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Fountain of Youth

As many readers of my articles are aware, my primary profession is Emergency Medicine. Over the past few days I have been recovering from an unusually brutal series of shifts. Work in the ER is always demanding. There is a continuous, unscheduled influx of patients, some of whom are critically ill, and some who have minor illnesses, and even some who use the ER's unimpeded access to healthcare professionals as an opportunity to get attention, drugs, avoid jail, or manipulate others. But some days are harder than others. In particular, Fridays, weekends, and Mondays are high volume and high acuity days. When you are scheduled to work a stretch of shifts that encompasses Friday, Saturday, Sunday, and Monday, you can plan on being pretty crispy when it is all done. Having completed such a stretch, you often find yourself asking... Why am I doing this? In the fog of fatigue, it is often difficult to remember the answer.

I was reading a passage from Sam Harris's book *The End of Faith* that reminded me of the answer. The passage is as follows:

“Consider it: every person you have ever met, every person you will pass on the street today, is going to die. Living long enough, each will suffer the loss of his friends and family. All are going to lose everything we love in this world. Why would one want to be anything but kind to them in the meantime?”

There in that passage was the motivator that I had forgotten. I went into Emergency Medicine to stand in the way of death, particularly premature death, and knowing that I would ultimately fail, to be kind in the meantime. Buried deeper in this premise, however, is the deeper desire to prolong life. The art and science of Medicine statistically has been very good at achieving this goal. But the goal has been achieved on a statistical/epidemiological level. The average lifespan of an adult male at the turn of the 20th century was 47; by the turn of the 21st century average lifespan had climbed to 76 years. This increase was not achieved by prolonging the lifespan of the individual, but instead by preventing the premature deaths of large numbers of people. The biggest impact was a decrease in infant and perinatal mortality. If you have any historic graveyards in your area, I suggest you visit them (particularly if some nurse midwife has convinced you to have your next child in your living room). You will find that in many cases up to half the graves belong to infants and mothers who died together during childbirth. Most men even in the early 20th century would have had several wives before they completed their child bearing years due to the problem of perinatal mortality. Technological advances as diverse as sewers and cars with crumple zones and air bags have added years to our collective life expectancy by preventing premature death in our cohorts. But the real goal of mankind has always eluded us. The goal to reverse aging in the individual is what we really want, but have been unable to achieve.

The history of anti-aging is old as mankind. The *Epic of Gilgamesh* is probably the earliest known literary work of man. The basis of the epic is the search for immortality. Gilgamesh probably ruled during the 3rd millennium BC, and his story was preserved on clay tablets by Assyrian King Ashurbanipal (who ruled in the 7th century BC). The story revolves around King Gilgamesh and his best friend Enkidu who go on many dangerous adventures together. When Enkidu dies on one of these adventures, Gilgamesh's feelings of loss drive him toward a quest for immortality. Ancient Chinese emperors sent ships of young men in a quest for a magic pearl that would reverse aging. Many Chinese believe that in the process of searching for this pearl, these men sowed the seeds of what would become Japan. In the 16th Century AD Spanish Explorer Juan Ponce de Leon led an expedition through the Caribbean islands and Florida in search for the Fountain of Youth. During the middle ages Alchemists sought the Philosopher's Stone that was believed capable of turning lead into gold, as well as prolonging life, and restoring youth. During the 20th century, as average lifespan increased, literary works also dealt with the potential complications of life-extension. One of the major themes in works such as *The Mars Trilogy* is the extreme boredom that comes with infinite lifespan, or the problem of becoming one's own ancestor as seen in Robert Heinlein's *Time Enough For Love*.

During the late 20th century the scientific community took up the cause of Life Extension. Many theories have been advanced, and promising discoveries have been announced. The general public has kept close track of these developments, and entire subcultures have lined up behind the various theories of age reversal. To provide the proper context for this article, we will review some of these theories and how they

pan out when tested scientifically. Information regarding these strategies was obtained from the *Wikipedia* website (en.wikipedia.org/wiki/Antiaging).

