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Culture Shock:
Thinking About Reintegration after Preservation

By Paul Beighley, M.D.

A common concern voiced by individuals contemplating cryopreservation is the possible difficulty in psychological adjustment to an unknowable future. While there is no way to predict the psychosocial milieu people will encounter on revival, to inform mitigation strategies to minimize psychological distress and promote adaptation it may be useful to look at lessons learned by American expatriates in dealing with 'culture shock' as they assimilate to new environments secondary to geographic displacement.

My experience with the issue of culture shock came after being hired to provide support as a psychiatrist for the U.S. Department of State medical program as a Regional Psychiatrist 15 years ago. The State Department started this program in the aftermath of the Iran hostage crisis and during a period of increased attacks upon U.S. diplomatic personnel and their families at embassies overseas. The idea was that by deploying psychiatrists with regional responsibilities at centrally located embassies abroad a measure of mental health support could be offered to help with distress experienced by our embassy families. The program started with three psychiatrists but by the time I was hired had expanded to 18. In order to enhance the credibility of the psychiatrists in this program they are assigned overseas, fully accredited as diplomats and integrated into the embassy community.

My first assignment was to the West African region where I was posted in Accra, Ghana. Like all the other diplomatic personnel my housing was in the community and I lived and worked in the same office setting at the embassy as the other Americans assigned there. Unlike most other diplomatic staff my responsibilities included providing support to 16 other embassies in the West Africa region and I was on travel status over half the time visiting these embassies, meeting with families, and providing general support. The experience of culture shock by Americans locating to these countries was an ongoing concern and I think informative in thinking about adjustment difficulties we might expect after revival from a similar population, although very different circumstances. Keep in mind that in these West African countries there needed to be adaptation to a different language, cultural and religious values, diet and socioeconomic issues. It's a long, long way from Washington DC to Ouagadougou in Burkina Faso!

The displacement from a typical U.S. suburb to an impoverished third world country, with no language training and no job, is highly stressful to most families. You start your day in a modern US airport, have a long series of flights, and suddenly are in a vastly different world than what you are used to. Perhaps this will be somewhat analogous to what an individual who undergoes cryopreservation might experience in terms of their having no sense of a gap in time between preservation and the new reality.

Because my wife, dog and I were integrated into the diplomatic staff we too were able to see from the ground level what this experience entailed. We were able to try out the very strategies I had been taught to see how well they worked, were they practical, and how culture shock is experienced on a very personal level. In talking with literally hundreds of individuals who described culture shock I found certain common coping mechanisms and experiences.

How can we best define 'culture shock'? A good working definition would be:

> A period of adaptation from one culture to another resulting from experiences challenging an individual's understanding of the world and basic values. This would include basic unconscious beliefs about customs, assumptions, values, and behaviors being universally shared. Culture shock is most commonly the result of cumulative experiences in a new environment not a single event.

Contributors to culture shock include:

- Being cut off from familiar cultural cues
- Living and working over an extended period of time in a situation that may be ambiguous
- Having values questioned, causing moral quandaries
- Being expected to function socially at normal skill and speed but not understanding social ground rules

When working with individuals who were in culture shock, the most common experience described to me was a sense of frustration. This resulted from the incongruity between preconceived notions and the actual situation. Unrealistic goals lead to frustration as well as the ambiguity and ignorance as to what should be normal. Other common contributors include language barriers, ignorance of the local culture, and the needs

to spend time, energy and money in ways that no longer worked. Trying to use methods that worked in the old culture, but not the new, led to frustration.

In observing my own emotional adjustment as well as sharing these experiences with many others, a pattern of adjustment became clear and something similar may apply for the newly revived individual. First, a euphoria or honeymoon phase (we would also call this a 'tourist' phase). Next, irritability and hostility, then a prolonged period of adjustment and finally a sense of mastery over the new situation and even sometimes an appreciation of the superiority of certain cultural aspects over those at home.

The first phase is commonly one of euphoria. There is a genuine excitement over the novelty of the new situation and expectations that are too positive. The emphasis is on similarities between the old and new culture. There is a sense that people everywhere are 'just alike' and glossing over of differences. I would envision this to be quite likely on revival.

The second stage, and this is the one I'd describe as being the actual culture shock, is one of irritability and hostility. Now, the expectations are overly negative. The emphasis becomes on the differences and a sense that 'these people are weird' and withdrawal into safety. This safety could be a familiar community of people or physical isolation. This period of time generally lasts weeks to months with a great deal of variability from person to person.

An area of concern was when I'd see a lack of ability to adapt that might manifest as aggression towards the local culture including chauvinism, hostility, stereotyping and making a decision to 'stay but hate' the local culture. This lack of adaptation could include poor coping like compulsive eating and drinking, exaggerated cleaning, verbal or physical aggression, family tensions and marital problems. Other symptoms included self-doubt, feelings of inadequacy, homesickness, fatigue, boredom, anxiety, tearfulness, helplessness, depression, confusion, paranoia, and physical symptoms. Less severe but concerning would be avoidance symptoms including excessive sleep, excessive reading, avoiding contact with others, poor attention span and diminished productivity, loss of ability to work or study, and returning back to the U.S. early.

Sounds pretty daunting!! But … it was also clear that **MOST folks didn't go through culture shock without recovery**. In the **vast majority** of cases things got better. So much so that at times individuals who had pretty significant symptoms at first actually began to prefer many aspects of the new culture to that at home. We would have 'Africa hands' who would volunteer to take assignments at austere African locations for a twenty years or longer career! These folks might even report 'reverse culture shock' when returning back to the U.S., having to readjust to their home culture!

So what was the typical course of adjustment? Initially most everyone would experience a varying degree of culture shock. Yes, you can get culture shock from living in London! Then, over time, a sense the worst was over and an ability to regain their bearings. Cultural cues became more evident. There was a sense of humor and hopefulness and appreciation for the new situation. This adaptation takes time, weeks to months, even a year or two for some, but was the most common situation. There could be some rough spots in the road … a period of time where things were going better, a setback, recurrence of some culture shock symptoms but then ability to move on and regain the lost ground. At the end of successful adaptation came 'biculturalism', a thorough adaptation, awareness that some things in the new culture were superior to the old, and even a resistance to returning back to the old culture.

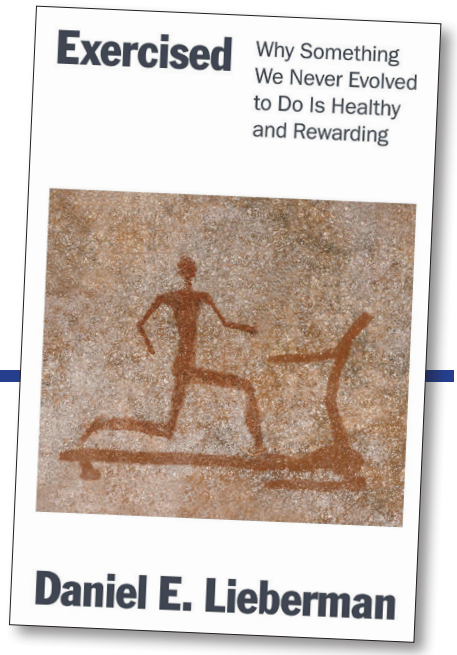
In numerous presentations that evolved over time, I offered the following list of tips and things to remember for those who may go through culture shock. Some may apply to our situation on revival:

- Develop new interests
- Begin to look for the logic behind seemingly strange things
- List the positive things you can identify about your present situation
- Avoid others who are in a "permanent state" of culture shock
- Resist disparaging the host culture
- Maintain a sense of humor
- Find others who have been in the new culture longer and have overcome culture shock – Network!
- Make friends
- Keep busy
- Tell yourself this culture shock is "temporary"

Having encountered culture shock on a personal and professional level through assignments in Eastern Europe, West Africa and the Middle East over a ten year career with the Foreign Service I can say that I feel confident that culture shock is NOT an insurmountable obstacle for those who are revived after cryopreservation. Yes, there will be emotional challenges including grief and despair, but human beings are capable of tremendous growth and adaptation. That's why I'm taking the journey too. ■

Review of *Exercized* by Daniel Lieberman

By Max More



Exercized: Why Something We Never Evolved to Do Is Healthy and Rewarding, by Daniel Lieberman. Pantheon.

Exercise (noun): voluntary physical activity that is planned, structured, repetitive, and undertaken to sustain or improve health and fitness.

Exercized (adjective): to be vexed, anxious, worried, harassed.

Cryonics is not guaranteed to work. The vast majority of Alcor members know and accept that. Cryonics is best seen as an extension of emergency medicine. No one wants to have to make use of medicine, especially emergency medicine. Any sensible cryonicist is interested in ways to live longer in good health. Since the outcome of cryonics in general and your own cryopreservation in particular is uncertain, you want to delay being cryopreserved as long as possible. More time means more life and better cryonics methods and practices. Living longer by living more healthily also helps get you cryopreserved in better condition by reducing the risk of sudden cardiovascular events, strokes, and aneurysms.

But challenges arise in going from "I know I should do this" to "I'm going to do this'" to "I'm doing this." One of the core themes of *Excercized* is that high levels of inactivity are normal for humans as we evolved. It is deliberate exercise for the purpose of health that is strange for our species. We didn't evolve to exercise. And yet exercise is good for us. Hence the book's subtitle: "Why Something We Never Evolved to Do Is Healthy and Rewarding".

Lieberman is professor of human evolutionary biology at Harvard University and a researcher on the evolution of human physical activity. Using his own research and relating some interesting experiences in the field, Lieberman explains how and why humans evolved to walk, run, dig, and do other necessary and rewarding physical activities while avoiding needless exertion. His approach, strongly informed by evolutionary biology and anthropology, yields insights sometimes familiar and sometimes fresh and stimulating.

In the main part of the book, Lieberman tackles what he sees as ten myths:

Myth #1: We evolved to exercise

Myth #2: It is unnatural to be indolent

Myth #3: Sitting is intrinsically unhealthy

Myth #4: You need 8 hours of sleep every night

Myth #5: Normal humans trade off speed for endurance

Myth #6: We evolved to be extremely strong

Myth #7: Sports = exercise

Myth #8: You can't lose weight by walking

Myth #9: Running is bad for your knees

Myth #10: It's normal to be less active as we age

Exercise is WEIRD

We are aware that modern Western countries have lower levels of physical activity than other cultures or our culture as it was decades and centuries ago. So, what is a normal amount of activity or exercise? Lieberman points out that you can't determine what is normal by looking only at the WEIRD (Western, educated, industrialized, rich, and democratic) countries. Until a few hundred generations ago, all human beings were hunter-gatherers, so that's a good place to start. Among all the hunter-gatherer groups, the most deeply studied is the Hadza from a dry, hot woodland region of Tanzania. When Lieberman first visited the Hadza in 2013, he was struck by how "everyone was apparently doing nothing."

Challenging commonly held notions of the degree of physical industriousness of hunter-gatherer groups, Lieberman relates how groups like the Hadza spend their day, and notes that their work is not backbreaking. Using the PAL (Physical Activity Level), we find that, among the Hadza hunter-gatherers, PAL is 1.9 for men and 1.8 for women. That's a little below PAL scores of subsistence farmers, and "about the same as those of factory workers and farmers in the developed world, and about 15 percent higher than PALs of people with desk jobs in

developed countries." We adults in the developed world have an average PAL of 1.67, a number considerably lower than just a few decades ago. But not drastically lower than the Hadza.

Although we are less active than our hunter-gatherer forebears, adult exercise – as distinct from physical work and play – is a modern creation. On a national level, we have pushed exercise over recent decades to strengthen people against attacks by others and because of anxiety over the health consequences of exercising too little. Lieberman also says that we have medicalized exercise. The US government even prescribes doses and types of exercise to help prevent and treat disease, recommending at least 150 minutes of moderate or 75 minutes of vigorous exercise per week, and weight training at least twice a week.

Why are we not naturally more physically active? Lieberman compares us to our closest genetic relatives and points out that humans spend a lot of energy just doing nothing noticeable. A 180-pound American male burns about 70 calories per hour while resting calmly in a chair. This is the resting metabolic rate (RMR). Such a person will need 1700 calories if he were to sit in his chair all day. When I was tested in 2000 at the Kronos Clinic (me being typically a bit over 180 pounds), my resting energy expenditure (REE) was 2038 calories. Lieberman notes that nearly two-thirds of the energy you expend each day is spent just on your resting metabolism. Adult humans spend about 30 calories daily for each kilogram (13.5 for each pound) of fat-free body mass just to maintain their bodies.

What happens when you starve people for an extended period of time? The results show that resting is not just a state of physical inactivity. A rather brutal experiment started in 1944, known as The Minnesota Starvation Experiment. After taking time to establish a pleasantly fed baseline, the subjects were starved for 24 weeks. Resting metabolism dropped by 40% and the subjects became lethargic, reduced their activity, lay in bed, and lost their ability to concentrate along with their interest in sex. Calories burned for maintenance dropped from 1,590/day to 964. Organs shrank and fewer blood cells were made. Many internal activities were curtailed for the sake of survival. When we look like we are resting from the outside, normally much activity is going on inside.

If you think of chimpanzees as highly active, you might be surprised that despite hunter-gatherers not working particularly hard, they are much more physically active than chimps. Even sedentary Americans spend about one-third more calories per day per pound than chimpanzees. We evolved from chimpanzee-like apes that are unusually sedentary, so something happened to make humans much more active. The driver of this was climate change combined with the environments in which we found ourselves. We evolved to cooperate, communicate, and make tools, and to develop a large, expensive brain. We also "evolved to be highly active to fuel a unique and unusually exorbitant reproductive strategy." The chimpanzee food budget allows a mother to have a child only once every five or six years, whereas hunter-gather mothers can have more babies, more often.

Sitting on our butts

We hear often that sitting is bad for our health. And it's true that the amount of time Americans spend sitting increased 43% between 1965 and 2009. But hunter-gatherers also sit a lot. The Hadza spend about nine non-ambulatory hours per day. They engage in more activity but also sit a lot. These statistics are imprecise since they bluntly classify people as either sitting or not sitting. In reality, sitting can be more or less active. The bottom line, so to speak, is that contemporary "Americans elevate their heart rates to moderate levels between half and one-tenth as much as nonindustrial people." We might feel better if we compare ourselves to chimpanzees, which spend an average of 87% of every day in sedentary activities such as resting, grooming, feeding quietly, and nesting.

What's wrong with excessive sitting? It can lead to chronic inflammation in several ways: By leading to more visceral fat which sets off chronic low-grade inflammation; by slowing the rate at which we take up fats and sugars; from the stress that may accompany sitting; and from lack of muscle activity. Using your muscles inhibits inflammation. The fidgeters among us may do better by practicing active sitting or *Sitzfleisch* in German, literally "butt flesh": a bold image with the connotation of the ability to sit patiently for long hours to accomplish something challenging. Fidgeting burns more calories and promotes blood flow to the arms and legs. One study even found 30% lower all-cause mortality among fidgeters.

"there is no sound evidence that slouching is bad for your back"

Lieberman doesn't definitively answer the question of whether you can make up for long periods of sitting with periods of exercise. He does tell us that there is no real correlation between time spent exercising and time spent sitting. To my surprise, he insists that there is no sound evidence that slouching is bad for your back – straightening the lower back and rounding the upper back. Dozens of meta-analyses and systematic reviews provide no evidence that sitting in a flexed or slouched manner leads to back pain, nor that sitting

longer without getting up leads to back pain. Less lower back pain *is* associated with having stronger, more fatigue-resistant back muscles. So, don't worry about sitting. Just try to practice *Sitzfleisch* and sit actively.

In the enervating hands of Morpheus

How much sleep is best for health and longevity? The standard advice is to get seven to eight hours a night, with youngsters needing more and older people less. The amount of sleep in the animal kingdom varies widely, from two hours a night for donkeys to 20 hours for armadillos. Most mammals sleep 8-12 hours/day. Most primates sleep 9-13 hours and chimpanzees sleep 11-12 hours.

According to Lieberman and the studies he cites, seven hours is the healthiest number of hours sleep. Americans who sleep eight hours per night have a 12% higher death rate compared to those who sleep 6.5 to 7.5 hours. Not one study found that eight hours is optimal. People who got less than seven hours tended to live longer than those who slept more than seven hours. It is not clear, however, whether long sleepers would benefit from reducing their sleep time.

"humans are the sweating champions of the world"

One interesting observation is that, before industrialization, it was normal to wake up for an hour or two before going back to sleep. There are even terms for this pattern: "first sleep" and "second sleep." During the time awake, people would chat, work, or have sex. In this chapter, Lieberman also speculates as to why we evolved to sleep less than chimps.

Runs with horses

One of the many interesting anecdotes related by Lieberman tells of the time he participated in the "Man Against Horse" race in Prescott, Arizona with 40 other runners and 53 horses and riders. He optimistically bet his daughter than he could beat at least one horse over the 25-mile course which ran up and down Mingus Mountain. As you would expect, for hours his prospects looked so dim the goal seemed impossible. Around the 20th mile, however, he passed his first horse, whose rider had stopped to allow the horse to cool down. In the end, Lieberman beat 40 of the 53 horses, with an "unremarkable" time of 4:20.

In this chapter, "Running and Dancing: Jumping from One Leg to the Other," Lieberman shows that the efficiency of humans at running compares well to horses, dogs, and antelopes, corrected for size. Yes, humans – even far-from-elite runners can outpace horses over long distances. Humans have a magnificent cooling system, uniquely benefiting from five to ten million sweat glands all over our skin. "Sweating effectively turns the entire body into a giant, wet tongue… humans are the sweating champions of the world." It is our efficiency at running and sweating that enabled Donald Ritch to run 100 miles at less than 7 minutes/mile (11h 30m 51s).

