1. **What Causes Aging?**
    a. Pre-diabetes and diabetes:[1] The CDC estimates that 55% of the adult US population over the age of 18 years has either pre-diabetes (96 million) or diabetes (37.5 million), with insulin resistance with elevated insulin and insulin-like growth factor (IGF) levels. About 1 in 5 people with diabetes don't know they have it. More than 8 in 10 adults with prediabetes don't know they have it.[2]
    b. Diabetes is diagnosed with a blood test called the hemoglobin A1c that is greater than 5.6%. For every 1% increase in A1c above 5.6% there is a 20-25% increase in mortality from all causes including heart disease and cancer.[3] It would be important to have this test to make sure you are not one at risk.
    c. Our diet, if it is rich in sugars and starchy foods, leads to higher blood sugars requiring higher levels of insulin to control this. This diet causing higher insulin levels will eventually lead to insulin resistance, requiring even higher levels of insulin to bring our blood sugar back to normal. This is when we develop prediabetes and diabetes because we struggle to get the blood sugar back to normal as it goes higher due to our high simple carbohydrate diet.
    d. Next Steps: As so clearly stated by Dr Janssen in his review article, "*For successful prevention, limitation, and treatment of the metabolic syndrome (insulin resistance and diabetes), the focus should be primarily on changing our diets and lifestyle in accordance with our genetic make-up, formed in adaptation to Paleolithic diets and lifestyles during a period of several million years of human evolution*." [4]
    e. Excess insulin is not our friend, promoting weight gain and the development of diabetes,[5] heart disease,[6] cancer,[7] dementia[8] (Type 3 diabetes), depression,[9] and early death.[10]
    f. Glycation: this is the excess blood sugar acting as a molecular glue, making our tissues stiff and yellow. This stiffening occurs in the skin (that we can see as wrinkles) as well as our heart, muscles and joints, blood vessels, our eyes[11] (requiring reading glasses), and our intestines. One of the major differences between the young and old is the pliability of our tissues. To be stiff is to be old. Like our need for reading glasses (the lens of our eyes can no longer expand for close vision). Much of this stiffness is due to glycation. The blood test for hemoglobin A1c (glycosylated hemoglobin) measures this glycation. By avoiding eating sugars and starches (and thereby avoiding diabetes) we can markedly reduce the accumulation of this glue that slows us down.
    g. Inflammation: elevated blood sugar and insulin levels turn on inflammation in our bodies, leading to heart disease, cancer, and dementia. This inflammation is the root cause of most of the complications of diabetes, including all the above. Autoimmune disorders also increase inflammation, some of which is related to our diet (food sensitivities) and our microbiome (from lack of good "pre-biotics", the high fiber foods). The Mediterranean diet can boost the healthy bacteria and suppress the "bad" ones.[12]
    h. Epigenetic changes leading to cellular senescence (aging): histones are cellular molecules that regulate the transcription (reading) of our DNA genetic code. We will discuss this in Section 4 below.
    i. Loss of mitochondrial function: The difference between the rest of us and the Jedi Warriors is the number and health of our mitochondria. Young people also have more mitochondria than those who are older. But people who exercise also have more. So, does exercise make us younger? You got it. More on this later, discussing the Centenarian Decathlon or what we want to be able to do at age 70, 80, 90 or 100 years old, if we are fortunate enough to get there.
    j. Excess mTOR activation in the elderly:[13] mTOR is a growth signal that is increased in response to increased presence of nutrients, particularly sugar and protein. This elevated level of mTOR activity reduces autophagy (recycling of waste in our cells) leading to increased accumulation of the mis-folded proteins that promote neurodegenerative diseases like Alzheimer's and Parkinson's. It also increases inflammation and promotes tumor growth.
    k. Shortening of our telomeres: The longer the telomeres the longer the cell survives, and vice versa. But it appears that we can do things to lengthen our telomeres.