Anti-aging nutritional supplementation and medicine

The free radical theory of aging is addressed by taking antioxidant supplements such as vitamin C, vitamin E, lipoic acid and N-acetylcysteine. While theoretical data support this notion, no animal or human experiments have proved its validity.

It is known that diabetes and high insulin levels accelerate aging. This may occur by cross-linking of important proteins by sugars. Anti-glycating supplements that reduce these cross bridges might slow aging. Examples include carnosine and pyridoxamine. Again, no animal or human experiments have proved their effectiveness.

Resveratrol has received much attention lately because it was shown to increase lifespan in fish and is currently being tested in rodents. Based on these studies, resveratrol has been flying off the shelves of health food stores.

Caloric Restriction

Caloric restriction with adequate nutrition (CRAN) has been shown to extend maximum lifespan on almost every species that has been tested. A 50% reduction in calories has resulted in up to 50% increase in lifespan. Success has been shown in rats, yeast, fruit flies and nematodes (worms). Experiments are currently being done in primates, but no proof currently exists for primates or humans. A group of people who strongly believe in this theory have the willpower to restrict their caloric intake are being followed by Dr. John Holloszy at Washington University in St. Louis.

Chemical and Genetic Interventions

Growth Hormone injections have become popular, particularly the act of supplementing to levels normally seen during youth. There is some data in mice to support this theory, but there is conflicting data suggesting that mice that lack a receptor for growth hormone actually live longer. No primate or human data have confirmed this theory. This theory has appealed enough to some physicians and the general public to support a burgeoning field of boutique medicine. Cenegenics Institute is the leader in this field, and has survived much criticism from the more conservative aspects of the medical community. Despite the large body of medical literature on this topic, no study has proven its effectiveness or long-term safety.

Genetic engineering of a gene called Sir2 in yeast has resulted in prolonged lifespan. Mice genetically engineered to lack insulin receptors in fat have been shown to live longer. No interventions in primates or humans have been done thus far.

Cloning and Body Part Replacement

Current cloning and stem cell research has demonstrated the feasibility of growing replacement body parts, most notably the fabrication of a dog's bladder that was successfully transplanted into a living dog. It is possible that in the near future, worn out body parts could be replaced by replacements cloned from our own tissue. The most fantastic extension of this vision would be to transplant our brains into a new body cloned from our own tissue. It is very likely that cloning technology will be available before life-extending technology becomes established. However, the technology is still very new and full development is being impeded by ethical questions and religious/political opposition.

We can see that much progress has been made and pieces of the life extension puzzle are just now starting to fall in place. However, no intervention has been shown to have an effect on humans, and the progress being made is unlikely to affect the lifespan of anyone currently living.

Something Amazing Occurs

On May 23, 2007 a major stride in the quest for life extension occurred. Researchers Simon Melov et al announced a treatment that successfully reversed aging. (<http://www.plosone.org/article/lookup?doi=10.1371/journal.pone.0000465>). This reversal occurred not in worms, fish, or rats; but actually occurred in human subjects. More importantly, this reversal was not simply a marker of aging, but an actual reversal toward normal youthful function at the genetic level. The researchers tested 596 genes that appeared to be markers of declining function as a result of age. Most of these genes were associated

with mitochondrial function. This is important for two reasons. First, the mitochondria are the powerhouses for the cells of your body; they are the engine that makes us run. Secondly, mitochondrial DNA is easier to study with greater certainty of accuracy because all of your mitochondrial DNA comes only from your mother. As a consequence, differences in expression cannot be accounted for by the contribution of another person's (i.e.-father's) DNA that may react differently under experimental conditions. The study definitively identified 179 genes that were reversed by the intervention, and as the study stated "the transcriptional signature of aging was markedly reversed back to that of younger levels for most genes that were affected by both age and exercise."

