leftrightarrow$ water decomposition
    - transformation into molecular decomposition products (H₂O₂, O₂, H₂, etc.)
    - alters electrochemical nature of water
    - potential for (1) corrosion (2) pressure rise
- **radical—molecular decomposition product RXs**
  - water reformation
  - reduces potential (1) corrosion (2) pressure rise.

**Within reaction radius?**
- yes
- no

**Decomposition**
- close proximity

**Reformation**
- sparsely distributed

Radicals diffuse into bulk of water

$\leq 10^{-15} \text{ sec}$

$10^{-15} - 10^{-12} \text{ sec}$

$10^6 \text{ sec}$
↑ Dose Rate Leads =
↑ Water Decomposition ⇔ ↑ Higher Lethality

- (+) frequency of particle tracks
- (+) overlapping of particle tracks
- (+) probability of radical-radical rx

[B₇O₂] = 2.25 x 10⁻⁷ mol/dm³

100 Gy in 100 sec

100 Gy in 1μs

Fig. 1. Radiolytic products in air-free pure water. Dose rate:
1 Gy per second. Doses up to 1000 Gy.

[Β₂O₂] = 9 x 10⁻⁶ mol/dm³

Fig. 2. Formation of radiolytic products in air-free pure water following a 100 Gy electron pulse delivered in 1 x 10⁻⁶ seconds.


Radiation w/ ↑Linear Energy Transfer (LET) = ↑Water Decomposition ⇔ ↑Damage Efficiency

- (+) higher energy deposition locally
- (+) radical production locally
- (+) radical packing density within the tracks & spurs
- (+) probability of radical-radical rx

1. Radiation with Higher LET has more RBE (relative biological effectiveness)  [less dose of higher LET rad. is needed to cause given damage]

2. higher LET produces type of damage that is more difficult to repair

   “Low LET radiation sometimes form clusters of ions along the particle track, i.e. produces high LET spots…High LET spots therefore increase the possibility of damage to both strands of the helix, causing a double strand break…In addition to double strand breaks being more difficult to repair than single strand breaks, double strand breaks caused by high LET radiation are more difficult to repair….It is believed that most single strand breaks are correctly repaired….Nevertheless, the repair is more difficult and the chances of “repair errors” (mutations) are much larger than for the single strand break….The chromosome aberrations only occur after double strand breaks.”

Impurities Affect the Net Outcome of Chemical Reactions by Competitively Scavenging Radicals

- Ionic & dissolved gases alter the chemistry by scavenging radicals.
  - “…in general, the presence of suspended or colloidal impurities does not result in increased decomposition rates or equilibrium concentrations of decomposition products.”
  - “…in general, the presence of ionic impurities results in increased decomposition rates and equilibrium concentrations of decomposition products, some impurities producing slight increase and other producing very large increases.”
  - “At low temperatures, some ionic impurities such as KBr, KI, and CuSO4 may produce partial pressures of 1,500 psi under radiation conditions that produce only a partial pressure of less than 10 psi for relatively pure water. At high temperature, i.e., above 400°F, exploratory work has shown that certain impurities strongly catalyze the backward reaction. Such impurities are copper, rhodium, palladium, platinum, silver, and iodine; and tin, iron, and titanium to a lesser extent.”

- Certain drugs provide radioprotection by acting as chemical modifiers in scavenging radicals.
  - “A number of radiosensitizing chemicals and drugs are known. Some sensitize hypoxic cells, but have little or no effect on normally aerated cells. Other agents known as radioprotectors reduce biological effectiveness….which scavenge free radicals.”

- Excess O₂ → H₂O₂ build up
- Excess H₂ depletes O₂ & H₂O₂


Similar Systematic Behavior: ‘Competing Processes w/ Critical Point’?