Exercise and disease

Exercise is more effective at pushing back morbidity and mortality than any supplement. Exercise slows and sometimes reverses the decline in health by preventing or ameliorating bad things that accelerate senescence. Exercise prevents or reduces the accumulation of fat, especially belly fat and its resultant inflammation; exercise lowers bloodstream levels of sugar, fat, and unhealthy cholesterol; causes more antioxidants to be produced; cleans out damaged proteins; lengthens telomeres; repairs DNA; and exercise improves cardiovascular function, lowers levels of stress hormones, boosts metabolism, strengthens bone, and so on. Lieberman explains why this is true using what he calls the "costly repair hypothesis" or the afterburn effect. Exercise can not only restore most structures (homeostasis), it can also rebuild structures better than before (allostasis).

Given the costly repair hypothesis, the challenge "is to maintain and repair any damage from physical activity just enough and in the right place." Evolution's answer is to match capacity to demand. The capacity is there to maintain and repair a stable internal environment, and these maintenance and repair mechanisms activated by physical activity don't completely go away as we age. Unfortunately, "we never evolved to activate these maintenance and repair responses as effectively in the absence of regular physical activity."

In discussing how evolution met the challenge of maintaining and repairing damage from physical activity just enough and in the right place and time, Lieberman explains the phenomenon of hormesis as "the physiological stresses caused by exercise trigger a reparative response yielding a general benefit." One thing that I think he gets wrong is his claim that "small doses of radiation cause only harm." There is abundant evidence that chronic low doses of ionizing radiation (such as we get from the sun, from the ground beneath us, and substances inside us) can promote survival and health.

Exercise can reduce our vulnerability to the diseases most likely to make us sick and kill us. Lieberman looks at the effect of exercise on various diseases in chapter 13 and examines the relationship of exercise to all-cause death rates. For each

major condition, he asks: What is the hypothesized mismatch? (Is the condition more common today than in the past because of less physical activity?) How does physical activity help prevent or treat the condition? What kind and dose of exercise are best? He asks these three questions with respect to obesity, metabolic syndrome and Type 2 diabetes, cardiovascular disease, respiratory tract infections and other contagion, chronic musculoskeletal conditions, cancer, Alzheimer's Disease, and depression and anxiety.

Some other salient points from this chapter:

- Antioxidants plus exercise may be bad for you.
- Rather than the expected U-shaped curve between exercise dose and mortality, "there is little solid evidence that extreme levels of exercise are either harmful or additionally healthy."
- "Fat but fit" is not as good as "unfit but lean."
- Advancing age does not need to mean less activity. Nor need all measures of health and function drop in older age. For instance, among the San and Hadza hunter gatherers, blood pressure was the same in 70-year-olds as in teenagers.
- Exercise helps us develop antibodies more rapidly and effectively. Moderate but not extreme exercise boosted survival in mice given a bad flu.

One thing I found frustrating about the book was the author's excessive focus on running. Lieberman gives no data for people doing resistance training. The discussion of resistance training is over in one page. He says only that resistance exercise is crucial for maintaining muscle mass, especially fast-twitch fibers that generate strength and power, and that it "can help prevent bone loss, augment muscles' ability to use sugar, enhance some metabolic functions, and improve cholesterol levels". In this area, he skimps on details.

I suspect that he is not using an optimal strategy when says he only wants to be "Just strong enough for my normal activities of living". That doesn't allow for tail events – low probability but high-impact events such as major illness, serious injury, or emergencies – and it's better to have some extra tissue (muscle rather than fat) and extra capacity to survive serious, long-term illnesses or to perform adequately in emergency situations.

Conclusion

Along the winding journey of discovery about why we get so worked up about exercise and how we should think of it, Lieberman entertains with stories and facts. Given how often we hear that humans are uniquely violent and don't deserve to live, it was refreshing to read that humans are remarkably peaceful compared to chimps. Humans fight 250 to 600 times less frequently than chimps – and that's for the *most* belligerent human groups studied. It's also cheering to hear that male baboons spend much of their time preventing other males from mating. Can you imagine what your life would be like (especially if you are male) if that's how you had to spend much of your time? So, if your mood needs uplifting, reading this book will at least allow you to feel superior to chimps and baboons.

Lieberman's discussion of exercise never gets far in making practical recommendations. You will get the occasional tip on why you probably should not combine antioxidant supplements and exercise, how to bend over and pick something up, and learn (not much) about how chimps cannot tear off your arm but can tear off your hands. (Yes, this last one is puzzling.) The author's advice on encouraging people to do more exercise or other activity comes down to little more than: we need to make exercise both necessary and fun.

As cryonicists wanting to enjoy life before we may have to be cryopreserved, it's important to know that an unhealthy lifestyle affects morbidity twice as much as mortality. A long life is not an unalloyed good. We want to live long *and* be healthy and vital. Put some effort into regular exercise, enjoy your life more, and improve your chances of a good cryopreservation. ■

Alcor Longevity Circle of Distinguished Donors

The Alcor Board of Directors is pleased to announce the formation of the **Alcor Longevity Circle of Distinguished Donors**. This new organization will honor those members and their foundations that have donated in excess of $100,000 over the past few years to support Alcor and its affiliated organizations. In addition to being recognized in Alcor publications and at conferences and other events, members will also be entitled to:

- Exclusive access and a quarterly conference call with Alcor Directors, officers, and officials to get in-depth briefings and ask questions and make suggestions.
- Special recognition, seating, and access to officials at Alcor conferences.
- An exclusive yearly, hosted in-person event honoring members with face-to-face interaction with Alcor Directors, officers, and officials.
- A unique, professionally designed and engraved memento of their membership.

These benefits are, of course, overshadowed by the immense gratitude members' and patients' families will always have for these especially generous individuals. The Board looks forward to announcing Charter members of the Longevity Circle who qualify by December 31, 2020. New levels of membership (higher and lower levels of participation) may also be announced in the future. ■

Support Alcor's **RAPID** Research

Readiness **A**nd **P**rocedure **I**nnovation/**D**eployment **(RAPID)**

In order to advance the science and reputation of cryonics, Alcor plans to conduct ongoing research to develop novel and near-future products related to cryopreservation procedures and protocols. The RAPID team is developing relationships and contracts to procure recently deceased human cadavers, which are not Alcor members or patients, but are already earmarked for medical research. The idea is to procure one to two cadavers per month to conduct research. We would go on a "light standby" to enable fast access to cadavers.

The RAPID initiative will support cryonics research in multiple ways. Most immediately, it will help advance research into liquid ventilation – using a patient's lungs as a heat exchanger to induce very rapid hypothermia. Animal studies alone cannot take LV development to the next level due to different chest anatomy. LV research will include cooling rate control; chest compression studies; and timing and sensor feedback.

RAPID will also enable research comparing chemical fixation to perfusion and will support rewarming studies. Another benefit will be a great improvement in cryonics-specific surgical training. That includes raising and cannulating the carotids; cephalic isolation; raising and cannulating the femoral arteries; field neuro procedure training; median sternotomy training; and alternate surgical approaches.

Alcor is requesting donations through GoFundMe. All donors will receive quarterly reports from Alcor regarding the progress with fundraising and milestone achievements rising from the RAPID program! Please donate today to support Alcor's RAPID initiative. Alcor is a non-profit, federally tax-exempt, 501(c)(3) corporation and your donation may be tax deductible. ■

Donate here: https://charity.gofundme.com/o/en/campaign/rapid-research/alcorlifeextensionfo

For more information, see the presentation here: https://www.youtube.com/watch?v=BUaVcVMuFWQ&feature=youtu.be

Restoration without Rediscovery: Authentic De Novo Recreation of Lost Information in a Multiple-Worlds Setting

By R. Michael Perry

Abstract

A method is proposed, in principle, for restoring lost information which cannot be recovered or rediscovered from the environment by any process usually conceived within the scope of archaeology. This includes future archaeological methods that may be developed. Instead, the lost information is recreated de novo using a quantum-random process. An assumption of a multiple-worlds cosmology provides that different, lost versions of the missing information are recreated across parallel branches of reality, so that overall, there is no violation of information conservation and the restorations are all authentic. Refinements including partial restoration and use of probability weights are explored.

1. Introduction

Information about past events has considerable interest, not merely from the academic perspective of scholarly pursuits, but in many facets of life, including the deeply personal. In many ways, we cherish the past, or otherwise find it informative and instructive, and wish to preserve a record of it. Information is lost, however: such processes as melting, burning and decay produce states that apparently cannot be reversed and we are left wondering what fascinating, horrific, or endearing material the obliterated remains might have described.

One strong motive for addressing information loss concerns the death of persons we care about. We try to preserve mementos of these people, and search records to see what other information may survive. In the field of cryonics, there is particular interest in the cryopreserved remains of humans as a source of information that might make it possible to revive these individuals at a future date.[1] If the information turns out to be missing or has large gaps, as might happen from any of several causes before, during, or after the cryopreservation occurred, what course would be best to follow? This question applies to other cases as well if one envisions a future with expected capabilities well beyond those at present.

Some envision a future "quantum archaeology" that will make it possible, directly, to restore lost information, which then must not have been "lost" after all, but only awaiting a proper technique of rediscovery.[4] Quoting Zoltan Istvan: "Once we have the computational power, we can reverse engineer parts of our galaxy or even nearly the entire universe to determine every little spark of energy, movement, moment and thought that has ever happened in it, including the complete personality, mind and life of [a lost loved one]."[17] A related scenario has it that our whole universe is presently in a computer simulation of some advanced civilization,[14] so that all "lost" information could be restored someday, if the "Sysop" so desires.

In the scenario imagined here, however, we are not in a simulation and the lost information stays lost – at least in the sense that no future technology is able to rediscover it by clever or dedicated processing in a single-world context. Yet a recovery of the lost original is still possible, if one grants the metaphysical assumption of parallel branches of reality such as encountered in the Everett many-worlds scenario (MWI).[6] There events are constantly occurring in different varieties, splitting the observer and associated environs into alternate versions of history. In this way new information is created, particularly when new history unfolds and is recorded. The new history, however, will be shadowed in other, freshly split branches of reality by alternate versions, so that overall, there is no net creation of information, in the sense that the process is deterministic. (The "new-information" is from the standpoint of a particular observer-continuer in a particular branch, but not the whole.) One knows in advance what will happen in all the branches: simply "whatever is possible under the laws of physics." Loss of information in turn can be interpreted in different ways but in essence, and from the point of view of the observer, the parallel branches coalesce (superpose) and a state is restored much like, if not identical to, what occurred originally, before the splitting occurred. As this happens, the observer-continuers in the parallel branches are restored to equivalent copies of each other, in effect a single observer comparable to what once existed. The state in fact is not identical to the original, however, since the loss is known to this (virtually) single observer, and we imagine, remedying it and restoring what is lost is seen as a desirable goal.

The restoration here envisioned involves a quantum-random process in which the missing material is restored by guesswork. As the restoration takes place, it is shadowed in the parallel branches of reality by other restorations, so again the observer splits into continuers: copies of the original, each with their own version of the lost history, and mathematically what once existed is fully restored. A possibility is realized, then, that could not have happened in a single branch of reality where a certain historical archive is lost, since information is now missing that would be needed for the restoration. When the multiple branches of reality are considered, all the possibilities are known, and a restoration can happen that recovers all of them in one operation.

Here we present a mathematical model of restoration de novo or recreation without prior knowledge based on a data structure called a "staging space." A staging space consists of a partially ordered set or poset with certain additional properties so that objects within model records or chunks of consistent information. There is a least object, in effect, an empty record with no information, and "atoms" consisting of minimal records that are not further subdivided. All other records have "floors" consisting of all the lower-bounding atoms under the partial order. Every record is uniquely characterized by its floor, and one record lower-bounds another if and only if its floor is included in that of the other. (Records can be subdivided down to the level of atoms.) A last property relates to the possibility of an infinite succession of increasingly complete records or "chain" which, it is assumed, would delineate one large, individual record, its floor being the union of the floors of the elements in the chain. (This "chain closure" property is important in establishing results that are needed, via Zorn's lemma.) Each record is also called a "singular" object.

Not every set of atoms is the floor of a singular object. The staging space is extended to cover cases of inconsistent floors to which is associated a set of records called the "surface." A record representing consistent information has just a singleton of itself as its surface and is "singular", while a "plural" object representing a multiplicity of inconsistent records will have a surface of more than one record. The plural object, then, represents a superposition of records as might occur, under a multiple-worlds scenario, when information is lost.

Mathematically, a surface element is a maximal, singular lower bound of the plural or singular object, which can be shown to exist using axiomatic set theory (ZFC, chain closure, Zorn's lemma).[14] Each surface element in turn corresponds to one version of the record in a parallel branch of reality. In its simplest form, the basic step of restoration involves replacing the plural object by its surface. In a practical implementation this would involve a (quantum) random selection process to choose one particular surface element. In keeping with multiple worlds, it would split reality, including any observer who may be resident, into different branches, each of which contains one and only one of the (singular) surface elements in place of the original, plural object. So, to the observer-copy in the given branch, the missing information has been restored in a particular way. Considering the different branches as a whole, however, there has been no net increase in information in terms of the consensus of the different surface elements – all together just recapitulate the original, plural object.

A surface element thus constructed may contain very detailed information, in fact, much more than is of interest. A weaker form of restoration, also explored and feasible, obtains objects that are plural but "less plural" than the original to allow essential information to be restored and inessential omitted. Finally, it is shown how probability weights can be incorporated without changing the basic formalism, so that parallel branches are appropriately emphasized or deemphasized according to likelihood of occurrence.

Following this Introduction is a brief Historical Note. Sections 3-9 that follow start with basic set theory and lead finally to the main results concerning the proposed restoration methods. A concluding section summarizes the results, considers some difficulties, and offers some thoughts for future work.

2. Historical Note

The nineteenth-century scientific-religious philosopher Nikolai Fedorov envisioned a future time when the dead would be restored to life by such scientific means as repositioning the particles that comprised their bodies. (If planetary motions could be tracked and retrodicted, then why not atomic motions, given that instrumentation to accomplish this might be developed at a future date? One could thereby determine where the particles of the body of some past individual once resided, then use sophisticated, future technology to reposition these particles and obtain the restored, living body.)[7,16] Later developments in physics saw hopes fade for this sort of single-world archaeology; quantum uncertainty makes the task Fedorov imagined infeasible, barring unexpected discoveries.

Fedorov was a philosopher, not a mathematician, and his writings, along with those of others who followed, usually adhere to a nontechnical standard, including some works by the author.[8,9,10,12] An exception is found in Frank Tipler's popular exposition, *The Physics of Immortality*, which includes a lengthy and technically deep "Appendix for Scientists."[3] There it is imagined that a particular cosmological outcome (itself not guaranteed) would make it possible to recover minute information about the distant past – but this is a form of quantum archaeology, not the scenario proposed here.

Here we are not concerned with "discovering the undiscoverable" via a novel method but with a process of recreating, de novo, what cannot be rediscovered. It is essential that the process proceed *only* when rediscovery is impossible, but then the process of random guessing arguably does fill in the missing details across parallel branches of reality, assuming our reality is structured in this way. (That such a prospect as MWI is true, is presently a controversial position, but it does at least have

significant support among the scientific community, and there are several popular expositions of this concept by supportive scientists.[2,3,5,13]) As seemed appropriate, a mathematical approach is used, and a literature search showed very little in the way of such studies.

An exception is a previous, mathematical study by the author which does deal with the problem of restoring lost information via guesswork under a multiple-worlds scenario.[11] There is a detailed treatment of "personlike" processes, showing a possible way that such notions as death, resurrection, and immortality could be mathematically modeled and related to physical reality. In the present study the focus is more specialized to one particularly important issue: the loss of information and how the loss might be remedied, given that straightforward recovery is assumed impossible. The results in this central specialty extend well beyond those obtained before, both in the theoretical formulation and the suggestions, albeit limited, for practical implementation.

3. Mathematical Framework and Basic Notation

Overall, as noted, we are modeling records or chunks of information as objects in a certain sort of partially ordered set, to be defined. We start with the apparatus of Zermelo-Frankel set theory, with axiom of choice (ZFC, implying Zorn's lemma). This in turn offers a standard treatment of the notions of set, set membership, ($x \in X$, "x is a member of or an element of set X"), subset ($Y \subseteq X$, "Y is a subset of X," in which case $X \supseteq Y$, X is a superset of Y). Proper subset (superset) is denoted by $Y \subset X$ ($X \supset Y$). The **union** of sets, $X \cup Y$, is the set of elements that are either in X or in Y, while the **intersection**, $X \cap Y$, is the set of elements that are both in X and in Y. The **difference**, $X \setminus Y$, is the set of elements in X that are not in Y, also known as the **complement** of Y in X. The set of all subsets of X or **powerset** of X, always exists and is denoted by $\mathcal{P}(X)$. (In particular, both X and the empty set $\varnothing$ containing no elements are members of $\mathcal{P}(X)$.)

Other notational conventions are introduced more-or-less as usage demands. In general, lower-case italicized single letters denote elements or objects in sets while upper-case italic is used for sets of objects. Objects could themselves be sets, of course (as always in pure set theory), and sets may play the role of objects, so care must be exercised to avoid ambiguity. Universal and existential quantification, "for all" and "for some," respectively, are used with their usual interpretation in defining sets, with free and bound variables, etc. Sets, particularly finite sets, may be denoted $\{x, y, z \ldots\}$. A set with just one element, x, or **singleton** set, is $\{x\}$. In general we use **set-builder notation**, writing $X = \{x \mid \psi\}$, "set of x such that ψ" where ψ is a formula in which x occurs as a free variable, and all other variables are bound, to mean that X is the set consisting of all and only those objects x for which ψ holds (assuming such a set exists). "The set of x such that ψ" may be stated informally when intentions are clear and, more generally, we may have x replaced by an ordered pair or n-tuple as in the definition of relation in the next section.