So what was this miracle treatment? The answer is STRENGTH TRAINING. Strength training performed twice a week for a period of 26 weeks. Even more amazing is that by standards of most people who participate in training facilities such as Ultimate Exercise, it was strength training that was done relatively poorly on substandard equipment. The researchers had subjects perform leg press, chest press, leg extension, leg flexion, shoulder press, lat pull-down, calf raise, abdominal crunch and back extension for 3 sets of 10 reps, and arm flexion and arm extension for 1 set of 10 reps. The equipment was Universal Gym, Inc. equipment. Resistance was based on 50% of a 1 rep max and progressed to 80% of a 1 rep max. Over the study period the subjects increased their strength by 50% which made them only 38% weaker than 25-year-old cohorts.

While impressive, it is not uncommon for state of the art training facilities to more than double strength in elderly clients. We have an 83-year-old that uses significantly more resistance than the average 25-year-old off the street. When I hired my current manager Ed Garbe, I told him that within 12-16 weeks of training he would likely be stronger than he ever had been at any point in his life. During our last workout together, he admitted to having skepticism with regard to that statement but that he is now a believer. He said "this stuff is literally the fountain of youth". Ed is 63 years old.

A New Definition of Aging

What is interesting about this landmark article is the genes that were identified to be related to aging were genes that were largely involved in synthesizing enzymes of anaerobic metabolism or transporting anaerobic substrate for aerobic use. What therefore appears to be a marker of youth, and consequently what gets lost with aging, is the ability to perform high-intensity anaerobic work. This fits well with a concept proposed by Dr. Arthur Devany (www.arthurdevany.com). Dr. Devany is an economist who developed the concept of Evolutionary Fitness. While I differ in specific details of his exercise recommendation, I believe his notions regarding diet, exercise and how they effect the expression of genes handed down to us by evolution are absolutely brilliant. The concept that Dr. Devany coined is *Physiologic Headroom*. Physiologic headroom is basically described as "the difference between the most you can do and the least you can do". Dr. Devany notes that when the difference between the most you can do and the least you can do becomes zero, you are dead. Consequently, it is easy to extrapolate that the process whereby the most you can do and the least you can do decreases could be called aging. What determines the most you can do is basically anaerobic metabolism. Anaerobic metabolism precedes aerobic metabolism and can cycle much more quickly than aerobic metabolism. This makes sense from an evolutionary standpoint because anaerobic metabolism is much more primitive than aerobic metabolism which was a much later evolutionary development. It therefore makes sense that aerobic metabolism requires substrate from the anaerobic metabolism to run. Once the ability to deliver that substrate declines, aerobic metabolism must decline as well, and the amount of output that can be generated from any kind of exercise will approach zero.

Clearly then, the type of exercise that can provide for maximal physiologic headroom is high-intensity exercise. Performing work at a rate that requires a fast turning of anaerobic metabolism up-regulates the enzymes that make physiologic headroom possible. It is no coincidence that these enzymes are found predominantly in fast-twitch muscle. Fast-twitch muscle is the last category of muscle that is recruited when we perform work. We will only tap these fibers if we have accumulated fatigue in slow- and intermediate-twitch fibers more quickly than they can recover, only then can we tap fast-twitch fibers almost exclusively. This is best accomplished with high-intensity strength training where fatigue is reached in 45-90 seconds. Fast-twitch fibers *can* be recruited through explosive training and sprint training, but they are recruited *in tandem* with slow and intermediate fibers which can result in enough force production to produce acute injury and enough chronic force to result in worn out joints over the course of years. I think a type of exercise (HIT/ SuperSlow) that stimulates the development of physiologic headroom without producing

injurious force makes incredible sense.