l. Sitting is the new smoking:
    i. NK cells and cancer: exercise turns on our natural killer cells (NK cells) that are our first line of defense against infections and cancer.[14] In a mouse study where two groups of mice were given an injection of cancer cells into their abdomen, one group of mice had exercise wheels and the other did not. The tumor-bearing mice randomized to voluntary wheel running showed over 60% reduction in tumor incidence and growth across five different tumor models. The NK cell population in the exercising mice were greatly expanded and activated against the cancers.[15] But this effect was greater if the mice were exercising for two weeks prior to tumor exposure, leading to greater tumor control at the injection site (active surveillance for cancer).
    ii. Mitochondrial function: oxidative stress from exercise is a strong signal for mitochondria to grow (mitochondrial fission/fusion) and recycle the old and worn-out mitochondria to new mitochondria (mitophagy and mitochondrial biogenesis). Jedi status.
    iii. Strength to rise from the toilet seat, climb a mountain, pick up a grandchild, etc.
m. Summary: Our diet and our movement (or lack thereof) appear to determine our fate.

2. What if we could slow and/or reverse aging?

a. What if we could remarkably reduce our risk of dementia, cancer and heart disease and stay healthy in the process? Well, it depends, you say. Can I take a pill? Yes and no, but we will get to that. First, we need to have some understanding of the medical concepts of insulin and insulin-like growth factor, AMP kinase as an energy sensor, autophagy (the recycling of toxic waste in our cells), mTOR as a growth factor that can also increase senescence (aging), and finally lifespan versus health span.
b. The problem with pills is they invariably have "off-target" effects, sometimes causing as much harm as good. The short answer to slowing aging depends on what we eat (and don't eat) and how we move (or don't move).

3. **Carbohydrate Intolerance**: Metabolic Syndrome, Fatty Liver disease, Diabetes, Dementia (Type 3 diabetes), heart disease, and cancer.
    a. Are some people more carbohydrate intolerant than others? Yes. Many of us are. Including me.
    b. Does this increase as we age? It appears so. If I eat the Standard American Diet (SAD), I become prediabetic (Hemoglobin A1c >5.6). Is that fair? No. Do I manage it? Yes. I have eaten the Mediterranean Hunter-Gatherer diet (Paleo-Mediterranean) since 1997, when I first saw the preface of a book The Schwarzbein Principle[16] that discussed the American Heart Association food pyramid diet as causing "new-onset" diabetes in patients with a recent heart attack (but they were likely pre-diabetic for years leading to their heart disease).
    c. "Nutritional Ketosis for Weight Management and Reversal of the Metabolic Syndrome"[17] written by Victoria Gershuni MD at UPenn Division of Gastroenterology presents the data. Shis is worried about fatty liver (non-alcoholic fatty liver disease: NAFLD) seen in patients with diabetes and pre-diabetes that is now the major cause of liver failure and liver transplantation in people over the age of 60 years old. We see fatty liver all the time in clinical practice. Hepatitis C is being cured. It is time to figure out fatty liver disease, and drugs are not the answer. It is the carbohydrate intolerance that must be addressed. But easier said than done.
4. **Yamanaka Factors: Longevity factors** (a short bit on the science of longevity)
    a. Dr. Yamanaka won the Nobel Prize in 2006 for his work on defining these longevity factors.
    b. These are OCK4, SOX2, KLF4 (OSK factors) and C-Myc (an oncogene, a cancer-causing gene). When you turn these on in transgenic mice or using AAV-9 gene therapy in aged mice they remain healthy and active for longer (healthspan) and live longer (lifespan).[18] Proof of concept, but not recommended. There are more natural approaches that we will be discussing below.
    c. The goal is to reset the cellular biologic clock and telomeres to an earlier (younger) setting.
    d. David Sinclair of Harvard is working on small molecules to turn on the Yamanaka Factors.[19] So far these are Valproate, Na Butyrate, and Forskolin. The following are the targets of these molecules:

i. To decrease Histone deacetylase (HDAC) activity: this inhibition helps to open our DNA for reading (transcription) and turning on many important pathways to reverse aging (hopefully focusing on the good ones). This is changing our "epigenetics" back to a younger setting or age.
ii. To increase stem cell production: growing new cells to replace the old ones. These are called induced pluripotential stem cells (iPSC).
iii. To increase cAMP and AMP-kinase activity, thereby reducing inflammation and cholesterol while increasing the recycling of cellular waste (autophagy) and DNA repair, as well as increasing the number and health of our mitochondria. AMP-kinase inhibits mTOR and thereby reduces senescence (aging) of cells as well as reducing the development and growth of malignancies. More on this below in section 5c.
iv. To decrease GSK3-beta activity: elevated GSK3-beta activity promotes the development of diabetes, Alzheimer's disease, cancer, depression, bipolar disorder, and anxiety. As well as misbehaving adolescents?!

5. How do we turn on the targets of the Yamanaka Factors naturally?

a. Decreasing histone deacetylase (HDAC) activity: Nutritional ketosis. The ketogenic diet has been used successfully for over 100 years in children with intractable seizures, yet it remains controversial. It turns out that ketosis reverses many of the findings of aging that we will be discussing, including increasing NAD+ levels. The Paleo-Mediterranean diet (a ketogenic diet) is a very low simple-carbohydrate diet, avoiding starches and sugars as discussed in the Staying Healthy handout and the table below.
b. Increase stem cells production: Exercise. You knew this was coming. Both Zone 2 and Zone 5. Zone 2 is basically like jogging while able to continue a conversation. Zone 5 is, wow, I am short of breath and when are we slowing down??? Thirty minutes of Zone 2 exercise per day, with some Zone 5 for 15-30 minutes at least twice weekly. But just getting up off the couch and taking the stairs is the most important starting point.
c. Increase AMP-Kinase activity: the energy sensor of the cell: the fasting-mimicking diet/time restricted eating/ nutritional ketosis/ and, of course, exercise (as above). This is what I try to focus on in my life, in both my diet and my movement. I ask myself, ***what will this do to my AMP-K activity?*** Excess nutrition with simple carbohydrates lowers AMP-K activity and shuts down healing. Exercise and the fasting-mimicking diet increase AMP-K activity leading to the following health promoting actions:
d. Increased AMP-kinase activity controls the following processes:[20]
    i. Decreases inflammation through increasing FOXO3 and decreasing NF-kappa B.
    ii. Increases autophagy for the recycling of cellular waste (like taking out the trash). This reduces the damage/aging caused by misfolded proteins like Tau and amyloid (associated with dementia).
    iii. Increases P53 expression, a cancer suppressing gene.
    iv. Increases the Tumor Associated Macrophages (TAMs) from M2 to M1 (from inhibitory to inflammatory) leading to increased cancer cell killing.
    v. Reduces HMG Co-reductase activity (like the statins Lipitor, Zocor, Crestor) reducing cholesterol and fatty acid synthesis, without the risks of statins including myopathy and liver issues.
    vi. Increases DNA repair through increased P53 activity.
    vii. Increases telomere length (a good thing for longevity).
    viii. Increases mitochondrial biogenesis and mitochondrial recycling (mitophagy).
    ix. Increased AMP-K signaling pathway inhibits mTOR pathway and have been shown to thereby reduce inflammation and death in COVID.[21]
e. Decrease GSK3-beta: a little lithium can go a long way. The parts of the world with the higher levels of lithium in their drinking water have lower rates of suicide and, evidently, better behaved adolescents with less violent antisocial activity. Lithium lowers GSK3-beta activity. It has been suggested that the 7 in 7-Up referred to the atomic mass of lithium and the Up referred to 'mood or lithium lift'. This mineral may be as important as magnesium, copper, and zinc yet we do not see it in our diet. The drinking water

data is very interesting, with lower suicide rates and lower adolescent violent crimes in areas with higher lithium levels in the water.[22] The dose for bipolar disorder is 800 to 1200 mg per day. So, a 5 mg per day is definitely "a poodle's dose."