We sometimes use a "record field" notation to indicate an object associated with another object: for example, $\boldsymbol{P}\bullet$Uls indicates the "underlying set" of "poset $\boldsymbol{P}$". Occasionally this notation is extended to subfields; association is from the left. Thus $\boldsymbol{P}\bullet\mathbf{PS}\bullet$Uls is interpreted as $(\boldsymbol{P}\bullet\mathbf{PS})\bullet$Uls.

Definitions are introduced by the symbol $\stackrel{\text{def}}{=}$ ("equals by definition," "is by definition," or "if and only if" (iff) by definition").

4. Relations and Functions

A **relation** R is any set of ordered pairs $\langle x,y\rangle$. (This is a **binary** relation; ordered triples would be a ternary relation, etc., not important here.) If R is nonempty and $\langle x,y\rangle \in R$ we say that R **holds** between x and y and write xRy. In case we also have relation S that holds between y and z we write $xRySz$ meaning xRy holds, and also, ySz; and similarly, for longer expressions involving multiple relations.

The set of x such that xRy for some y is the **left image** of R, written $R^{\Leftarrow}$, expressed in set-builder notation as $\{x \mid xRy \text{ for some } y\}$. Similarly, the **right image** $R^{\Rightarrow} \stackrel{\text{def}}{=} \{y \mid xRy \text{ for some } x\}$. Every R has a **converse** or **transpose** R^{T} defined as the set of ordered pairs $\{\langle y,x\rangle \mid \langle x,y\rangle \in R\}$.

As an illustration, a simple sort of relation R is the **cartesian product** $X \times Y \stackrel{\text{def}}{=} \{\langle x,y\rangle \mid x \in X, y \in Y\}$. For this case we have $R^{\Leftarrow} = X$, $R^{\Rightarrow} = Y$, and $S \subseteq R$ whenever $S^{\Leftarrow} \subseteq X$ and $S^{\Rightarrow} \subseteq Y$.

Given any set X, the **left image** of X **under** R, $R^{\leftarrow}(X)$, is the set of all x for which xRy, for some $y \in X$: $R^{\leftarrow}(X) \stackrel{\text{def}}{=} \{x \mid xRy \text{ for some } y \in X\}$. (Note that it is not necessary that $X \subseteq R^{\Leftarrow}$ for $R^{\leftarrow}(X)$ to be defined, though always $R^{\leftarrow}(X) \subseteq R^{\Leftarrow}$.) Similarly, the right image $= R^{\rightarrow}(X) \stackrel{\text{def}}{=} \{y \mid xRy \text{ for some } x \in X\}$. When necessary to distinguish between the left image $R^{\leftarrow}(X)$ of some specific set X and the left image $R^{\Leftarrow}$, the latter will be referred to as the **global left image**, and similarly in the case of **global right** image, $R^{\Rightarrow}$. It will also be convenient to consider the **left point-image** of an element z, defined as $R^{\leftarrow}(\{z\})$; and similarly, the **right point-image** $\stackrel{\text{def}}{=} R^{\rightarrow}(\{z\})$.

R is **right-unique**, **functional**, a **map**, **mapping**, or **function** $\stackrel{\text{def}}{=}$ no two of its ordered pairs have the same first element, so that, for all $x \in R^{\Leftarrow}$, the right point-image $R^{\rightarrow}(\{x\})$ is a singleton. We then write $y = R(x)$ to indicate that y is the unique element for which xRy. (A left-unique relation similarly makes the left point-image $R^{\leftarrow}(\{x\})$ a singleton for all $x \in R^{\Rightarrow}$, but is not used here.)

Often, we use F to denote a relation which is, in addition, a function. We will sometimes have occasion to use **pure function** or **maps-to** notation, where we represent a function F by the action it has on its argument x by $x \mapsto F(x)$, and also, $F\!:\!x \mapsto y$, where $y = F(x)$. $x \mapsto x$ ($F\!:\ x \mapsto x$) would be an identity; $x \mapsto \{x\}$ would assign to each x its singleton set, etc. The empty set $\varnothing$

thus qualifies vacuously as a function, and any identity relation is also a function, as noted. It may also happen that F is both left- and right-preserving. F then is an **invertible**, or **one-to-one** function, also called a **bijection**, as also is the transpose, F^{T}. In this case, the transpose F^{T} is often, and here generally, denoted by F^{-1}.

Other common notation is $F{:}X{\to}Y$ to indicate that F is a function with $X = F^{\Leftarrow}$, $Y \supseteq F^{\Rightarrow}$. X, the left image, is called the **domain**, and Y the **codomain**. Note that Y is not the right image but only includes the right image, a possible source of confusion since some usage would have it that functions with different codomains but otherwise the same are different functions. (Their "types" are different even if their "graphs" – the respective sets of ordered pairs – are the same.) It may happen that function F is a bijection, so that codomain Y is actually the domain of F^{T}. To indicate this we write $F{:}X{\leftrightarrow}Y$, from which it follows that $F^{\mathrm{T}}{:}Y{\leftrightarrow}X$. In maps-to notation we write $x{\leftrightarrow}F(x)$ or similarly, $y{\leftrightarrow}F^{\mathrm{T}}(y)$. In this case F is invertible and we are justified in writing F^{-1} for F^{T}.

5. Partially Ordered Sets

A **partial order** on a set X is a binary relation $\leq$ which is **reflexive** ($x \leq x$), **antisymmetric** ($x \leq y$ and $y \leq x$ iff $x = y$), and **transitive** (if $x \leq y$ and $y \leq z$, then $x \leq z$). (The more general **preorder**, in which the antisymmetry requirement is relaxed but reflexivity and transitivity still hold, is sometimes also used here.) In view of the reflexive property, for every $x{\in}X$ there must exist both y and $z{\in}X$ such that $x \leq y$ and $z \leq x$ (let $y = z = x$). Thus, using the notation introduced above, we have $\leq^{\Leftarrow} = \leq^{\Rightarrow} = X$. The partial order (relation), together with the associated set comprise **a partially ordered set** or **poset**, represented as the ordered pair $\boldsymbol{P} = \langle X, \leq \rangle$. It will be convenient to refer to X as the **underlying set** of $\boldsymbol{P}$, $\boldsymbol{P}_{\bullet}$Uls, while $\leq$ is the **graph**, $\boldsymbol{P}_{\bullet}$Gph. (Where no confusion seems likely, $\boldsymbol{P}_{\bullet}$Gph is understood to be the restriction of $\leq$ to the set X^2 in cases where it may otherwise extend beyond these limits, as, for example, if $\leq$ is the set inclusion relation, $\subseteq$.)

By standard convention $y \geq x$ ("y is greater than or equal to x") $\stackrel{\text{def}}{=} x \leq y$. Also, we say that $x < y$ ("x is less than y") and $y > x$ ("y is greater than x") in case $x \leq y$ and $x \neq y$. If neither $x \leq y$ nor $y \leq x$ then x and y are **unordered** and we write $x \parallel y$. A subset $S \subseteq X = \boldsymbol{P}_{\bullet}$Uls is a **chain** $\stackrel{\text{def}}{=}$ it is totally ordered under $\leq = \boldsymbol{P}_{\bullet}$Gph: either $x \leq y$ or $y \leq x$ for all $x, y{\in}S$. S in turn is an **antichain** $\stackrel{\text{def}}{=}$ for any two $x, y{\in}S$, either $x = y$ or $x \parallel y$.

Given $x \leq y$, x is a **lower bound** of y and y is an **upper bound** of x; in case $x < y$, x is a **strict** lower bound of y and y is a strict upper bound of x. For a partial order, the image terminology for relations, left, right, left-right images etc. is extended by equating "lower" with "left" and "upper" with "right." So, the **lower image** (= left image) of a subset $S{\subseteq}\boldsymbol{P}_{\bullet}$Uls, is $\leq^{\leftarrow}(S) = \{y{\in}\boldsymbol{P}_{\bullet}\text{Uls} \mid y \leq x \text{ for some } x{\in}S\}$, the lower global image is $\leq^{\Leftarrow}$, in this case equal to upper global image: $\leq^{\Leftarrow} = \leq^{\Rightarrow}$. The lower (upper) image of the associated restriction $<$ of $\leq$ is the strict lower (upper) image, and this terminology also extends to point-images. Thus, for instance, $<^{\leftarrow}(S)$ is the strict lower image of S, and $\leq^{\leftarrow}(\{x\})$ is the (unstrict) lower point-image of element x. (Note that an equivalent definition of the lower image of S would be $\geq^{\rightarrow}(S)$, with upper image $\geq^{\leftarrow}(S)$, with similar modifications in the other cases. Here we prefer the "less" rather than "greater" notation as a matter of convention.)

x is a **lower bound** of $S \stackrel{\text{def}}{=} x \leq y$ for all $y{\in}S$. For this case, then, we have $S{\subseteq}{\leq^{\rightarrow}}(\{x\})$. Dually, x is an **upper bound** $\stackrel{\text{def}}{=} S{\subseteq}{\leq^{\leftarrow}}(\{x\})$. For x a lower bound of S, if x is greater than every other lower bound it is the greatest lower bound of S and dually for least upper bound. The greatest lower bound of S (if it exists) is often referred to as the **meet** of S, written $\wedge S$, and dually, the least upper bound is the **join**, $\vee S$. In the case of individual elements x, y we write $x \wedge y$ for $\wedge\{x,y\}$ and $x \vee y$ for $\vee\{x,y\}$. Important, basic properties are that $\wedge$ and $\vee$ are **commutative** and **associative** binary operators (not relations): $x \wedge y = y \wedge x$, $x \wedge (y \wedge z) = (x \wedge y) \wedge z$, and dually for $\vee$, assuming again, all the relevant objects are defined. (The associative property is easily verified if we let $a = x \wedge (y \wedge z)$, $b = (x \wedge y) \wedge z$. Then $a \leq x \wedge y$, $a \leq z$, so $a \leq b$. Similarly, $b \leq a$, thus by antisymmetry, $a{=}b$; a similar result holds for the dual operator $\vee$.)

In particular, $\boldsymbol{P}$ might have a meet and a join defined for each x, y; $\boldsymbol{P}$ is then said to be a **lattice**. If every nonempty subset has a join and a meet $\boldsymbol{P}$ is a **complete** lattice. If only a meet (join) is always defined for two-element sets, $\boldsymbol{P}$ is a **lower** or **meet** (**upper**, **join**) **semilattice**, complete if the meet (join) extends to arbitrary, nonempty subsets $Y \subseteq X$. In a lower-complete semilattice, every lower point-image is a complete lattice: If a nonempty set has an upper bound it has a least upper bound, which will be the greatest lower bound (meet) of all the upper bounds. A dual property holds for the upper-complete case.

For a complete lattice, the underlying set X must have both a meet (**bottom**, **origin**, **initial element**, **empty element**, **least element**), denoted by $\bot$, and a join (**top**, **terminus**, **terminal element**, **universal element**, **greatest element**), denoted by $\top$. An **upper-complete** semilattice will have a top but not necessarily a bottom; such a structure is **consistent**. A **lower-complete** semilattice will similarly have a bottom but not necessarily a top, and is **coconsistent**.

If it happens in $\boldsymbol{P}$ that $x < y$ and for no z is $x < z < y$ then we say that y is an **upper cover** of x and x is a **lower cover** of y. An **atom** in poset $\boldsymbol{P}$ is an upper cover of a least element. (Note that a least element is not the same as a minimal element but there is an additional requirement that it must lower-bound all the other elements.) For any $Y \subseteq X$ the set of atoms which are lower bounds of Y is its **floor**, written $\mathrm{Flr}(Y)$. It will also be useful to define "floor" for individual elements x: $\mathrm{flr}(x) = \mathrm{Flr}(\{x\})$. Where necessary to distinguish between the two definitions, Flr is "upper floor" and flr is "lower floor."

Poset $\boldsymbol{P}$ is **floor-unique** $\stackrel{\text{def}}{=}$ no two elements have the same floor. If nonempty it must also have a least element and, if it has at least one other element, must have an atom.

6. Isomorphism, Inclusion Order, Powerspaces

Given posets $\boldsymbol{P}_0=\langle X_0,\leq_0\rangle$, $\boldsymbol{P}_1=\langle X_1,\leq_1\rangle$, an **order-preserving map** from $\boldsymbol{P}_0$ to $\boldsymbol{P}_1$ is a function F: $X_0\rightarrow X_1$ such that, for all $x,y\in X_0$, if $x\leq_0 y$ then $F(x)\leq_1 F(y)$. Suppose that F is a bijection (F:$X_0\leftrightarrow X_1$, thus $F^{\Rightarrow}=X_1$ and not merely $\subset X_1$, and similarly, F^{-1}:$X_1\leftrightarrow X_0$ with $F^{-1\Rightarrow} = X_0$). If, in addition, F^{-1} is also an order-preserving map from $\boldsymbol{P}_1$ to $\boldsymbol{P}_0$ then F is an **order isomorphism** from $\boldsymbol{P}_0$ to $\boldsymbol{P}_1$, and similarly, F^{-1} is an order isomorphism from $\boldsymbol{P}_1$ to $\boldsymbol{P}_0$. We then say that $\boldsymbol{P}_0$, $\boldsymbol{P}_1$ are **order isomorphic**, or order-isomorphic images, and write $\boldsymbol{P}_0 \cong \boldsymbol{P}_1$.

A poset $\boldsymbol{P}=\langle X, \leq\rangle$ is **inclusion-ordered** $\stackrel{\text{def}}{=}$ its elements are sets which are ordered by set-inclusion. That is, for all $x,y\in X$, $x\leq y$ iff $x\subseteq y$, so that $\leq = \subseteq$ (suitably restricted). X in turn is a subset of the set $X^{+} = \boldsymbol{\mathcal{P}}(X_0)$, where $X_0 = \cup X$ is the **member-element set** or set of **member-elements** of $\boldsymbol{P}$, here denoted as $\boldsymbol{P}_{\bullet}$Mes. X^{+} in turn is called the **superset**, $\boldsymbol{P}_{\bullet}$Sus $\supseteq$ $\boldsymbol{P}_{\bullet}$Uls. ($\boldsymbol{P}_{\bullet}$Sus = $\boldsymbol{\mathcal{P}}(\boldsymbol{P}_{\bullet}$Mes))).

A simple example of an inclusion-ordered poset is the **powerspace**. We start with a set defined as the powerset of some chosen set, ordered by inclusion: $\boldsymbol{P}=\langle X, \subseteq\rangle$. In this case $X = \boldsymbol{\mathcal{P}}(X_0)$, for some $X_0 = \cup X$, so that $X_0 = \boldsymbol{P}_{\bullet}$Mes. Sets of member-elements are the elements of $\boldsymbol{P}$, so $\boldsymbol{P}_{\bullet}$Uls = $\boldsymbol{P}_{\bullet}$Sus = $\boldsymbol{\mathcal{P}}(\boldsymbol{P}_{\bullet}$Mes). So $\boldsymbol{P}$ is a complete lattice, with $\bot = \cap X = \varnothing$, and $\top = \cup X = \boldsymbol{P}_{\bullet}$Mes. The meet of any family (set) of elements is the set intersection, and the join is the union. In particular, for any x, $y \subseteq X$, $x \wedge y = x\cap y$ and $x \vee y = x\cup y$. $\boldsymbol{P}$ is a complete lattice: joins and meets of sets are given by union and intersection, respectively. $\boldsymbol{P}$ is also **distributive**: for x, y, z, $x \wedge (y \vee z) = (x \wedge y) \vee (x \wedge z)$, $x \vee (y \wedge z) = (x \vee y) \wedge (x \vee z)$, as is easily verified. Finally, $\boldsymbol{P}$ has **relative complements**: for all $x\subseteq X$, if $y\leq x$ ($y\subseteq x$), there exists unique $z\leq x$ such that $y \wedge z = \bot$, $y \vee z = x$. In this case, z is just the set difference, $x \setminus y$.

Another interesting property of the powerspace is that singleton sets serve as atoms. Each nonempty $x\subseteq X$ in fact has at least one lower-bounding atom. The set of singletons of elements of x is its floor, so $\text{flr}(x)=\{\{y\}\mid y\subseteq x\} = \text{Sng}^{\rightarrow}(x)$ for the singleton map defined, in maps-to notation, by Sng:$x \mapsto \{x\}$. Floor elements, then, are singletons of member-elements of x; each x is the join (in this case, union) of its floor, and no two x's have the same floor: the space is floor-unique. In fact, we see that $\text{flr}(x) \subseteq \text{flr}(y)$ iff $x\leq y$ (floor inclusion property). Each set S of atoms, in this case singletons of member-elements, $S=\text{Sng}^{\rightarrow}(A)$ for $A\subseteq X_0$, is uniquely the floor of some $x\subseteq X$; we write $x = \text{flr}^{-1}(S) = \vee S = \cup S$. Thus far we have considered the lower floor. As for the upper floor, when it comes to sets of elements $S\subseteq \boldsymbol{P}_{\bullet}$Uls, we have $\text{Flr}(S) = \cup\text{flr}^{\rightarrow}(S)$, again, the result of "collapsing" S down to singletons of its member-element constituents. So in particular we have $\text{Flr}(\boldsymbol{P}_{\bullet}\text{Uls}) = \{\text{all atoms in } \boldsymbol{P}\} = \text{Sng}^{\rightarrow}(\boldsymbol{P}_{\bullet}\text{Mes})$, while, at the other extreme, $\text{Flr}(\varnothing) = \varnothing$. In the latter case, note that the empty set is both an element of the powerspace, and also a set of elements in its own right. So, both upper and lower floors are defined in this one case, and, it turns out, equal.