**Decomposition of Light and Heavy Water Boric Acid Solutions by Nuclear Reactor Radiations**

- **High LET** ($\text{B(n,}\alpha\text{)}$)
- **Low LET** ($\gamma$, e$^-$)


H₂, CO, & H₂S Medical Gas Countermeasure to Support & Supplement Our Natural Repair System to Increase Tolerance Before Damage Causes Disease

**Mitigation of Chemical Changes by Direct & Indirect Ionizations**
- SHIELDING – mass attenuation & force deflection (magnetic, electrostatic)
- Prevent uptake radioactive isotope (i.e. I tablets)
- Natural cell insensitivity (non-critical cell component, mitotic rate, cycle stage)
- DNA repair mechanism
- Temporarily & reversibly inhibit cell cycle to increase time for DNA repair
- Repair organic radicals
- Increase antioxidant radical scavenging capacity
- Decrease radical generation

**Mitigation of Mutations**
- Triggering of apoptosis of mutated cells
- Natural DNA repair mechanisms
- Apoptosis (cell death)
- Non harmful modification

**Mitigation of Biological Response**
- Regulation of Immune system response (anti-inflammatory)

**Mitigation of Disease**
- Medical treatments
- Radiotherapy
- Surgery

**Sources of Oxidative Stress**
- Radiation Exposure
- Endogenous ROS

**Damage Mitigation**

**Immune System Response**
- Anti-inflammatory

**Damage Pathway**

**Exposure**

**Protection**
Is this feasible?
Preliminary Compelling Evidence

- Natural repair mechanisms exist & can be supported by various biochemical mechanisms: (1) scavenging, (2) modifying radiosensitivity, & (3) biological promoters/'signaling'/triggering processes
  
  • The cell contains natural radical scavengers. As long as they are in excess of the radiolysis products, the DNA may be protected. When the products exceed the amount of scavengers, radiation damage and cancer induction may occur. In principle, there could thus be a threshold dose for radiation damage, at which the free radicals formed exceed the capacity of scavenging."
  

  • Also, chemical protectors can be introduced into the system which will compete successfully for the OH and H radicals formed. This will reduce the indirect effect"
  

  • A number of radiosensitizing chemicals and drugs are known. Some sensitize hypoxic cells, but have little or no effect on normally aerated cells. Other agents known as radioprotectors reduce biological effectiveness….which scavenge free radicals. Still other chemicals modifiers have little effect on cell killing but substantially enhance some multistep processes, such as oncogenic cell transformation. For carcinogenesis or transformation, such biological promoters can dwarf the effects of physical factors (on dose-response relationships) such as LET and dose rate,"
  

- Multiple DNA repair mechanisms exist
  
  • The cell is protected by different DNA repair mechanism which try to restore the damage. We don’t know the details, except when the repair goes wrong (e.g. a replacement of a lost nucleotide by a “wrong” base pair, etc.)…"
  

  • DNA damage response involves (a) removal of DNA damage & restoration of DNA duplex continuity (b) activation of DNA damage check points that arrests cell cycle (c) transcriptional responses that change profile in potentially beneficial way to cell & (d) apoptosis or cell death of un-repairable DNA.
  

- Natural repair appears to be more effective in-vivo
  
  • The repair system is believed to be more effective in a living organism, where the cells are in continuous exchange with the surrounding cells and body fluids, than in the tissue samples often studied in the laboratory…”
Evidence Among Various Fields

- **Radio-sensitivity & protection ⇔ Effect of Dissolved Gases on Radical Scavenging**
  - **Water Chemistry** - ionic & dissolved gas impurities scavenge free radicals promoting various outcomes depending upon type
  - **Radiobiology** - some radioprotectors function by scavenging radicals
  - **Health** - role of antioxidants in disease prevention
  - **Water Chemistry** - O₂ promotes water decomposition & formation of H₂O₂
  - **Radiobiology** - O₂ is a radiosensitizer & causes peroxidation damage of DNA. Also, tissue hypoxia has been attributed with radioprotective effects
  - **Medical Gases** - CO appears to mitigate oxidative stress
  - **Water Chemistry** - H₂ promotes water reformation, inhibits formation of H₂O₂ & reduces open circuit potential of water
  - **Radiobiology** - repair of organic radicals by H atom donation demonstrated in polymers
  - **Medical Gases** - H₂ appears to mitigate oxidative stress