6. **Foods that affect the Yamanaka Factors**

Positive Effects for Yamanaka Factors (Eat these)	Negative Effects for Yamanaka Factors (Avoid these)
Cruciferous vegetables like broccoli, cauliflower, Brussel sprouts, cabbage, Bok choy, arugula, collards, watercress, chard, kale, turnip, and radishes	Sugar and Starches and anything that raises Insulin/IGF (Insulin-like Growth Factor). Insulin and IGF turn on a cascade of enzymes that increase inflammation, elevated cholesterol, cancer growth, and mTOR (leading to aging).
Omega-3 and Olive Oil, avocado oil	Omega-6 oils, soybean oil and farm-raised fish (salmon)
Turmeric/Ginger/Pepper	Most desserts, which tend to be high in glycemic index
All other "green" vegetables like spinach, Zucchini, cucumbers, mustard greens, squash, celery, artichokes, leeks, endive, asparagus, lettuce, kohlrabi, parsley, garlic. Nightshades: tomatoes, eggplant, peppers (avoid if you have arthritis).	Most starches, including pasta, bread, potatoes, rice, tortillas, crackers, etc. Starches are rapidly converted to sugar, even in our mouths! Amylase in the saliva is a quick actor.
Fresh or frozen berries including strawberries, blueberries, raspberries, blackberries.	Sweet fruits like apples, oranges, bananas, watermelon, mango, pears, peaches, pineapple, figs, raisins, etc. Fruit juices and dried fruits as they are high in sugar.
Ketogenic diet as discussed above (less than 30-50 grams of digestible carbohydrates per day). Plus, water and Mg.	High glycemic foods including bread, cereals, crackers, rice, potatoes, corn, chips, pretzels, rice cakes, corn chips
Summary: Eat a primarily whole food <u>living</u> plant-based diet, with some healthy protein (1-1.5 grams/Kg) and all the healthy oils including lots of olive oil, avocado oil, and fish oils. With a few supplements like Vit D, Magnesium, etc. And drink water, green tea, coffee, and nut milks.	Summary: Avoid the primarily <u>dead</u> plant-based diet (most grains, beans, and rice) and products produced from them, as well as most fast food like pizza, French fries, hoagies, etc. Avoid all sodas (Coke and Pepsi, etc.). Try to substitute cauliflower rice for rice, hoagy salad for the hoagy with a roll, eat the top of the pizza on salad and throw away the crust, then have a second piece in a similar manner.

7. **Exercise**
   a. See Peter Attia MD's information on the <u>Centenarian Decathlon</u>:[23] what do you want to do when you are 100 years old? Get up off the toilet seat by yourself? (must be able to do a squat at 100 years). Climb a mountain? (V02max of 30), lift a carry-on bag into an overhead compartment (20 lbs) on the airplane? But we lose 10-15% per decade from age 50 until age 100 years. So, we need to pump it up a bit now if we are going to be able to do what we want to do then. Now is the time. That means today.
   b. <u>Exercise: Zone 2 and Zone 5</u>. Zone 2 is exercise where you can still hold a conversation, like jogging. Zone 5 is, wow, I am really short of breath and sweating and how much further can I go? Both are good and important. Zone 2 for 30-60 minutes five times per week, Zone 5 for 15-20 minutes twice per week are ideal. But ok to just do what we can do??
   c. <u>But what do I want to do when I am 100 years old?</u> Climb mountains? <u>We will need a V02max of 30</u>. Assuming we lose 10-15% per year (or more?), what V02max do we need at the ages of 50, 60, 70, 80, and 90 years of age. But you ask, what is my current V02max? Well, get on the treadmill at 1% grade and jog at 6 miles per hour for 1.5 miles. That is a V02max of 35.