In general, if $\boldsymbol{P}=\langle X, \leq\rangle$ is floor-unique we can define an **order-isomorphic inclusion space** $\boldsymbol{P}_{\bullet}$**OIS** as $\langle \text{flr}^{\rightarrow}(X), \subseteq\rangle$. Explicitly, we have $\boldsymbol{P}\cong\boldsymbol{P}_{\bullet}$**OIS** via the map, flr:$\boldsymbol{P}_{\bullet}$Uls$\leftrightarrow\boldsymbol{P}_{\bullet}$**OIS**$_{\bullet}$Uls which, under floor-uniqueness, is invertible. Also note that the member-element set, $\boldsymbol{P}_{\bullet}$**OIS**$_{\bullet}$Mes, is just the set of atoms, Flr(X).

Denoting the set of floors $\text{flr}^{\rightarrow}(X)$ by W we can further extend $\boldsymbol{P}_{\bullet}$**OIS** to a **partial powerspace**, $\boldsymbol{P}_{\bullet}$**PPS** = $\langle \cup\boldsymbol{\mathcal{P}}^{\rightarrow}(W), \subseteq\rangle$. $\boldsymbol{P}_{\bullet}$**PPS**, then, will have as elements, all floors of elements of $\boldsymbol{P}$, but all subsets of these floors, too. It may be that $\boldsymbol{P}$ already contains elements corresponding to these subsets. We then say that $\boldsymbol{P}$ is **powerset closed**, in addition to being floor-unique. In terms of the floor map flr it means that, if $Y\subseteq\text{flr}(x)$ for some $x\in X$, then there exists $y \leq x$ with $\text{flr}(y) = Y$. In terms of the powerset map, for all $x\in X$, $\text{flr}^{-1\rightarrow}(\boldsymbol{\mathcal{P}}(\text{flr}(x)))$ is defined and = the lower point-image, $\leq^{\leftarrow}(\{x\})$. $\boldsymbol{P}$ will then be a **prestaging space**, considered in the next section, and we will have $\boldsymbol{P}_{\bullet}$**OIS** = $\boldsymbol{P}_{\bullet}$**PPS** $\cong \boldsymbol{P}$. $\boldsymbol{P}_{\bullet}$**PPS** in any case is a lower-complete semilattice, with the properties outlined earlier, including lower point-images of objects being complete lattices. Another property worth noting is **lower-distributivity**, distributivity which holds, along with relative complements, within a lower point-image.

Finally, we further extend the space to a full or **total powerspace**, $\boldsymbol{P}_{\bullet}$**TPS** = $\langle\boldsymbol{\mathcal{P}}(\text{Flr}(X)), \subseteq\rangle$ which includes all subsets of the set of atoms, Flr(X). All three spaces have the same member element set, Flr(X). The underlying sets of all but $\boldsymbol{P}_{\bullet}$**TPS**, however, are restricted to certain "admissible" sets in the powerset $\boldsymbol{\mathcal{P}}(\text{Flr}(X))$ or, in the case of the original $\boldsymbol{P}$, their isomorphic images. $\boldsymbol{P}_{\bullet}$**TPS**, on the other hand, is unique given its member element set.

Thus far what we have referred to as total or partial powerspaces, including $\boldsymbol{P}_{\bullet}$**TPS** and $\boldsymbol{P}_{\bullet}$**PPS**, are inclusion ordered. It will be useful to extend these concepts to order-isomorphic images, not inclusion ordered, such as possibly $\boldsymbol{P}$ itself. Rather than adopt new terminology, instead we modify what we have introduced above. Henceforth an **elemental** (total, partial) powerspace is a (total, partial) powerspace as defined above, whereas an isomorphic image of such a space is referred to by omitting "elemental." A total powerspace will then have the properties outlined above for the elemental case: distributivity and relative complements, as isomorphically captured in the corresponding elemental space. In the case of a partial powerspace, we similarly have relative complements plus lower distributivity.

7. Staging, Prestaging, and Multistaging Spaces

Nonempty poset $\boldsymbol{S} = \langle X, \leq \rangle$ is a **staging space** $\stackrel{\text{def}}{=}$ the following hold.

SS1 (floor inclusion). For $x, y \in X$, $x \leq y$ iff $\text{flr}(x) \subseteq \text{flr}(y)$.

SS2 (powerset closure). If $Y \subseteq \text{flr}(x)$ for some x, then there exists y such that $\text{flr}(y) = Y$. By SS1, y is then $\leq x$ and is called a **subobject** of x.

SS3 (chain closure). Every nonempty chain of objects in X has an upper bound.

In view of SS1, no two elements in $\boldsymbol{S}$ have the same floor (floor uniqueness), while SS2 additionally ensures that $\boldsymbol{S}$ is a partial powerspace, thus a lower-complete semilattice with the usual properties such as associativity of meet and join where defined, and relative complements. $\boldsymbol{S}$ must always have a least element, $\bot = \wedge X$ ($\boldsymbol{S}$ is coconsistent), and, if consistent, a greatest element, $\top = \vee X = \text{flr}^{-1}(\text{Flr}(X))$. For this latter case X is just the lower point-image, $\leq^{\leftarrow}(\{\top\})$.

A poset $\boldsymbol{S}$ satisfying SS1-2 we call a **prestaging** space. $\boldsymbol{S}$ then is a partial powerspace, as defined in the previous section (generalized definition), and we have $\boldsymbol{S}\bullet\textbf{OIS} = \boldsymbol{S}\bullet\textbf{PPS}$; this latter property must, of course, carry over to a staging space.

For the staging space, chain closure (SS3) implies, via Zorn's lemma, that every element of $\boldsymbol{S}$ is upper-bounded by some maximal (not necessarily greatest) element. This must include every atom, a property useful in the section that follows. A nonempty chain $C \subseteq X$ has not merely an upper bound but must have a least upper bound $= \vee C$, this property guaranteed by $\boldsymbol{S}$ being a lower-complete semilattice. These properties carry over to order-isomorphic images, including $\boldsymbol{S}\bullet\textbf{OIS} = \boldsymbol{S}\bullet\textbf{PPS}$.

We are now ready to consider the more general, **multistaging** space. We start with staging space $\boldsymbol{S} = \langle X, \leq \rangle$. $\boldsymbol{S}$ is extended to a second staging space, $\boldsymbol{S}^{+} = \langle X^{+}, \leq^{+} \rangle$, by allowing additional objects in the underlying set X, and extending the partial order (graph) $\leq$ accordingly. The extension, it turns out, can happen essentially in only one way, up to a naming convention for the added ("plural") objects. So, any staging space is already a multistaging space, through a different "type coercion" which will bring out the additional properties. The assumptions for a multistaging space $\boldsymbol{S} = \langle X, \leq \rangle$ are:

MS1. (floor extension). Let $U = \boldsymbol{\mathcal{P}}(\text{Flr}(X))$. Then for all $Y \subseteq U$, there exists unique y with $\text{flr}(y) = Y$; this y is just the join $\vee Y = \vee\text{Flr}(Y)$. The definition of the map flr, then, has been extended beyond the set X to allow any set of atoms to be the floor of some object. Let X^{+} = this extended set = $\text{flr}^{\leftarrow}(U)$; X^{+} is the **underlying set, extended** of $\boldsymbol{S}$, $\boldsymbol{S}\bullet\text{Uls}^{+} = \boldsymbol{S}^{+}\bullet\text{Uls}$. We say that an object in X is **singular** and an object in $X^{+} \backslash X$ is **plural** (for reasons to be clarified).

MS2. (floor inclusion). For all $x, y \in X^{+}$, $x \leq y$ iff $\text{flr}(x) \subseteq \text{flr}(y)$, So, we extend the partial order $\leq$ to include plural objects and singular-plural combinations. As before (SS2), a lower bound, in this case x, is a subobject of upper-bounding y. The extended partial order is the **graph, extended**, $\boldsymbol{S}\bullet\text{Gph}^{+} = \boldsymbol{S}^{+}\bullet\text{Gph}$. (Though strictly speaking, we should use "$\leq^{+}$" to denote the extension of the original partial order, we retain the original notation in the interest of readability, where no confusion seems likely.) The partial order of a multistaging space will be called the **subobject partial order**.

MS3. (subobject singularity). Every subobject of a singular object is singular. Thus, the bottom $\bot$ and any atoms must be singular.

MS4 (chain closure). Every nonempty chain of singular objects has a singular upper bound.

So, just as $\boldsymbol{S} \cong \boldsymbol{S}\bullet\textbf{PPS}$, $\boldsymbol{S}^{+} \cong \boldsymbol{S}\bullet\textbf{TPS}$, and it is a straightforward exercise to show that, when restricted to singular objects only, a multistaging space reverts to a staging space, satisfying SS1-3. On the other hand, based on MS1-2, the extended space becomes a powerspace and a complete lattice with bottom $\bot$ as in the restricted case, and top $\top = \vee X^{+} = \text{flr}^{-1}(\text{Flr}(X))$. Every $Y \subseteq X^{+}$ has meet given by $\wedge Y = \text{flr}^{-1}(\cap\text{flr}^{\rightarrow}(Y))$ and join $\vee Y = \text{flr}^{-1}(\cup\text{flr}^{\rightarrow}(Y)) = \text{flr}^{-1}(\text{Flr}(Y))$.

8. Surfaces, Consensus, Nullifier

We have seen how the multistaging space, like a staging space, is built around a partial order $\leq$ that establishes when one object is a subobject of another – that is, has a floor which is a subset. The subobject partial order does not recognize any difference between singular and plural objects but only depends on their floors. In what follows, however, we need a second partial order, actually this time a preorder, that will be sensitive to the difference between a singular and a plural object. Each object, it turns out, will have a "consensus" – a singular object corresponding to "uncontested information content." A singular object will be its own consensus but a plural object will have a consensus that is a proper subobject.

To develop the notion of consensus, a prior notion of "surface" is needed. For each $x \in X^{+}$, and atom $a \leq x$ let $B_{x,a}$ denote the set of *singular* lower bounds of x which are also upper bounds of a. So clearly, $\text{Flr}(B_{x,a}) \subseteq \text{flr}(x)$. Let $C \subseteq B_{x,a}$ be a nonempty chain. C must have a singular, least upper bound $b = \vee C = \text{flr}^{-1}(\text{Flr}(C))$. Since $C \subseteq B_{x,a}$ it follows that $b \leq x$. By Zorn's lemma, $B_{x,a}$ contains a maximal element c which both upper-bounds the atom a and lower-bounds x.

We define the **surface** $\text{srf}(x)$ as the set of maximal, singular lower bounds of x. The preceding argument shows that $x = \vee\text{srf}(x)$. If x itself is singular, then it is the maximal upper bound of all its singular lower bounds and we have $\text{Srf}(x) = \{x\}$. Otherwise, there could not be just one, maximal singular

lower bound of x (since it would have to upper-bound every lower-bounding atom, thus $= x$) so it must have two or more elements. (So x is "plural" as opposed to the singular case where the surface is a singleton.) In any case, the surface must be an antichain: for $z,w \in \mathrm{srf}(x)$, either $z=w$ or $z \| w$.

We define the **consensus** $\mathrm{cns}(x)$ as $\wedge\mathrm{srf}(x)$. Intuitively, the consensus is the "uncontradicted information" in x. Thus if x is singular, there is no contradiction and x equals its own consensus. But otherwise, $\mathrm{srf}(x)$ is a nontrivial antichain, and we must have $z > \mathrm{cns}(x)$ for all $z \in \mathrm{srf}(x)$ – every component in $\mathrm{srf}(x)$ has something in it that is contradicted in some other component. Here it is convenient to introduce a limited arithmetic of objects: $x+y = x \vee y =$ $\mathrm{flr}^{-1}(\mathrm{flr}(x) \cup \mathrm{flr}(y))$; $x-y = \mathrm{flr}^{-1}(\mathrm{flr}(x) \setminus \mathrm{flr}(y))$. (Addition is, of course, associative and commutative since it is just the binary join.) We see then that, for $y = x\text{-}\mathrm{cns}(x)$, we must have $\mathrm{cns}(y) = \bot$; we then say that y is the **nullifier** of x and write $y = \mathrm{nlf}(x)$. In fact we must have $x = \mathrm{cns}(x) + \mathrm{nlf}(x)$: every object is the sum of a singular object (its consensus) and a nullifier, with the nullifier being empty ($\bot$) iff x is singular.

To compare objects based on their consensus, we define the **consensus preorder** $\leq_{\mathrm{cns}}$ by $x \leq_{\mathrm{cns}} y \stackrel{\mathrm{def}}{=} \mathrm{cns}(x) \leq \mathrm{cns}(y)$. More than one object will generally have the same consensus (so the relation is a preorder not a partial order) but all but one of the objects in each equivalence class will be plural.

It will be convenient at this point to extend the notion of surface to sets of objects or **object-sets**: for $Y \subseteq X$, $\mathrm{Srf}(Y) = \mathrm{srf}(\vee Y)$. We see that, at this level, Srf is idempotent: $\mathrm{Srf}(\mathrm{Srf}(Y)) = \mathrm{srf}(\vee\mathrm{srf}(\vee Y)) = \mathrm{srf}(\vee Y) = \mathrm{Srf}(Y)$. Notions of consensus and nullifier are similarly extended: $\mathrm{Cns}(Y) = \mathrm{cns}(\vee Y)$; $\mathrm{Nlf}(Y) = \mathrm{nlf}(\vee Y)$. We also extend the consensus preorder: $Y \leq_{\mathrm{Cns}} Z \stackrel{\mathrm{def}}{=} \mathrm{Cns}(Y) \leq \mathrm{Cns}(Z)$, equivalent to $\mathrm{cns}(\vee Y) \leq \mathrm{cns}(\vee Z)$ or $\vee Y \leq_{\mathrm{cns}} \vee Z$.

As a simple illustration, let $\boldsymbol{S}^+ = \langle X^+, \subseteq \rangle$ for X^+ = the powerset of the set of integers {1, 2, 3, 4}, ordered, as indicated, by inclusion. So X^+ has sixteen elements, with $\bot = \varnothing$, $\top$ = {1, 2, 3, 4}. Similarly, let $\boldsymbol{S} = \langle X, \subseteq \rangle$ be the associated staging space in which X is restricted to those subsets of integers in which any two integers are relatively prime. So, for example, $\{1, 2, 3\} \in X$ and is a singular object, but $\top$ itself is excluded from X and is plural. Indeed we see that $\mathrm{srf}(\top)$ = {{1, 2, 3}, {1, 3, 4}}, $\mathrm{cns}(\top)$ = {1, 3}, and $\mathrm{nlf}(\top)$ = {2, 4}. For this simple case, chain closure holds trivially since all chains are finite. If we expand X^+ to range over all sets of positive integers, keeping the restriction that singular objects (sets) have any two elements relatively prime, it is straightforward to show that chain closure must hold. (If, in a union of nonempty chains of sets of positive integers, a pair of integers is not relatively prime, the pair itself must be in one set in the chain, thus disqualified from singularity.) For this case, the surface ranges over all sets of integers that include 1 and, in addition, for every prime p, exactly one element in which p is a factor, for example, the primes themselves, or the products of pairs of distinct primes with each prime occurring in exactly one pair. We then have $\mathrm{cns}(\top) = \{1\}$, $\mathrm{nlf}(\top) = \top \setminus \{1\}$.

A few other concepts will be useful in the main results which follow. We start with a **proset** or preordered set $\boldsymbol{P} = \langle X, \leq \rangle$ where, as with a poset, $X = \boldsymbol{P}_\bullet\mathrm{Uls}$, $\leq = \boldsymbol{P}_\bullet\mathrm{Gph}$. (The only difference is that $\leq$ is now a preorder, with antisymmetry relaxed.) We then define the **powerset extension** (not to be confused with $\boldsymbol{P}_\bullet$**TPT** defined earlier) as the proset $\boldsymbol{P}^{(1)}$ given by $\boldsymbol{P}^{(1)}{}_\bullet\mathrm{Uls} = \boldsymbol{\mathcal{P}}(\boldsymbol{P}_\bullet\mathrm{Uls}) = \boldsymbol{\mathcal{P}}(X)$, $\boldsymbol{P}^{(1)}{}_\bullet\mathrm{Gph} = \leq^{(1)}$ defined by $U \leq^{(1)} V$ iff the "bisimulation" conditions hold: for all $u \in U$ there is $v \in V$ such that $u \leq v$ **and** similarly, for all $v \in V$ there is $u \in U$ such that, again, $u \leq v$. So, for instance, under preorder $\leq^{(1)}$ the empty set is **discrete**: for all $U \in \boldsymbol{\mathcal{P}}(X)$, either $\varnothing = U$ or $\varnothing \| U$.

9. Main Results

Our main results depend on the mapping $\mathrm{srf}(x) \mapsto x$ being invertible, which it is, the above discussion having shown that every x has a unique surface so that the inverse mapping $x \mapsto \mathrm{srf}(x)$, which we call the **active map**, is always defined. If x is plural, we can resolve x into a collection of sharp images, the elements of the surface of x, even when x is as "indistinct" as possible, that is, a nullifier. Each sharp image, we imagine, would occupy a parallel branch in a multiple-worlds setting and appear to an observer in that setting to be a restoration from the original. Different observers in different alternate branches would, of course, perceive different restorations. But this differing in varieties would simply be a reversal of the original loss of information, in which the same collection of differing varieties underwent superposition as the information was lost at each local level and the different localities effectively merged. The restoration process is conservative in that no new information is created and none is lost: $\mathrm{cns}(x) = \mathrm{Cns}(\mathrm{srf}(x))$. The old superposition, however, can be said to be redistributed to replicate its original configuration. We refer to this map, $x \mapsto \mathrm{srf}(x)$, as a **full** or **total restoration**.

In practice it might be imagined that a total restoration is not desired but only a **partial restoration** that captured essential details. (As an example, the text of a lost paper document might be of interest, but not the details of the paper's wood fibers.) For this more general case we imagine the active map takes the form $x \mapsto Z$ where Z is a set of objects, generally plural, with the following properties: (1) mapping $x \mapsto Z$ is invertible, with $\mathrm{Cns}(Z) = \mathrm{cns}(x)$ (conservation of information) and (2) $\{x\} \leq_{\mathrm{cns}}{}^{(1)} Z \leq_{\mathrm{cns}}{}^{(1)} \mathrm{srf}(x)$. Property (2), which we shall refer to as the **interval inequality**, ensures that Z will have intermediate restoration "strength" between $\{x\}$ (effectively, no strength at all, nothing accomplished) and $\mathrm{srf}(x)$ (100% strength).