- **Similarities in systematic behavior of ‘competing processes’ in which critical point of process domination can be altered**
  - **Radiobiology** - Biological effects at high doses are linear while at low doses are unpredictable likely attributed to variation in natural antioxidant capacity & repair mechanisms.
  - **Radiobiology** - Lower dose rates are less lethal implying repair mechanisms can keep up better till overwhelmed by rapid rate of damage production at higher dose rates
  - **Radiobiology** - Fractionation of exposure (broken up into a series vs. single time) decreases lethality implying that breaks between exposure allow repair processes to attempt to catch up.
  - **Water Chemistry** - H₂ shifts critical point where water decomposition, promoted by high LET component of radiation field, overcomes water reformation promoted by low LET component of radiation field (seen aqueous solutions of boric acid)

- **Management of Host Response**
  - **Radiobiology** - While hibernation doesn’t decrease lethal dose, it does delays the radiation response. As well, CNS depressants extend survival time for lethal exposures from hours to days.
  - **Medical Gases** - Inducing a reduced metabolic state may prove to be an ideal therapy for various shock or trauma in which dramatic reduction in metabolic demands may be highly protective
  - **Medical Gases** - H₂S produces a “suspended animation-like” metabolic status & transiently and reversibly inhibits mitochondrial respiration
  - **DNA Repair** - DNA damage checkpoint arrests cell cycle progression to allow for repair prevention before replication of damage.
H₂ Protects Human Lymphocyte Cells from γ Irradiation

H₂ appears to have a dose dependent relationship to cell survival

Protection only afforded from pretreatment implying antioxidant role

Cell survival stems from a decrease of apoptosis either from enhanced repair or damage prevention

H₂ Protection by Damage Prevention

H₂ reduced lipid & DNA oxidation in mice and cellular membrane oxidation in Human lymphocyte AHHH-1 cells exposed to γ irradiation

H₂ supports antioxidants as natural antioxidant levels (SOD & GSH) in mice are sustained through exposure to γ irradiation

H₂ decreases dROMs & increases BAP in patients undergoing radiotherapy


# Suggested H₂ & CO Protective Mechanisms

## H₂

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<tr>
<th>Biochemical Mechanism</th>
<th>Notes</th>
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<tr>
<td>radical scavenging antioxidant</td>
<td>• selectively reduces hydroxyl radicals (•OH) and peroxynitrite (ONOO⁻) but did not eliminate O₂⁻ or H₂O₂ when tested in <em>in vitro</em> [42].</td>
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<td>• does not decrease the steady-state levels of nitric oxide (NO) [42] which may be beneficial as endogenous NO signaling pathways modulate pulmonary vascular tone and leukocyte/endothelial interactions [61].</td>
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<td>• increases antioxidant enzymes such as catalase, superoxide dismutase or heme oxygenase-1 [45,46].</td>
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## CO

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<td>radical scavenging antioxidant</td>
<td>• binds to the heme moiety of mitochondrial cytochrome c oxidase. By binding to the heme, CO may prevent degradation of heme proteins which induce tissue injury by rapidly promoting peroxidation of the lipid membranes of cells [69, 70].</td>
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<td>• reduces mitochondria-derived ROS thus resulting in lower levels of ROS generation in which an adaptive cellular response is triggered leading to cell survival rather than cell death [71-73].</td>
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<td>• can induce HO-1 in cells to protect against injury [74-76]. Thus, detrimental excess of heme can be immediately removed by HO-1 enzymatic activity induced by CO.</td>
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<tr>
<td>decrease radiosensitivity</td>
<td>• impedes O₂ transport as it binds to hemoglobin with an affinity 240 times higher than that of O₂.</td>
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# Suggested H$_2$S Protective Mechanisms

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| radical scavenging antioxidant | • antioxidant inhibitor of peroxynitrite-mediated processes via activation of N-methly-D-aspartate (NMDA) receptors (Whiteman et al., 2004)  
• shield cultured neurons from oxidative damage by increasing levels of glutathione (Kimura et al., 2004)  
• induce upregulation of HO-1, anti-inflammatory and cytoprotective genes (Oh et al., 2006; Qingyou, 2004)  
• inhibits myeloperoxidase and destroys H$_2$O$_2$ (Laggner, et al., 2007) |
| anti-apoptotic | • reduces IR induced apoptosis via reduction of cleaved caspase-3 and cleaved poly (ADP-ribose) polymerase (PARP) (Sodha, 2008) |
| anti-inflammatory | • inhibit leukocyte adherence in the rat mesenteric microcirculation during vascular inflammation (Lefer, 2007) |
| decrease radiosensitivity | • vasorelaxation and vasodilation of isolated blood vessels via vascular smooth muscle K$_{ATP}$ channel-mediated hyperpolarization (Lefer, 2007; Nakao, et al., 2009)  
• transiently and reversibly inhibiting mitochondrial respiration (Lefer, 2007) |
| metabolic alteration | • produces a “suspended animation-like” metabolic status with hypothermia and reduced oxygen demand in pigs (who received it intravenously) (Simon, 2008)  
and mice (who received hydrogen sulfide via inhalation) (Blackstone, 2005; Blackstone, 2007). |