Age	50's	60's	70's	80's	90's	100's
V02 max	55	50	45	40	35	30
Min/Mile	6	7	8	9	10	12
MPH	10	8.5	7.5	6.7	6	5

d. So, you can see if we want to climb mountains at the age of 70, 80, 90, or 100 years, we must step it up now. But please check with your physician prior to trying to do this to make sure you have no conditions that would prevent you from doing this safely. And a trainer is helpful to push us past our comfort zone.
e. In a meta-analysis of 15 international cohorts looking at daily steps and all-cause mortality, in a total sample of 47,471 adults, among whom there were 3013 deaths (10·1 per 1000 participant-years) over a median follow-up of 7·1 years ([IQR 4·3–9·9]; total sum of follow-up across studies was 297 837 person-years). Quartile median steps per day were 3553 for quartile 1, 5801 for quartile 2, 7842 for quartile 3, and 10 901 for quartile 4. Compared with the lowest quartile, the adjusted HR for all-cause mortality was 0·60 (95% CI 0·51–0·71) for quartile 2, 0·55 (0·49–0·62) for quartile 3, and 0·47 (0·39–0·57) for quartile 4.[24] This what they mean by just "Get up off the couch."
f. Kinetics and Intensity of NK Cell Mobilization to prevent and treat cancer. NK cells are the first line of defense against cancer, as discussed in the mouse study in Section 1-l above. Exercise-mediated mobilization of NK cells is a very rapid phenomenon. As little as 70 seconds of stair climbing has been shown to increase the frequency of NK cells in the blood by 6-fold. Subsequently, several studies have shown mobilization of NK cells within minutes with exercise, when performed with an intensity associated with breathlessness, increased heart rate, and elevated plasma epinephrine levels.[25] So just take the stairs.

8. **CISD2: Longevity gene**:[26] (the low hanging fruit?)
   a. CISD2 is one of the few pro-longevity genes identified in mammals. Genetic evidence from loss-of-function (knockout mice) and gain-of-function (transgenic mice) studies have demonstrated that CISD2 is essential to lifespan control. An age-dependent decrease in CISD2 expression during the natural aging of mice has been reported in a range of tissues, including the brain, spinal cord, skeletal muscle, heart, and skin.
   b. CISD2 deficiency is associated with many hallmarks of aging, including mitochondrial dysfunction accompanied by autophagy and cell death, disorganized proteostasis (misfolded proteins leading to Alzheimers disease, etc), deregulated nutrient sensing with metabolism disturbances, stem cell exhaustion, and alterations in intercellular communication.
   c. CISD2 alleviates age-associated disorders. A higher level of CISD2 during natural aging, when achieved by transgenic overexpression, improves Alzheimer's disease, ameliorates non-alcoholic fatty liver disease and steatohepatitis, and maintains corneal epithelial homeostasis without an increase in malignancy. CISD2, the expression of which otherwise decreases during natural aging, can be pharmaceutically activated at a late-life stage of aged mice.
   d. Hesperidin/orange peel: 3rd arm in the transgenic study the mice given hespiritin looked like the transgenic mice (younger and healthier) and lived longer.[27] Gene therapy may be a third option. But…
   e. A higher level of CISD2 is able to protect the liver from oxidative stress, reduce the occurrence of mitochondrial DNA deletions, and attenuate the pathogenesis of NAFLD and NASH.[28] A clinical trial in patients with fatty liver disease using 1,000 mg daily for 12 weeks showed a significant reduction in liver enzymes, total cholesterol, triglyceride, hepatic steatosis, high-sensitivity C-reactive protein, tumor necrosis factor-α, and nuclear factor-κB (NF-κB, this promotes inflammation).[29]
   f. Cycling study:[30] Hesperidin 500 mg per day maintained VO2max and ERG output in the racing off-season. So not like metformin that blocks the training effect of exercise.[31] But this requires the right microbiome to convert the hesperidin to hespiritin, the active molecule. So, eat the orange peel to help support your microbiome? Mediterranean Paleo with lots of living vegetables as pre-biotics for the microbiome.