Starting with x we choose $y \leq x$ (actually, y can be arbitrary) so that $x\text{-}y$ is a "diminished" version of x, chosen to "blunt" the surface elements to objects that contain what is of interest without obliterating too much. The restoration then takes the form $x \mapsto Z$, with $Z = F^{\rightarrow}(\mathrm{srf}(x))$, F in turn given as $F: u \mapsto \vee V_u$, and $V_u = \leq^{\rightarrow}(\{u\text{-}y\}) \cap \mathrm{srf}(x)$. V_u, then, is the set of upper bounds of $u\text{-}y$ that are also surface elements of x, thus singular. With $u\text{-}y \leq u$, there must be an upper-bounding element of $u\text{-}y$ in $\mathrm{srf}(x)$,

in particular, u itself, but other upper-bounding surface elements are possible also. Meanwhile the construction ensures that each $V_u \subseteq \mathrm{srf}(x)$, so $\cup_{u\in \mathrm{srf}(x)} V_u = \cup V_u = \mathrm{srf}(x)$. $\cup\mathrm{Flr}(V_u) = \mathrm{Flr}(\mathrm{srf}(x)) = \mathrm{flr}(x)$. On the other hand, $\mathrm{Flr}(Z) = \cup\mathrm{flr}^{\rightarrow}(\vee V_u) = \cup\mathrm{Flr}(V_u)$, again $= \mathrm{flr}(x)$. Similarly, it follows that $\mathrm{flr}(\vee Z) = \mathrm{flr}(x)$, implying $\vee Z = x$ and $\mathrm{Cns}(Z) = \mathrm{cns}(x)$, establishing property (1). Property (2) also follows easily. $\{x\} \leq_{\mathrm{cns}}^{(1)} Z$ will hold iff $x \leq_{\mathrm{cns}} \vee V_u$ for each V_u. This follows because each V_u is a nonempty subset of $\mathrm{srf}(x)$, which must therefore have consensus (intersection) $\geq$ that of the whole of $\mathrm{srf}(x)$. For the rest of the interval inequality, $Z \leq_{\mathrm{cns}}^{(1)} \mathrm{srf}(x)$, the situation is reversed: each V_u contains the singular element u. It therefore must have consensus (again, intersection) less than that of $\{u\}$ which in turn is just u.

For the last topic in "main results" we wish to consider probability weights of the different branches of alternate reality, an issue which has been ignored up to now. But a possible approach is offered by the flexibility provided in the basic formalism, in which singular elements are limited to certain combinations of atoms. Let u be such an element, and suppose a, b, c are "weighting" atoms allowed to combine with u to produce "augmented," singular values: $u_a = u+a$, $u_b = u+b$, $u_c = u+c$. (We do not allow more than one atom at a time to combine with u, except to create a plural object.) Similarly, for element v we have atoms d, e with $v_d = v+d$, $v_e = v+e$. We assume that $u+v$ is a plural object, which means that the sum of all the augmented u and v values is also plural. If we apply mapping $x \mapsto \mathrm{srf}(x)$ to $u+v$ we obtain a two-element surface with one u-variant and one v-variant, so both have equal weight. The same map applied to the sum of the augmented u's and v's yields a surface map with five variants altogether, with u-variants in a 3:2 ratio with v-variants. With similar variant choices we can achieve an m:n ratio for positive integers m,n. So in this way we might enforce rational-number probability weights for the choice of surface element u versus v. This would burden us with the extra baggage that each surface element would, in addition to its previous content, have an extra atom needed to enforce the weighting, but that could be remedied by invoking a partial restoration in which the weighting atoms are omitted from the end result. (Let the subtracted element y consist of the sum of all these weighting atoms, a plural object.) We could also expand our set of weighting atoms to a continuum, so that each atom, say, is indexed by a real number between 0 and 1. If the atoms assigned to u had indices from 0 up to r, with the rest assigned to v, it would, in effect, enforce a probability of r for u and 1-r for v.

In a practical application r could be adequately approximated by a rational number m/n, so the previous considerations would still apply. Furthermore, one would never deal explicitly with weighting atoms. The choice of surface element, whether u or v, would require nothing more than a quantum random operation that achieved the desired probabilities, that is, r for u and 1-r for v. In effect the atoms would silently "come in when needed" then disappear, all by the enforcement of probability weights. The procedure could be extended to a partial restoration more generally, again, by making choices with the correct probability weights when called for.

10. Summary, Conclusions, and Afterthoughts

A mathematical approach has been followed to model the recovery of lost information which cannot be recovered by conventional means, including archaeology. Records (chunks of information) are represented as objects in a partially ordered set or poset that allows for subrecords (subobjects) and chain closure of successively more complete records. (The chain closure allows the possibility of an infinite record occurring via a succession of telescoping, finite records.) An uncontested record is a "singular" object while a record with contradictions is a "plural" object whose "consensus" or uncontested component, is less than the whole. The recovery process consists of filling in missing information by random guesswork, to obtain a "sharper" object with greater consensus. The rationale behind this is that "random" events are not really that but are shadowed in alternate, parallel branches of reality by other, similar choices. On this basis the random choices are seen to fill in authentic information as it once existed in these alternate branches, no one branch being specially singled out. Thus, the observers in the different branches are not aware of which was originally the "home branch" they individually occupied. Instead, the concept is not defined; the alternate branches are on a strictly equal footing.

Turning to criticism, we can certainly raise the basic question of whether the parallel branches really exist, in a way that would be adequate to the needs at hand. This question is, of course, well beyond the scope of the present study. Much has already been said on it, much more no doubt will. The present study was one outcome of an assessment, on the part of the author, that the outlook at least is hopeful. More than that will have to await a future judgment. But with that hopeful premise cautiously accepted, we can proceed with other issues.

One difficulty with the approach is uncertainty in historical records. Errors, falsifications, and ambiguities occur. If a document *says* a thing happened, the proper interpretation may attach a certain probability that it did, but never absolute certainty.

Another difficulty is that information that is "filled in by guesswork" may already exist, awaiting discovery. The probability of agreement between a guessed and a discovered record for any sizable record is negligible, and the discovery must have priority, if and when it occurs, leading to revision in what one accepts as history. So all information filled in by guesswork must have a provisional character. Yet it seems unlikely future breakthroughs in science and technology will permit the straightforward recovery of detailed historical information, including, for instance, the detailed brain structure of vanished individuals one would like to restore to life. Much must remain undiscoverable, and one is probably on safe ground in recreating it through guesswork as suggested.

Still, there could be major pitfalls. Reconstructing the more distant past might be increasingly hazardous, if, again, one is trying to restore vanished individuals to life. More distant individuals may or may not have been present at all. The case of an individual who was recreated then whose presence in our timeline was rendered improbable by a later discovery could still be accommodated, perhaps as a "traveler from afar," who had crossed from a parallel timeline and is now making their home in a "new country."

For the example of cryonics, referred to earlier, a possible approach is suggested for any cases where sufficient information is lacking in the remains to complete a satisfactory revival. Missing portions could filled in by guesswork, guided as far as possible by surviving information. Still, great care would be needed, particularly because information added for one person must reasonably be consistent with that added for someone else, particularly if the two were close associates, but not only then. The difficulty with persons of the distant past, however, should be minimal; one could be sure the persons in question really existed.

Cryonics is certainly a controversial practice now, but its intentions are worthy, to try to preserve personal information sufficiently well that guesswork will not be needed in the future to restore the person to a healthy state. How far that premise may be valid is one more issue that the future must decide, but the present study suggests reasons for optimism. If cryonics alone would not be good enough, there is an additional strategy that could be brought to bear.

More generally, the sort of results obtained challenge the notion that death in any form should be considered "final." A pathway appears to be opened for further investigation, and it appears that much can and should be done. The present study has not attempted to incorporate physics more than minimally, basic set theory seeming adequate at the aimed-for level. Future investigations with greater scientific underpinning will perhaps yield far greater results. ■

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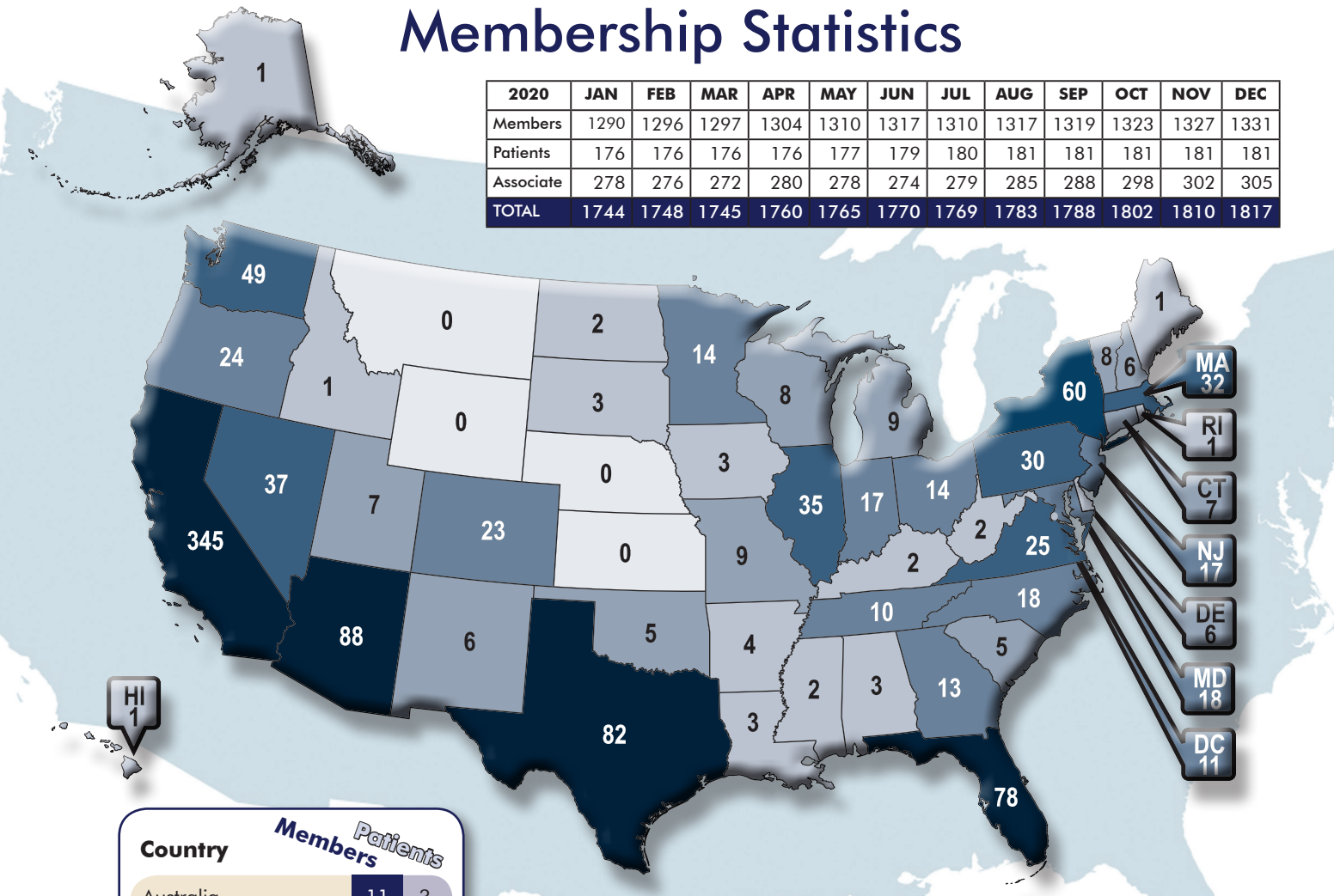
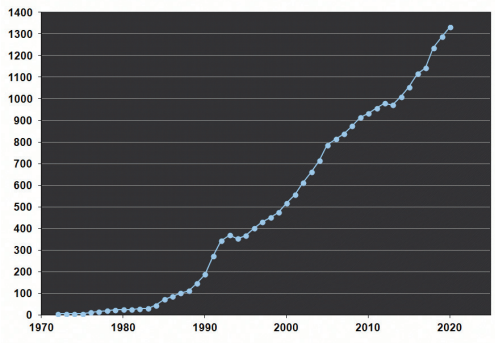
2020	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1290	1296	1297	1304	1310	1317	1310	1317	1319	1323	1327	1331
Patients	176	176	176	176	177	179	180	181	181	181	181	181
Associate	278	276	272	280	278	274	279	285	288	298	302	305
TOTAL	1744	1748	1745	1760	1765	1770	1769	1783	1788	1802	1810	1817



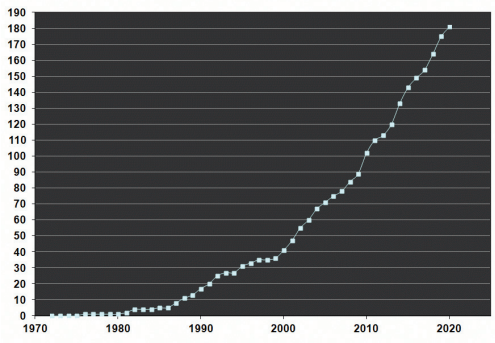
International Members & Patients

Country	Members	Patients
Australia	11	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	69	4
China	0	1
Finland	1	0
France	1	1
Germany	20	0
Hong Kong	2	0
Hungary	1	0
Israel	1	1
Italy	2	0
Japan	4	0
Luxembourg	1	0
Malaysia	1	0
Mexico	5	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	2	0
Portugal	4	1
Puerto Rico	1	0
Spain	5	1
Sweden	1	0
Switzerland	2	0
Taiwan	1	0
Thailand	3	1
United Kingdom	41	3
TOTAL	186	16

- 0 Members
- 1–4 Members
- 5–9 Members
- 10–24 Members
- 25–49 Members
- 50–74 Members
- 75+ Members



Number of Alcor members



Number of Alcor patients

Cephalon Cooling Curves, Practice and Theory:
A Brief Progress Report

By R. Michael Perry

Introduction

The initial stages of cryopreservation of a cryonics patient involve cooling from body temperature to the temperature of water ice (from approximately 37°C down to 0°C). Ideally, this cooling (and further cooling down to cryogenic temperatures, -100°C or lower) should happen as fast as possible to minimize damage from warm ischemia. Though the effects of warmer temperatures on tissue are complex, as a start in estimating or quantizing them we would like to know simply how the temperature varies as a function of time at different points within the cooling subject. Toward this end, temperatures are monitored using probes as cryopreservation proceeds, but opportunities are limited by the necessity of minimizing any possible harm to the patient while cryopreservation is in progress.

Recent work at Oregon Cryonics with cadaver cephalons has furnished additional data on temperatures within the brain during various cooling protocols. Mathematical modeling of such processes can furnish useful insights into problems that might be encountered in the clinical (cryonics) setting, as well as serving as a low-cost, noninvasive adjunct and possible alternative to expensive and invasive laboratory procedures. Here we compare experimental cephalon cooling curves as the temperature is reduced from body temperature (37°) to near 0° over an eight-hour period, with temperatures calculated from a spherical model of the human head, based on work of Art Quaife in the 1980s.[2] The calculated cooling curves overall showed good, sometimes excellent, correspondence to the experimental curves, with some unexplained discrepancies perhaps pointing to deeper insight to be gained from further study.

Main Results

For the Oregon Cryonics results, cephalons starting at body temperature (37°) were immersed in an unstirred ice water bath, and temperatures were tracked as cooling proceeded toward water ice temperature (0°). Depths within the brain at which temperatures were monitored consisted of core (approximate brain center, 8 cm. downward from calvarium vertex, exterior top of skull), mid-range (5 cm. down) to surface of the brain, with nasopharyngeal and average temperature also plotted.[1] (Further details, some involving other cooling protocols, will be found in the reference cited.) Results representing an average over 13 individual cases are shown in fig.1 for the different cooling curves. (Note: the curves for "Naso" and "Brain Surf" are nearly coincident.)

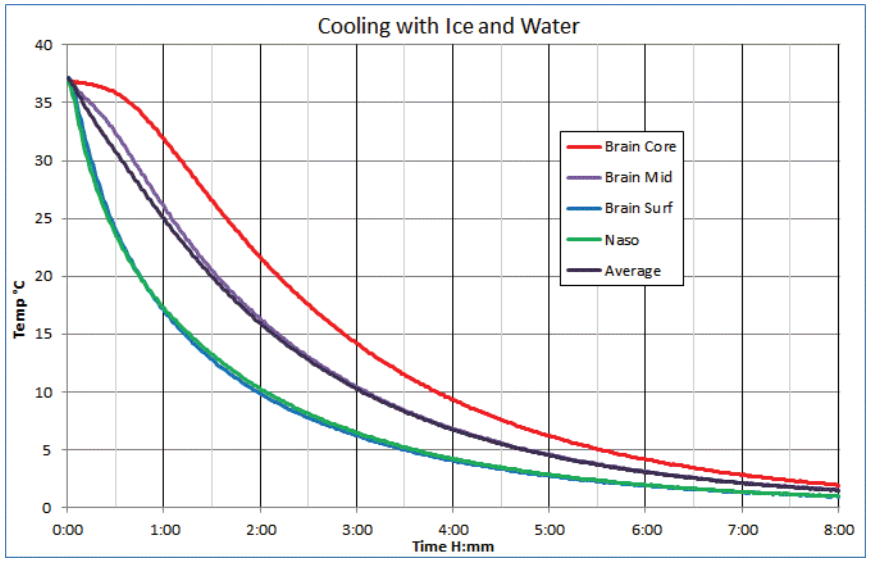


Figure 1. Cephalon cooling data from Oregon Cryonics, used with kind permission.