**Lefer DJ, King AL, “Cytoprotective actions of hydrogen sulfide in ischamea-reperfusion injury”, Exp Physiol 2011.**
Administration by Drinking, Injection, or Inhalation

**Generation By Chemical Reaction**

\[ 	ext{Magnesium Stick Insert} \]

\[ 	ext{Mg} + 2\text{H}_2\text{O} \rightarrow \text{Mg(OH)}_2 + \text{H}_2 \]

**Dissolution In Solution**

**DRINKING WATER**

**SALINE INJECTION**


**Non-Flammable Gas Mixtures As Additions to Atmosphere (Spacecraft/Station/Suit)**

**Hydreliox for Diving**

- \( \text{H}_2 \): 49%
- \( \text{He} \): 50%
- \( \text{O}_2 \): 1%

Is Additional Protection Possible by Directly Enhancing DNA Damage Checkpoints & Repair Mechanisms?

1. Damage sensor proteins don’t preferentially bind to damage DNA.
   - “DNA repair nor damage checkpoints should not be envisioned as operated by molecular switches. Rather, both processes are operative at all times, but the magnitudes of the repair or checkpoint reactions are amplified by the presence of DNA damage”
   - “Damage sensors not only bind to undamaged DNA in search of damage but they also contact undamaged DNA during specific binding…since the amount of undamaged DNA vastly exceeds that of damaged DNA, the DNA damage sensors spend far more time associated with undamaged DNA than with damaged DNA”

2. Damage DNA appears to have a charged & thus can be acted on
   - “The Comet Assay is based on the ability of negatively charged loops/fragments of DNA to be drawn through an agarose gel in response to an electric field. The extent of DNA migration depends directly upon the DNA damage present in the cells”

Utilize electric or magnetic fields to enhance DNA damage detection or increase protein interaction rate?
- nucleotide pool size has been indicated to have an important role in radiosensitivity → relate to ability of molecular diffusion within nucleotide pool?
- electric field centrifuge for assembly of damaged DNA damage?
- stirring of nucleotide pool to increase interaction frequency?

Some Papers Yet to Review
- Checkpoint mechanisms at the intersection between DNA damage and repair (Sept. 2009)
- Surveillance mechanisms for monitoring chromosome breaks during mitosis and meiosis (April 2008)
- Mechanisms of DNA double-strand break repair by non-homologous end joining (June 2005)
- ……
Summary

1. High charge & energy (HZE) nature of space radiation makes it difficult to shield and particularly damaging to DNA. Posed concern of increasing effective dose as spacecraft travel faster.

2. Biological damage develops from a series of events that start with chemical modifications initiated by ionization (direct & indirect) and which lead to molecular transformations that manifest into biological diseases.

3. Hypothesized a biochemical approach to interrupt the damage process by interfering with chemical reactions and managing biological responses.

4. Hypothesized that medical gases can support natural repair & protection as: radical scavengers, tissue preconditioners, and signaling molecules in managing biological response to exposure. Posed idea if DNA repair mechanism & damage check points could be enhanced themselves?

5. Administration of a medical gas therapy in space applications appears feasible & reasonable.

6. Approach addresses biological damage from oxidative stress caused by reactive oxygen species (ROS) & therefore may have implications for other diseases related to oxidative stress such as:
   - cardiovascular disease
   - cancer
   - chronic inflammatory disease
   - hypertension
   - Ischemia/reperfusion injury
   - acute respiratory distress syndrome
   - Parkinson’s & Alzheimer’s
   - cataracts
   - aging
Discussion & Questions

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