9. **Measures of Effectiveness**
   a. Blood work: HS-CRP < 1.0, Hemoglobin A1c < 5.4, Ferritin < 50, Triglycerides < 50, Vitamin D > 50 (closer to 100), Fasting insulin < 2.5. Life Extension Foundation has a blood test to check these: Healthy Aging Panel (basic) Test $149. The comprehensive panel ($249) adds ApoB and Homocysteine but the basic is good enough if we are taking a good vitamin B complex and following a nutritional ketosis diet. Checking your Lipoprotein (a) is good to do once to make sure you do not have a genetically high level.

b. Wearables to monitor heart rate, steps, sleep quality, and possibly continuous glucose monitoring (CGM). One of my patients with diabetes and Rheumatoid arthritis bought a CGM monitor. She discovered that when she ate two tortillas her blood sugar rose by almost 100 points. This was after 7 years of me telling her to cut the tortillas. She did after that. Her blood sugar normalized when she cut the simple carbs (pasta, bread, potatoes, rice and most beans) and sweet fruits (apples, oranges, bananas, etc). CGM may be helpful to convince people what we eat really does make a difference.
c. VO2max of 35 to 50. (35 is running on the treadmill at 6 mph at 1% grade for 1.5 miles).
d. Pull ups, sit ups, squats, Russian twists, planks, side planks, etc. As many as you can do. The trainer will help you get stronger and more fit and steady on your feet (also key!).

10. **Ketogenic diet, the Fasting Mimicking Diet, and Time-Restricted Eating**
    a. Diabetes study[32]:
    b. Cleveland Clinic Handout[33]
    c. Fasting Mimicking Diet
    d. Time-Restricted Eating
11. **Sleep:** Apple Watch and Fitbit (etc.) will monitor your sleep quality. This turns out to be a very important parameter for wellness and longevity. The heart rate variability (HRV) is correlated with reduced heart disease risk and a greater sense of wellness. Drinking alcohol has a detrimental effect on this, as well as the overall stress people are experiencing and the presence of depression and anxiety.
12. **Saunas**: Sauna use (150-190 degrees F) for 15-30 minutes 3-5 times per week are associated with reduced cardiovascular disease, dementia,[34] and overall mortality.[35] Turning on the heat shock proteins. Cold therapy may have benefit (not yet clearly demonstrated in clinical studies) but can also increase the risk of vasospastic complications of heart disease. So cold therapy remains controversial, particularly in the older population at increased risk of undiagnosed heart disease.
13. **Excess Iron toxicity and Ferroptosis:** (One last thing!)
    a. Excess iron is toxic to the heart, liver, pancreas, and brain, thereby promoting the development of heart failure, cirrhosis and liver failure, diabetes, and dementia. Our bodies are designed to over-absorb iron to compensate for intestinal parasites and other blood loss. This leads to excess iron stores in healthy people because we are not facing these illnesses/infestations.
    b. Excess iron is also a carcinogen, increasing the risk of liver cancer 200-fold in patients with hemochromatosis, the most common inherited genetic disorder for the over-absorption of iron. It increases the risk of other cancers[36] as well in all of us, even with iron levels in the so-called "normal range." A healthy ferritin is less than 50 and the goal for patients with hemochromatosis is less than 20.
    c. Ferroptosis is programmed cell death mediated by excess iron increasing oxidative stress in the cell leading to cell death. This appears to be promoting cancer and neurodegeneration but may also be a target in cancer therapeutics.[37]
    d. How does one eliminate excess iron? The Red Cross. It is thought that women develop heart disease 10 years later than men because the iron storage levels do not begin to accumulate until after menopause. So, after menopause all women should donate blood if they qualify at the Red Cross. Men, since you never had the benefit of menstrual blood loss, should be donating blood from our early 20's onward until we reach 100+ years old.
    e. The goal for level of ferritin (the test for iron stores) is less than 50 ng/ml. Normal range is 12-300 ng/ml for men, 12-150 ng/ml for women. But healthy is less than 50. My ferritin is 23 ng/ml and I have donated a total of 11 gallons of blood (88 units of blood) to the Red Cross.
    f. Vitamin C increases the absorption of iron, in addition to blocking the training effect of exercise. I do not recommend a vitamin C supplement. Red wine increases the absorption of iron as well. The Red Cross is the answer to all of this.

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