For the mathematical work, software was created in Mathematica for modeling heat flow in a sphere, based on the work of Art Quaife in the 1980s[2], to approximate the cooling of an isolated cephalon. Quaife's simplifying assumptions, adopted here, are that initially the sphere is at a temperature that is uniform throughout and that the surrounding medium is likewise at a uniform but lower, temperature. Further, the heat conductance is uniform and independent of temperature within the sphere, which does not generate heat but only loses it as cooling proceeds. Similarly, there is uniform, temperature-independent conductance out of the sphere into the surrounding medium.

With these assumptions, plots were obtained from calculations of cooling curves for the temperature at different points (radii r) within the sphere as a function of time t, ranging from core (r = 0) to surface (r = 1), plus an average temperature for the whole sphere. (Due to symmetry, the temperature within the sphere depends only on the radius r and time t.) The temperature range

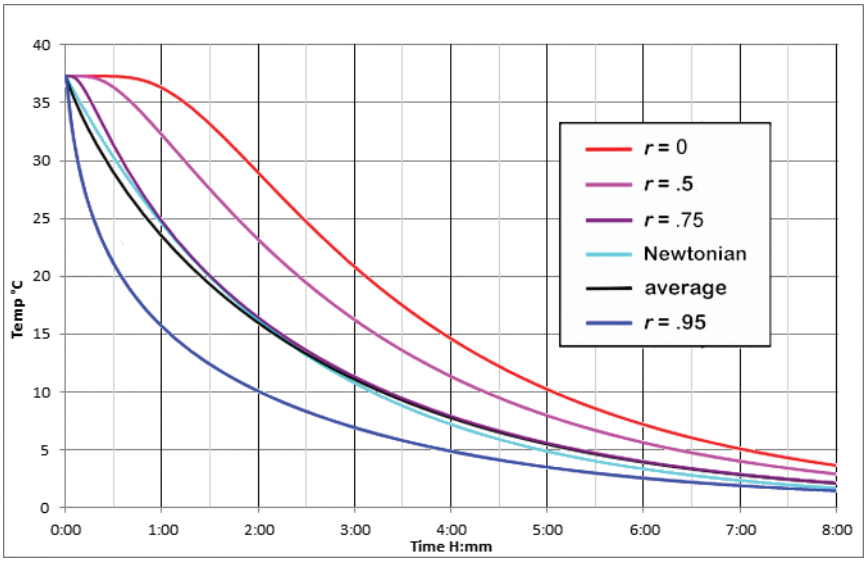


Figure 2. Cooling curves calculated from spherical model, Biot number = 4, plus Newtonian.

was scaled linearly to conform to the experimental range of 0°-37°C. Time was similarly scaled so that the "time constant" for the average temperature to drop to 1/*e* of the temperature range of 37° down to 0°, or 13.6°C, would match the value seen in the experimental results. This in turn is found by considering the average (black) curve in Fig. 1; here the temperature of 13.6° is reached at about 2.35 hours.

The calculated temperature depends additionally on the choice of the "Biot number" *Bi* giving the ratio of the rate of heat convection from the surface of the sphere to the surrounding medium, to the rate of heat conduction within the sphere. A small value of *Bi* corresponds to a high rate of heat conduction compared to the rate of convection, so the temperatures within the object will be nearly uniform and the cooling will be nearly Newtonian, making the cooling curves nearly the same for different points within the sphere. The surrounding medium in turn will show significant temperature differences (temporary increases) with time. A large value of *Bi* reverses this condition, so that convection of heat out of the object creates large temperature differences within the object, but the surrounding medium will have small temperature differences only as the heat is rapidly transported away. An intermediate condition occurs with *Bi*=1 meaning the conduction and convection rates are equal.

The experimental results clearly show substantial temperature differences, suggesting a large *Bi* (>1) would better account for them in the spherical model. Figure 2 shows calculated cooling curves at different radii *r* within the sphere, plus an average temperature, all with *Bi* = 4. In addition, for comparison a plot is included for the case *Bi* = 0, in which there are no temperature differences within the object (all radii show the same temperature) and the cooling is Newtonian: The cooling rate is proportional at all times to the difference between the temperature of the object and the final temperature, here 0°, resulting in an exponential decay.

Two of the calculated curves are especially close to the Newtonian curve: *r* = .75 and the average temperature. The Newtonian curve is also nearly identical to the experimentally derived average for the cephalon (Fig. 3). (The experimental average of the curves at different depths in the object, is not strictly comparable to the weighted average calculated curve shown in Fig. 2, where the weighting is proportional to r^2. But the two curves both in fact fit the Newtonian curve fairly well, the experimental curve actually showing a better fit than the calculated curve.) The curve for *r* = .95 also matches well the brain surface and nasopharyngeal curves for the cephalon; note that the two experimental curves are not from the surface of the cephalon but a short distance inside.

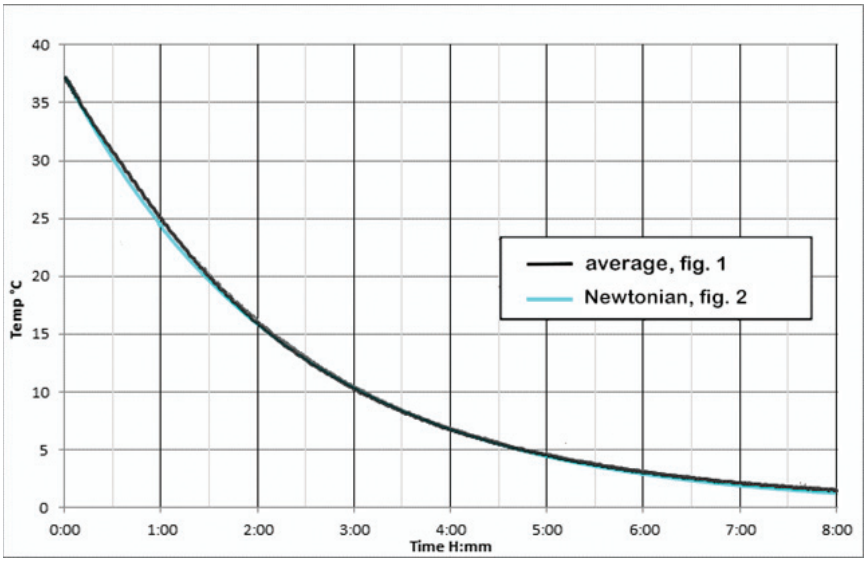


Figure 3. Comparison of experimental "average" curve, with calculated, "Newtonian" curve, showing near coincidence of the two curves.

It is only when the calculated curves for smaller *r* are compared with the experimental curves that significant discrepancies appear, the experimental temperatures appearing lower and more "Newtonian" than their calculated counterparts, if we identify the experimental "core" temperature with the calculated curve for *r* = 0, and the "mid" temperature with the

curve for $r = .5$. Instead, the calculation for $r = .5$ is a better match for the "core" experimental curve, and the calculation for $r = .75$ is similarly better for the "mid" experimental curve. The cause of these discrepancies is unclear – whether a simple matter of which probe position should be matched with which radius r, or something more substantial. But overall, the spherical model seems to capture the main features of cooling in the experimental case. One consequence is to lend confidence to the assumption that overall, the cephalon cooling is approximately Newtonian, at least for the protocol considered: The cephalon was immersed in ice and water, with ice added periodically and water from melting drained off, but there was no stirring of the bath. Further studies should provide additional insight for this and other cooling protocols, including addressing the question of how serious the slower cooling of the inner brain regions might be in terms of extra ischemic exposure. ■

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2. 2. Art Quaife, "Heat Flow in the Cryonic Suspension of Humans: A Survey of the General Theory," *Cryonics* 6(9) (Sep. 1985) 9-30, ascii version at https://www.alcor.org/docs/cryonics-magazine-1985-09.txt, accessed 3 Feb. 2021.

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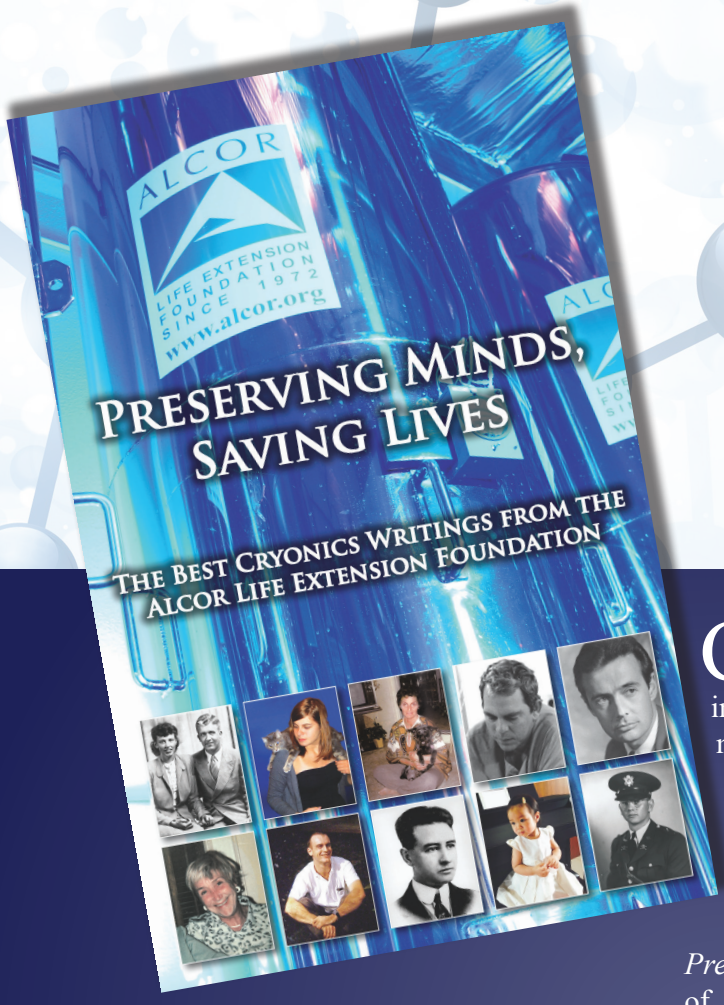

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"Society's failure to take cryonics seriously is a tragedy that is probably costing countless lives. Alcor, notably via its magazine, is leading the fight to change that."
– Aubrey de Grey, Ph.D.
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– Michael D. West, Ph.D.
Stem Cell Scientist and Chief Executive Officer of BioTime, Inc.

What if Senolytics Fail?

By Aschwin de Wolf

There is a school of thought within the life extension movement that favors prioritizing the promotion of cryonics over anti-aging efforts. There are a number of arguments for this. A technical argument has been put forward in Thomas Donaldson's seminal article "Why Cryonics Will Probably Help You More Than Anti-aging."

The most rigorous test to determine whether an anti-aging therapy works entails giving it to a group of people and determining whether these people live longer (without any detrimental side-effects). The timescales entailed do not permit rapid progress in a field. Aiming for outright *rejuvenation* might be a better strategy because it allows for more short-term objective metrics to be used. Some of these metrics are common sense (athletic performance, skin appearance, cognitive tests etc.), others are more controversial (biochemical "biomarkers" of aging).

Wherever one comes down in this debate, it cannot be denied that cryobiological research can be pursued in a more precise, time-efficient manner. For example, if you want to determine whether a vitrification solution resists freezing when it is cooled to cryogenic temperatures, you need no more than a day to perform the experiment and document the results. This vitrification solution can then be introduced to an organ to determine whether the organ can be vitrified and recovered without ice formation.

This is not just conjecture. Since the mid-20th century a small number of dedicated cryobiologists have solved the problem of designing cryoprotectants that do not freeze at realistic cooling-and-warming rates. Major progress has been made in mitigating toxicity and chilling injury of those cryoprotectants as well. It is important to keep this in mind when cryonics advocates are taken to task for not making as much progress as the people in the anti-aging field.

Another advantage of the field of cryobiology is that most of its findings are observed in all popular mammalian animal models. Phenomena such as cryoprotectant toxicity and cryoprotectant-induced brain shrinking are observed in both small- and large animal models. In aging research, however, the important role of evolution and genetics makes translating results from small animal models to humans a lot trickier. After all, an evolutionary perspective on aging needs to explain different lifespans in different animals and species (and even *within*). An intervention that prolongs the life in a small animal may only have minor health benefits in humans (like caloric restriction).

On a conceptual level the major figures in the life extension advocacy field cannot even agree on what aging *is* (put Aubrey de Grey, Michael Rose, and Joshua Mitteldorf in one room and see the sparks fly!) and the field is not immune to succumbing to one fad after another (while believing that this time it is for real). Part of this problem is related to the lack of objective, short-term measures to determine the effectiveness of an anti-aging treatment in humans. If it would be possible to assess the effectiveness of an anti-aging therapy in a quick and unambiguous manner, one theory of aging might be more easily favored over another.

Recent developments in the field of biomarkers of aging and "aging clocks" have given hope to those who believe that it now will be easier and time-efficient to determine the effectiveness of an anti-aging intervention. As of writing, there are several different biomarkers of aging and there is no consensus if these measures capture all the important aspects of aging. In fact, whether one clock is favored over another is itself reflective of one's perspective on what aging is, which brings us back to the fundamental disagreements over aging that continue to divide biogerontologists. One thing that these biomarkers of aging will *not* be able to tell is whether an intervention is effective and safe in the long run. Or whether the maximum human life span would be altered by a specific intervention.

It cannot be emphasized enough that, as of writing, there is not one single anti-aging biotechnology that has been demonstrated to produce extension of the maximum human lifespan, let alone unambiguous evidence of rejuvenation. This should have a sobering effect on dispassionate observers of the field but it is no exaggeration to claim that many movers and shakers in the field are not dispassionate and actually prone to embracing the next big thing, which often generates (predictable) cycles of great enthusiasm and disillusion.

The current big thing in the anti-aging field is the identification and validation of senolytics. Since the clearing of senescent cells is one of the pillars of the SENS program, the success of this approach will have important consequences for the "aging as damage accumulation" school of aging. Billions are flowing into this field in the anticipation of successful biomedical applications. So far, the results in small animal models look modestly

encouraging and human trials have shown mixed results. The failure of a major phase II study for knee osteoarthritis is not encouraging and no doubt supporters will claim that systemic administration of senolytics is the way to go. Or that this is the wrong kind of senolytic. Or that the dosage and administration frequency is not right. Or that senolytics are necessary but not sufficient to produce meaningful anti-aging results etc. Not to speak of the possibility that senescent cells can also play a positive role (like the much dreaded "free radicals" of older anti-aging efforts).

At some point it would behoove the life extension community to seek a better balance between the funding of anti-aging therapies and the funding of (applied) cryonics research. Many wealthy people prefer to fund anti-aging research because it captures their hope that they do not have to die at all. Anti-aging therapies also offer a more attractive investment potential, which is often mistaken as the field being further advanced than biopreservation technologies. And let us not ignore the obvious point that for many very old people the rejuvenation approach will not come in time.

Given enough time, all people will suffer a fatal accident, major trauma, or a type of (infectious) disease for which there is no treatment available (yet). For this reason alone, a comprehensive life extension plan should include arrangements for biopreservation to survive long-term.

What if senolytics fail? I suspect this will produce a major disillusion of the growing anti-aging biotechnology field and the SENS program in particular. A prudent approach would be to work from the premise that many of these therapies won't work, or only have modest effects, and also invest in an evidence-based cryonics infrastructure so that, in principle, all people can access rejuvenation technologies regardless of health condition or age. One of the attractive features of medical time travel is that it can transport today's people to a time when rejuvenation biotechnologies are fact, not hope. ■

[In part 2 of this series, we will delve deeper into the field of biogerontology, its complexities, and how to prevent wasteful research spending….]

Hal Finney Cryonics Research Fund

The Hal Finney Cryonics Research Fund aims to advance the technology behind cryopreservation for future revival. The fund was established in 2018 through a generous donation by Brad Armstrong, a successful cryptocurrency entrepreneur, Alcor member, and admirer of cryoptocurrency pioneer Hal Finney.

The fund is currently focused on research with the potential to:

- Advance the cryopreservation of brain tissue or whole brains, or
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1. Principal investigator and key research personnel
2. A brief summary of the project goals, approaches employed
3. Estimated budgetary needs
4. Overall significance if the project succeeds
5. Any other information you deem worth including

Letters of interest are reviewed on a rolling basis by Alcor's research committee, and if the project is of interest you will be contacted to submit a full application. The length of a full grant application varies according to the size of the request, but it is typically shorter than government research grant proposals (e.g. NIH, NSF, CIHR) of the same scope. ■

Why Cryonics Will Probably Help You More Than Anti-Aging

By Thomas Donaldson

Originally published in *Physical Immortality* 2(4) (2004), p. 28-29

I will begin here by stating first that ultimately we want means to prevent and reverse aging, and second that research into the mechanisms of aging deserves more support than research into either cancer or heart/circulation problems (presently the two leading subjects for which proponents call for donations and lots of research gets done). It's quite clear by simply walking into any doctor's office that aging must ultimately cause most health problems we normally see. Most patients waiting to see their doctor turn out to be old. In an almost unconscious way this situation also causes a lot of worry among politicians about an impending time when older, decrepit people will form a much larger proportion among the population than before. At the same time I will here argue that cryonics right now provides the best strategy to prolong our lives, while research on antiaging may take far longer to achieve its goals than anyone living now expects.