If we embrace this concept of aging (the gap between maximal and minimal output), and the type of training that enhances this capability, then we must acknowledge that there is a type of exercise that can produce the opposite result. Low-intensity, steady-state exercise will actually accelerate aging by this definition. When exercise is of low intensity, the slow and intermediate fibers are called upon at a rate that does not result in fatigue and does not stimulate rapid cycling of anaerobic metabolic pathways. As a result, anaerobic enzymes down-regulate and fast-twitch fibers are never called upon. An adaptive response then occurs whereby the fast-twitch fibers are allowed to atrophy and die. This is because, if they are never used in the face of this activity, they are simply dead weight that must be carried along. While one may argue that this is an adaptation, we must remember that not all adaptations are beneficial.

In the process of losing our fast-twitch fibers, we do not just lose physiologic headroom. We begin to lose the largest glucose sink in our body. Glucose is stored as glycogen (long chains of glucose strung together like a tinker-toy model). About 70 grams of glycogen can be stored in the liver and 220 grams can be stored in the skeletal muscle. The glycogen in the liver is used mainly to maintain a stable blood glucose level. The glycogen stored in the muscle is used as emergency on-site fuel for bursts of high-intensity muscular work.

The majority of the glucose stored in muscle is in the fast-twitch fibers because that is where the fuel is needed for emergency anaerobic metabolism. When we jettison these fast-twitch fibers, we set up a scenario for a rapid decline in metabolic health. By losing the largest storage warehouse for glucose in our body, we begin to lose insulin sensitivity. We already only have a storage capacity of 290 grams at baseline (which is way less carbohydrate than the average American consumes in a given day). As we lose the glucose storing capability of these fast-twitch fibers, we have nowhere for our dietary glucose to be stored and glucose stacks up in the bloodstream. The liver and muscles become completely full and decrease the number and sensitivity of their insulin receptors to protect themselves from excess glucose being transported into the cell (excess glucose binds to metabolic proteins and enzymes in a process called glycosylation—imagine pouring pancake syrup on your keyboard).

Glucose then begins to stack up in the blood that in turn stimulates the pancreas to make more insulin. This creates a stimulus for continued decreases in muscle insulin sensitivity. The body tries to protect itself by *increasing* insulin sensitivity in other areas, most notably your fat cells. A circuitous metabolic process then occurs where excess glucose is circulated to the liver where it is converted to Triacylglycerol (triglycerides) and is circulated to the fat cells for assembly and storage. The relative increase in glucose metabolism through aerobic pathways produces oxidative free radicals that produce inflammation and accelerate the aging process.

The details of all of this downstream metabolic mayhem will be the subject of future articles and are discussed in further detail (with supporting literature) in *Body by Science*. Interestingly, if you ever get yourself into this predicament and visit your doctor, you will be told to eat a high-carbohydrate, low-fat diet and to take up steady-state activity. If you are lucky, you may get started on meds that kill your testosterone production and produce weakness in what little muscle you still have left. What will really turn around this metabolic process is high-intensity strength training combined with a diet based on evolutionary principles.

Finally, The Most Amazing Thing

After this article was released, the most amazing thing that happened was...NOT MUCH! Despite the epic search for life extension throughout the history of mankind, the first documented success in this regard was not met with much fanfare. There were a few articles in the media, but they were not very prominent and did not produce much response. The amount of coverage this received was miniscule when compared to the coverage received by resveratrol or caloric restriction.

I believe the real reason this research has not gotten the response it deserves is because we are not talking about a pill. The benefit can only be obtained through one's own effort, and (by the standards of the general public) damned hard effort at that. In the end, personal effort is the only answer for just about any goal we desire. In any entropic system, breakdown can only be prevented by the input of energy. This is the true joy of running a high intensity exercise facility; we get to interface with the small and dynamic portion of the population who understands this fact. As to the portion of the population who choose to

abdicate this responsibility... we harbor no hard feelings. We and our clients will be happy to drive you to your doctor appointments, push your wheelchairs, and attend your funerals.

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