The difficulty comes both from the scientific side and the social/political side of the problem of aging. From the scientific side, the best possible proof that a treatment will indefinitely prolong the lives of human beings must come from a demonstration of its effects on human beings. Not fruit flies, worms, mice, or rats, but human beings. Yet there's a small problem here: we are human beings ourselves, and a proof that a treatment prolongs the lifespan of people will take … at least the lifespan of some people. And as with mice or rats, such a study must take care that it uses healthy people, not those suffering from some disease known to shorten their lives. This is one of those hard truths that researchers in antiaging still search for means to work around. So far, they haven't found any means not subject to some quite easy criticisms. Yes, with understanding of genetics some gerontologists have found similarities among genes closely related to aging among not just those mammals studied but among fruit flies and mammals. This constitutes an advance in the study of aging. However, whether it leads to treatment of aging in human beings runs into a problem. The action of one set of genes depends on the action of others.

Antioxidants provide one simple example of what this might mean for our longevity. Giving mice genes which increase the amount of antioxidant biochemicals their bodies make will lengthen the lifespans of these modified mice. However human beings live much longer than mice, and already produce much higher levels of antioxidant biochemicals than mice. Beyond a certain amount of antioxidants their effect will fall off. It should not be surprising if more antioxidants have only a small effect on our lifespans even though they have a larger effect on the lifespans of mice.

Calorie restriction raises a similar question. The current ongoing experiment with calorie restriction in monkeys will help deal with exactly that problem. If calorie restriction causes significantly less increase in lifespan of the test monkeys than it does of mice, that will suggest it may act even less strongly in human beings. We live much longer than mice. To some unknown degree, the metabolic changes which make us live longer may also include changes similar to those caused by calorie restriction. Yes, if this ongoing experiment with monkeys were to show a significantly smaller effect of calorie restriction in monkeys than in mice, I and many others would be disappointed. This problem arises with any drug or treatment shown to work on short-lived animals.

We live significantly longer already than any of the experimental animals used in aging research. (And yes, despite some claims, more than one drug has experiments in mice or rats which not just increases in average lifespan but increases in maximum lifespan too (1). What we really want and don't now have is a test of aging independent of lifespan of the species tested. We do have a sign of aging, but not a test: animals that do not age at all will have lifespans forming an exponentially decreasing curve. (See Figure 1) Yet a sign of aging hardly constitutes a test. Still worse, if we used that sign to work out whether or not we were prolonging our lives, we ourselves would never live long enough to get the benefits of such a "test." Even to devise a test independent of species lifespan may take more than a human lifespan. Could we do it not by waiting for creatures to die but by a far deeper understanding of how aging worked itself? Yes, but we're still far from that level of understanding, and will need more time to reach it. Even calorie restriction, now accepted by almost all gerontologists as a treatment which affects aging, fails to cause that exponentially decreasing curve; instead the more-than-exponential period just happens later. We will not

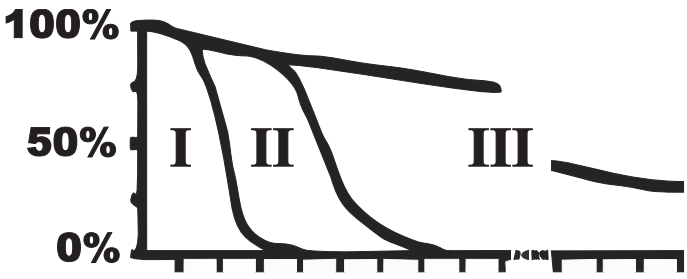

Figure 1: Aging and Lifespans

have truly dealt with aging itself until our lifespans follow that exponential curve (upon which we should then try to prevent the random accidents still causing our deaths).

If our deathrate remained independent of how long we had previously lived, then a curve showing lifespans of a population would look like an exponential curve $A\exp(-at)$ where A is the population at time $t = 0$ and $a > 0$. However, curves of the lifespans of humans aren't exponential. They show the effect of aging on deathrate: as we grow older, our deathrate increases. For a short period, they look as if they will be exponential, but then go to zero much more rapidly than the exponential curve. This remains true for calorie restriction experiments. In this figure, III shows an exponential curve starting with 100% of the population (of mice or humans). I shows a normal lifespan curve. II shows the lifespans of a calorie-restricted population, with an average approximately doubling that of a normally fed population. Units on the horizontal axis depend on the lifespan of the species studied; the vertical axis gives the % of surviving members at various times. A curve showing the effect if deathrate actually decreased the longer an individual lived is omitted. It would look a bit like an exponential curve but could tend to a positive limit.

The fundamental problem with all current experiments on aging comes from the simple fact that humans already live much longer than most animals. In one way, the scientific/medical problem of aging and means to prevent it resembles that of the very early days of astronomy. Planets moved slowly, and clouds interfered with seeing them. To come to enough understanding of their motions that anyone, even Ptolemy, could make a theory of how they moved took generations of observations, by many workers now completely unknown to us. We can hope that the scientific problem of aging won't take nearly as long; but it still may take more than one generation, from the early work of McCay on calorie restriction to the implementation in human beings of treatments which abolish or reverse their aging.

Is there anything we can do to get around this problem? Yes, but it will involve a violation of accepted standards of current medicine (2). This gets us directly into the social-political side of the problem of aging. No law of nature prevents us from taking drugs shown to increase the lifespan of rats and mice even if their effect on our human lifespans remains unproven. However doing this violates current standards of medical practice, not simply because it tries to deal with aging, but because taking unproven drugs just isn't normally done. Yes, it's done as part of experiments, usually fairly short-term. It takes a long time and the actual reports on clinical use of a drug for physicians to get an idea of the effects of long-term use of that drug. Very few drugs of any kind get formal tests for the entire lifespan of normal people taking them. Moreover, genetic experiments on human beings, even those which try to fix well-known inherited diseases such as hemophilia, still run into lots of opposition.

To fix ourselves so that we do not age, or even age at a slower rate than normal, will activate even more opposition, just as any treatment which improves patients rather than cures their "illness." The many (and almost totally unopposed) genetic modifications of mice made to study some metabolic factor, and the opposition to any such modifications of humans, shows how this opposition works. Moreover, aging, of course, still isn't normally seen as an illness. It's not so much the direct opposition which slows down advances here, but the effects of such opposition on funding for experiments, and the willingness of scientists to risk their careers in studying a treatment, say, to increase lifespan (or intelligence, et cetera). It's not that these social-political problems in the study of human antiaging, and the application of that study, will prevent it entirely: instead they slow it down. No one opposed the development of transistors, so we saw electronics make great leaps forward. We should not decide from this example that work on aging will happen as rapidly, even with the latest genetic methods.

What, then, of cryonics? The major and important difference between cryonics and antiaging comes from the simple fact that discovery of methods to preserve our living brains avoids the scientific problems in the study of aging completely. Of course suspension, too, involves lots of scientific problems. Still, none of them involve work which will necessarily use up time. A lifespan experiment on mice requires at least 3 years. A cryobiological experiment testing a modified preservation method takes no more than a week at most. Neither antiaging nor cryonics meet with lots of social approval, so funding will be low (but still nonzero) for both fields. However cryobiology can progress much faster than antiaging. Not only that, but its progress almost totally lacks the problems of proving that an advance has happened. The state of a brain, or even a section of brain, after vitrification and rewarming to normal temperature, shows directly whether or not the method used improved on previous methods.

In one sense, opposition to antiaging research has actually had a much stronger effect on its speed than any opposition to cryonics. No explicitly immortalist society promoting immortality (i.e. total absence of aging) yet exists. It's thought quite extreme among doctors for a doctor to suggest that we might even increase lifespans by 50%. Yet at least two different

societies exist right now, Alcor and the Cryonics Institute, which are actively suspending people and working to improve their methods. I've known, ever since I was a child, older people who thought that the problem of aging would be solved in time for them, and found themselves decrepit, old, and financially dependent, still without any means to cure their aging.

No matter what some scientists say, a cure for aging involves many problems all of which will need time for their solution. Even now, you may be young and feel that you need not think about cryonics because some means to slow your aging will come before you've gotten very old, and from that still other means to slow your aging even more … and so on to true agelessness. In this article we have seen why such dreams of a rapid solution to aging cannot come fast for any of us. At the same time, cryonic suspension able at least to preserve our brains in a reversible form, allowing restoration of vital functions, looks likely to come much sooner. ■

Notes

1. Scrutiny of the discussion of antiaging drugs in my book, A Guide to Antiaging Drugs, will produce several drugs which this feature.

2. The strategy is simple but hard to implement. Those taking a drug shown to increase lifespan in some class of healthy mammal sign onto an experiment so that their state of health is monitored for the rest of their lives. It is both the length of such an experiment, and the impracticality of really long term tests of any specific drug or treatment, plus the simple fact that these drugs do not cure any illness, which makes such a procedure violate current medical procedures. There are fully accepted studies of the health of some population of people under "natural" conditions, following how their health changes over time. Subjects, however, aren't taking any special treatment.

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Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

Fight Aging! exists to help ensure that initiatives with a good shot at greatly extending healthy human longevity become well known, supported, and accepted throughout the world. To this end, Fight Aging! publishes material intended to publicize, educate, and raise awareness of progress in longevity science, as well as the potential offered by future research. These are activities that form a vital step on the road towards far healthier, far longer lives for all.

The Public Cannot Distinguish Between Scientific versus Unscientific, Likely Good versus Likely Bad Approaches to Longevity

August, 2020

One of the challenges inherent in patient advocacy for greater human longevity, for more research into aging and rejuvenation, is that journalists and the public at large either cannot or will not put in the effort needed to distinguish between: (a) scientific, plausible, and likely useful projects, those with a good expectation of addressing aging to a meaningful degree; (b) scientific, plausible, and likely unhelpful projects, those that will do little to move the needle on life expectancy, and (c) products and programs that consist of marketing, lies, and little else. This last category is depressingly large, and the first category still depressingly small.

There are examples of useful, high-expectation scientific projects in the senolytics industry, working on the means of removing senescent cells from old tissues. In animal models this is far and away the most impressive approach to rejuvenation attempted to date, applicable to many age-related diseases. The first good senolytic therapy will be revolutionary for human health in later life. As a counterpoint, an example of a poor and unhelpful scientific project is the use of metformin as a geroprotective drug, an approach that appears to very modestly and unreliably slow the progression of aging. Beneficial effects in animal studies are haphazard and small. The single study in diabetic humans shows only a small effect size. If devoting vast expense to clinical trials that target the mechanisms of aging, then why do so for a marginal therapy? Lastly, for examples of marketing and lies, one has to look no further than the established "anti-aging" industry and all of its nonsense and magical thinking. Apple stem cells. Random peptides with cherry-picked studies. Clearly no meaningful effects in the many humans using these products.

As meaningful attempts to produce rejuvenation therapies progress, and begin to attract greater attention in the world at large, we continue to see articles such as the one I'll point out today, in which no attempt is made to differentiate between sleep strategies, stem cell therapies, senolytics, metformin, and other approaches good and bad. High expectation versus low expectation of gains in health, good data versus bad data in animal studies, scientific or unscientific, it is all just lumped into the same bucket. This is unfortunate, as it leads to the situation in which any arbitrary health-focused demagogue selling branded coffee is presented just as legitimate and useful to the field as an industry leader in the clinical development of actual rejuvenation therapies, or another industry leader working on projects that can in principle only produce small gains in late life health. Which is clearly not the case. As a 60-year-old, you can practice changing your sleep and coffee habits, you can take a calorie restriction mimetic, or you can take senolytics, and only one of those three things is going to make a very sizable difference to your health and remaining life expectancy.

Why Silicon Valley Execs Are Investing Billions to Stay Young

Dave Asprey, 48, is the founder of the Bulletproof wellness empire and a vocal champion of the movement to extend human life expectancy beyond 100 years. He's made millions by experimenting on his own body and packaging his home-brewed discoveries into books, a podcast, consulting services and consumer products (you may have even tried his butter-laced coffee). Thanks to a recent explosion of advances in longevity medicine, Asprey's vision of living healthfully into his second century might not be so crazy. In fact, for people in middle age right now, a handful of therapies in clinical trials have the potential, for the first time in human history, to radically transform what "old age" looks like. If the life extensionists are right, a person who's 40 today might reasonably expect to still be downhill skiing, running a 10K or playing singles tennis at 100.

It might be an exaggeration to say BioViva CEO Liz Parrish believes death is optional, but for her, Asprey's goal of living to 180 shows a distinct lack of ambition. "If you can reach homeostasis in the body, where it's regenerating itself just a little bit faster than it's degrading, then what do you die of? An accident or natural disaster, probably. There's no expiration date at 90 or 100 years old." Like Asprey, she has received criticism from the longevity research community for becoming "patient zero" in her own experimental drug trial, aimed at halting aging at the cellular level. In 2015, Parrish underwent telomerase and follistatin gene therapies in Bogotá, Colombia. The procedures involved receiving around a hundred injections of a cocktail of genes and a virus modified to deliver those new genes into her body's cells.

Humans have always aspired to find the fountain of youth, so "people might be skeptical about the fact that anti-aging technologies are working now," says British investor and businessman Jim Mellon. "But the fact is that this is finally happening, and we need to seize the moment." Mellon cofounded Juvenescence, a three-year-old pharmaceutical company that's investing in multiple technologies simultaneously to increase the odds of bringing winning products to market. Mellon, 63, has made his fortune betting on well-timed investment opportunities, and he predicts that a new "stock-market mania" for life extension is just around the corner. "This is like the internet dial-up phase of longevity biotech. If you'd invested in the internet in the very early days, you'd be one of the richest people on the planet. We're at that stage now, so the opportunity for investors is huge." One of Mellon's bets is on a class of drugs called senolytics, which destroy senescent cells. Senescent cells harm the body by secreting compounds that cause inflammation in surrounding tissues. Many age-related conditions - arthritis, diabetes, Alzheimer's, cancer - have an inflammatory component, and studies suggest that a buildup of senescent cells is a large part of the problem.

Eric Verdin, 63, is president and CEO of the Buck Institute, a globally renowned center for aging research just outside San Francisco in Marin County. Verdin is bullish on the promise of living healthfully to at least 100. Today. But 180? Don't count on it. "My prediction, based on everything we know today, is that getting to 120 is about the best we can do for the foreseeable future. I'll bet my house we're not going to see anyone live to 180 for another 200 years, if ever. But making everyone a healthy centenarian, this is something we can do today. And that's something to be excited about." Verdin's own lab at the Buck Institute studies the aging immune system and how it's affected by lifestyle factors, such as nutrition and exercise. Take, for instance, rapalogs, a class of drugs derived from rapamycin that interact with a protein called mTOR, which serves as a linchpin for multiple critical biological processes, including cell growth and metabolism. Rapalog drugs tamp down mTOR, possibly preventing age-related diseases such as diabetes, stroke, and some cancers. One of the many effects of rapamycin is that it mimics the mechanisms of calorie restriction. As Verdin's lab and others have shown, fasting provides a number of anti-aging benefits, including insulin regulation, reduced inflammation and, to put it colloquially, clearing out the gunky by-products of metabolism.

Destroying Existing Microglia is Necessary for Replacement Strategies to Work

August, 2020

This open access research is a demonstration in mice of approaches to replace nearly all microglia in the central nervous system. Microglia are innate immune cells of the brain, involved not just in destroying pathogens and errant cells, but also in ensuring the correct function of neural connections. With the progression of aging, their behavior shifts to become more harmful and inflammatory, and their numbers include ever more senescent cells. Senescent cells generate tissue dysfunction and chronic inflammation via the senescence-associated secretory phenotype, but beyond that microglia tend to adopt a more aggressive and inflammatory set of behaviors even when not senescent. This detrimental change is the consequence of some mix of persistent infection, protein aggregates, and other forms of the underlying molecular damage that drives aging.

Microglial dysfunction contributes meaningfully to age-related neurodegeneration, as illustrated by the benefits produced in animal models by the selective destruction of senescent microglia. That approach has turned back the tau pathology characteristic of Alzheimer's disease in mice, for example. There is also evidence for inflammatory microglia to be involved in the progression of Parkinson's disease.

More than just the senescent cells need to be replaced, or otherwise have their behavior changed for the better, however. Approaches involving clearance of a large fraction of microglia, and allowing them to regenerate thereafter, have seemed viable. Efforts to replace microglia with transplanted cells have proven challenging, however: even hematopoietic stem cell transplantation, such as via a bone marrow transplant, doesn't replace more than a small fraction of the existing microglia. As researchers here demonstrate, it is necessary to first destroy near all microglia in order to leave an empty niche in the brain that will generate signals telling the body to replace these cells. Will replacement be necessary for the treatment of age-related microglial dysfunction, rather than genetic dysfunction? It seems plausible that hematopoietic stem cell replacement will be adopted as an approach to immune system rejuvenation, so why not pair it with clearance of cell populations that should be replaced?

Efficient Strategies for Microglia Replacement in the Central Nervous System

Microglia are important immune cells in the central nervous system (CNS). Dysfunctions of gene-deficient microglia contribute to the development and progression of multiple CNS diseases. Microglia replacement by nonself cells has been proposed to treat microglia-associated disorders. However, some attempts have failed due to low replacement efficiency, such as with the traditional bone marrow transplantation approach.

Engrafted cells in previous transplantation approaches do not extensively proliferate in the recipient brain, which explains the low efficiency of transplantation. Indeed, the proliferation-dependent turnover rate of microglia is rather slow in homeostatic conditions. In contrast, we have demonstrated that residual microglia exhibit an astonishing proliferation capacity after pharmacological depletion (~99%). This potentially suggests that microglial proliferation relies on an empty microglial niche. We therefore reasoned that the microglia-free niche is a vital prerequisite for successful engraftment of nonself microglia (or microglia-like cells). Colony-stimulating factor 1 receptor (CSF1R) is essential for microglia survival. PLX5622 is a CSF1R inhibitor with improved specificity compared to its analog, PLX3397. To create the microglia-free niche, we utilized PLX5622 to inhibit CSF1R.

We then developed highly efficient approaches for nonself microglia replacement that are effective in the adult normal mouse at the CNS-wide scale. First, microglia replacement by bone marrow transplantation (mrBMT) is capable of inducing allografted bone marrow cells (BMCs) to differentiate into microglia-like cells in the entire CNS, replacing 92.66% of resident microglia in the brain, 99.46% in the retina, and 92.61% in the spinal cord, respectively. Second, microglia replacement by peripheral blood (mrPB) is able to induce peripheral blood cells (PBCs) to microglia-like cells and replace 80.74% of resident microglia in the brain and 74.01% in the retina. Third, to precisely manipulate microglia in a specified brain region without affecting the rest of the brain, we further developed microglia replacement by microglia transplantation (mrMT). The engrafted microglia via mrMT resemble the natural characteristics of naive microglia.

When determining superiority of a strategy, replacement efficiency and source availability are the two most important dimensions to take into consideration. Among the three microglia replacement approaches, mrBMT achieves the highest replacement efficiency - 92.66% in the brain, 99.46% in the retina, and 92.61% in the spinal cord. However, mrBMT uses the BMC as the donor cell, which is clinically hard to acquire due to the invasive nature of the procedure and the aversive response from the donor. Such scarce availability of the source is likely to restrict its potential of becoming a widely used standard clinical method for microglial replacement. On the other hand, mrPB greatly broadens the donor source by using PBC, the largest donor cell pool, while maintaining high replacement efficiency CNS wide, just slightly inferior to mrBMT. Abundant availability of donor cells and the relatively high efficiency of cell replacement make mrPB an ideal approach to manipulate microglia at the whole-CNS scale.

Assessing the Utility of Six of the Better Known Epigenetic Clocks in a Large Study Population

September, 2020

Epigenetic clocks to measure age emerged from the ability to cost-effectively obtain the moment to moment epigenome of an individual, the distribution of epigenetic marks on nuclear DNA that control gene expression. Cells react to their environment, and some of those reactions are characteristic of the ways in which the cellular environment changes with age. Given this data and ample computational power, it is possible to find weighted combinations of, for example, DNA methylation status at specific CpG sites that fairly accurately correlate with age. More interestingly, this appears to be a measure of biological age rather than chronological age, in that people with a higher epigenetic age than chronological age tend to have a higher incidence and later risk of age-related disease and dysfunction - and vice versa.

It remains unclear what exactly it is that is being measured by an epigenetic clock. Which processes of aging, the accumulation of damage and downstream change, actually cause these characteristic epigenetic changes across all individuals? Is it all of them? Or only some of them? Researchers have produced clocks based on patterns of transcription and protein levels in addition to epigenetic marks, and some of these later clocks use only a handful of transcripts, proteins, or marks. It seems unlikely that the more abbreviated clocks measure more than a fraction of the causative processes of aging. Since these processes interact, and all of the facets of aging proceed at much the same pace in most people, then a clock that measures, say, only chronic inflammation, might be just as good today as a clock that is affected by all mechanisms of aging.

This is true, at least, until we start being able to repair specific forms of underlying cell and tissue damage, such as the presence of senescent cells. Some clocks will stop working usefully, and we don't really know which ones are vulnerable to the deployment of any given approach to rejuvenation. Which is a challenge, because assessing the results of therapies that repair specific forms of underlying cell and tissue damage is exactly how we'd like to use these clocks. As things stand, no clock, epigenetic or otherwise, can be trusted for such a task until it is

fairly well calibrated against a class of rejuvenation therapy via multiple life span studies.

Epigenetic measures of ageing predict the prevalence and incidence of leading causes of death and disease burden

Individuals of the same chronological age display different rates of biological ageing. A number of measures of biological age have been proposed which harness age-related changes in DNA methylation profiles. These measures include five 'epigenetic clocks' which provide an index of how much an individual's biological age differs from their chronological age at the time of measurement. The five clocks encompass methylation-based predictors of chronological age (HorvathAge, HannumAge), all-cause mortality (DNAm PhenoAge, DNAm GrimAge) and telomere length (DNAm Telomere Length). A sixth epigenetic measure of ageing differs from these clocks in that it acts as a speedometer providing a single time-point measurement of the pace of an individual's biological ageing. This measure of ageing is termed DunedinPoAm.

In this study, we examined associations between six major epigenetic measures of ageing and the prevalence and incidence of the leading causes of mortality and disease burden in high-income countries. DNAm GrimAge, a predictor of mortality, associated with the prevalence of COPD and incidence of various disease states, including COPD, type 2 diabetes, and cardiovascular disease. It was associated with death due to all-cause mortality and outperformed competitor epigenetic measures of ageing in capturing variability across clinically associated continuous traits. Higher values for DunedinPoAm, which captures faster rates of biological ageing, associated with the incidence of COPD and lung cancer. Higher-than-expected DNAm PhenoAge predicted the incidence of type 2 diabetes in the present study. Age-adjusted measures of DNAm Telomere Length associated with the incidence of ischemic heart disease. Our results replicate previous cross-sectional findings between DNAm PhenoAge and body mass index, diabetes, and socioeconomic position (in a basic model). We also replicated associations between DNAm GrimAge and heart disease.

In conclusion, using a large cohort with rich health and DNA methylation data, we provide the first comparison of six major epigenetic measures of biological ageing with respect to their associations with leading causes of mortality and disease burden. DNAm GrimAge outperformed the other measures in its associations with disease data and associated clinical traits. This may suggest that predicting mortality, rather than age or homeostatic characteristics, may be more informative for common disease prediction. Thus, proteomic-based methods (as utilised by DNAm GrimAge) using large, physiologically diverse protein sets for predicting ageing and health may be of particular interest in future studies. Our results may help to refine the future use and development of biological age estimators, particularly in studies which aim to comprehensively examine their ability to predict stringent clinically defined outcomes. Our analyses suggest that epigenetic measures of ageing can predict the incidence of common disease states, even after accounting for major confounding risk factors. This may have significant implications for their potential utility in clinical settings to complement gold-standard methods of clinical disease assessment and management.

Kimer Med Founded to Develop the DRACO Antiviral Strategy

September, 2020

A biotech startup, Kimer Med, has been founded to develop the DRACO approach to defeating viral infections. Those of us who have been following developments in antiviral technologies that might be applied to persistent infections relevant to aging, such as cytomegalovirus (CMV) and other herpesviruses, may recall a burst of interest in DRACO some years ago, particularly the research crowdfunding efforts in 2015 and 2016.

DRACO (Double-stranded RNA Activated Caspase Oligomerizer) works by selectively killing cells that exhibit one of the distinctive signs of viral replication. This replication produces long double-stranded RNA, whereas mammalian cells only produce short double-stranded RNA in the normal course of events. It is possible to deliver a form of molecule into the cell that interacts with only long double-stranded RNA and triggers cell death via caspase induced apoptosis as a result, depriving the viral particles of their factory. The fine details of the approach are outlined in the original 2011 paper, and DRACO has been proven to do quite well by a few different research groups in several different animal models of viral infection.

There are two reasons as why this is interesting. Firstly, it can be applied, with little additional work on a per-case basis, to a broad range of virus types, becoming a potentially near-universal antiviral platform. The economics of such a technology look very good in comparison to most other antiviral approaches. Secondly, it has the potential to clear the body of persistent viruses such as CMV. CMV causes great harm to the immune system over a lifetime because it can only be suppressed by present strategies, never fully cleared from the body. The evidence strongly suggests that it is one of the major causes of age-related immunosenescence.

Unfortunately, DRACO went the way of all too many novel research initiatives. It was a struggle to obtain following grants for such a radical departure from the established approaches, the research crowdfunding efforts didn't go that well (as is usually the case - it is very hard to crowdfund scientific research), the researchers involved moved on, the institutions involved abandoned any effort to maintain and license the intellectual

property. All of this happens to many projects in the research community, year after year, regardless of their scientific merits and potential to produce viable, useful therapies.

Sadly, intellectual property is such a linchpin in the standard approach to biotechnology investment, as well as in Big Pharma business models, that technologies in the public domain tend to be left for dead. The view is that no-one can monopolize them, own that whole part of the field, which is seen as necessary in order to justify the enormous resources needed to push a therapy through the present heavy-handed regulatory system. Yet it is nonsense to think that any approach to therapy can in practice be monopolized. Every successful development program quickly results in other organizations putting significant efforts into finding ways to achieve a similar result via the same mechanism that nonetheless bypass existing patents. Still, near all investors and institutions in the commercial space steer clear of public domain science until such time as someone produces clinical success by doing otherwise.

Thankfully, the Kimer Med team are willing to be outliers in this matter. They have picked DRACO as their cause to champion, and intend to raise funds to replicate the work, expand it, and bring this radical new approach to antiviral therapy to the clinic. To the degree that they achieve success, others will follow.

An Example of the Beneficial Role of Senescence in Injury

October, 2020

Researchers here provide an interesting demonstration of the beneficial role of transient cellular senescence in injury. Applying senolytics to selectively destroy senescent cells immediately following traumatic injury greatly worsens the consequences. Senescent cells are harmful when they build up and linger in tissues over the course of later life. The signaling they generate is useful in the short-term, such as by mobilizing the response to injury in numerous cell populations, but very damaging when sustained for the long term. This dynamic is one of the reasons why we should favor infrequent senolytic therapies that destroy only the harmful, lingering senescent cells, rather than continuing treatments that would negatively impact regeneration and other functions by also destroying transient senescent cells.

It's called senescence, when stressed cells can no longer divide to make new cells, and it's considered a factor in aging and in some diseases. Now scientists have some of the first evidence that at a younger age at least, senescent cells show up quickly after a major injury and are protective. Their model is hemorrhagic shock, a significant loss of blood and the essential oxygen and nutrients it delivers that accounts for about 30-40% of trauma-related deaths from things like car accidents and shootings; and their focus the liver, one of the many major organs that can fail in response.

Shortly after hemorrhagic shock occurs, a population of liver cells quickly become senescent. To find out if the rapid movement to senescence they saw for some liver cells was good or bad, researchers gave some of the rats in their studies senolytics, a relatively new class of drugs that target senescent cells for elimination. Laboratory studies of these drugs have shown they can prevent or improve age-related problems like frailty, cataracts, and vascular and heart dysfunction. Early trials in humans have also reported success in reducing the progression of problems like diabetes and kidney related damage.

But when younger rats in hemorrhagic shock were given the drugs as part of the fluids used for resuscitation shortly after blood loss, they all quickly died. When the researchers gave the same senolytics to healthy rats, they were fine. Death of the senescent cells appears to exacerbate the tissue injury resulting from blood loss. Researchers suspect the rapid transition to senescence that occurred in a population of liver cells was an attempt to stabilize after the trauma, and likely transient. While he says you can't generalize that what happens in one tissue, like the liver, will happen in another organ, the researchers expect something similar happens in other organs in the face of serious injury.

Link: https://jagwire.augusta.edu/senescent-cells-may-be-good-when-it-comes-to-a-bad-injury/

A Coda to the C60 in Olive Oil Saga

November, 2020

The matter of buckminsterfullerene (C60) in olive oil is an instructive example of how bad work can lead a field astray for some time, but is ultimately squashed. Back in 2012, a paper was published claiming a sizable effect on life span in rats via treatment with C60 in olive oil. There were red flags at the time: it was published in a journal outside the field of aging research, used a very small number of animals, and the size of the effect on life span was just too large to be credible. Peer review would have sunk this paper if submitted to an aging-focused journal. C60 is an antioxidant, so even if it is acting in the best possible way for antioxidants to act (i.e. targeting mitochondria while leaving the rest of the cell alone) it shouldn't be doing much better than other existing mitochondrially targeted antioxidants, many of which have a fair amount of published animal data to reference.

Unfortunately, one can't ignore large effect sizes, even when they are implausible and the study that produced them looks dubious. I said at the time that this was likely to go nowhere, didn't look good on the face of it, but nonetheless people were

going to spend funds on trying to replicate it and dig into the biochemistry. It took a couple of years for those efforts to start up in earnest. The Methuselah Foundation funded some of this work, alongside Longecity and a few other organizations. The Ichor Therapeutics team carried out the heavy lifting. From the get-go, the work cast doubt on the original paper, discovering that C60 in olive oil is quite challenging to formulate in ways that prevent toxicity. It took some years of working at the problem to carry out a reasonable animal study.

Now, eight years later, the results of that labor are published. As suspected, this is a dead end, and that initial 2012 paper looks the worse for someone taking the time to properly close the door on this line of work. This exercise illustrates why one should apply an appropriate level of skepticism to what one reads in the literature, and why journal boards should refrain from publishing data that lies outside their area of specialty. It also shows the self-correcting nature of scientific progress at work: replication is vital, as that is how errors are checked and removed once they take place. It takes far too long and costs far too much, but remains the least worst option.

C60 in olive oil causes light-dependent toxicity and does not extend lifespan in mice

C60 is a potent antioxidant that has been reported to substantially extend the lifespan of rodents when formulated in olive oil (C60-OO) or extra virgin olive oil (C60-EVOO). Despite there being no regulated form of C60-OO, people have begun obtaining it from online sources and dosing it to themselves or their pets, presumably with the assumption of safety and efficacy.

In this study, we obtain C60-OO from a sample of online vendors, and find marked discrepancies in appearance, impurity profile, concentration, and activity relative to pristine C60-OO formulated in-house. We additionally find that pristine C60-OO causes no acute toxicity in a rodent model but does form toxic species that can cause significant morbidity and mortality in mice in under 2 weeks when exposed to light levels consistent with ambient light.

Intraperitoneal injections of C60-OO did not affect the lifespan of CB6F1 female mice. Finally, we conduct a lifespan and health span study in males and females C57BL/6 J mice comparing oral treatment with pristine C60-EVOO and EVOO alone versus untreated controls. We failed to observe significant lifespan and health span benefits of C60-EVOO or EVOO supplementation compared to untreated controls, both starting the treatment in adult or old age. Our results call into question the biological benefit of C60-OO in aging.

A Look Back at 2020: Progress Towards the Treatment of Aging as a Medical Condition

December, 2020

[Excerpted]

The Longevity Community

….The longevity industry has been relatively insulated from the impact of COVID-19, which is to say progress has been slowed, but not derailed. Setting aside the dramatic reduction in biotech investment for much of 2020, the usual investor reaction to panic and uncertainty, most life science companies are classed as essential businesses in the US and have continued to work through the shutdown. The more advanced of the early companies have treatments in clinical trials, even while most are still at the preclinical stage. New companies have launched, though we still need many more to cover areas yet to be worked on in earnest. Existing companies made progress and raised funding throughout the year: covered were Juvena Therapeutics, Senisca, SIWA Therapeutics, Calico, Oisin Biotechnologies and OncoSenX, the other senolytics companies as a whole, Kimer Med, Insilico Medicine, Five Alarm Bio and Biosens, OneSkin's DNA methylation clock for skin aging, Lygenesis, Juvenescence (several times), Turn.bio and other Methuselah Fund porfolio companies.

EnClear Therapies brought in $10 million for their approach to cerebrospinal fluid filtration to remove molecular wastes that contribute to neurodegeneration. Revel Pharmaceuticals finally obtained seed funding to work on glucosepane cross-link breakers. BioAge raised $90 million for clinical trials of small molecules to slow aging. Investors are building funds and other vehicles (such as the Moonshot Venture Fellowship) to focus on the longevity industry. Examples include Ronjon Nag, Kingsley Advani, and the folk at SP8CEVC, Longevitytech.fund, and LongeVC. It nonetheless remains the case that there are too few experienced biotech funders involved able to support later, larger investments. That is changing, slowly.

Some initial clinical trials have been failing, as often takes place in the early years of an industry. Unity Biotechnology's first senolytic failed phase 2 trial for knee osteoarthritis, provoking a great deal of discussion (some justified, some unfairly post-hoc) as to why it was a poor design and strategy. Still, Big Pharma entities are starting to launch their own senolytics programs. There is gold in those hills.

Conferences of Interest

I attended a few conferences in person in early 2020, prior to the COVID-19 shutdowns, and wrote up notes. The SENS Research Foundation pitch day during the J.P. Morgan Healthcare

conference offered a most interesting selection of startups from the longevity industry. Much the same could be said of the Longevity Therapeutics conference, with the addition of researchers presenting on their academic programs. It was all online conferences after that, however. Later in the year I noted a selection of senolytic company showcases from the Longevity Leaders event, and some of the panels from Longevity Week events.

Senescent Cells and Senolytic Therapies

The development of senolytic drugs to clear senescent cells, as well as methods of assessing their effectiveness, is rolling onwards, broadening to include many novel strategies, and attracting greater attention from beyond the scientific community. Further data arrived this year to support the use of senolytics to expand the donor organ supply by salvaging otherwise unusable organs. Additionally, studies have shown or suggested that senolytics can treat a very wide selection of conditions: osteoporosis, cardiovascular disease, the chondrocyte hypertrophy characteristic of osteoarthritis, osteoarthritis more generally, vulnerability to the cytokine storm of SARS-CoV-2 infection, fibrotic disease, atrial fibrillation, a range of other heart issues, peripheral neuropathy caused by chemotherapy, Alzheimer's disease (a fair amount of research here) and other neurodegenerative conditions, pulmonary fibrosis, glaucoma and other eye conditions, non-healing wounds, even when caused by diabetes, chronic kidney disease, loss of insulin sensitivity, cancers of bone marrow, cervical cancer, accelerated aging resulting from cancer treatments, the atrophy of the thymus, and lung disease. Demonstrating that nothing is ever universally true in biology, researchers found this year that uterine fibrosis does not respond to senolytic treatment, unlike the other forms of fibrotic disease tested.

This year OneSkin launched their topical senolytic treatment, ahead of any published data on its effectiveness in humans, though the data in skin models is intriguing. Of other new approaches to senolytics, taking existing cell-killing drugs and making them safe prodrugs - only activated in the target cells, rather than generally - is perhaps most interesting. Conjugating navitoclax with galactose, for example, ensuring that it is only cleaved into the cytotoxic navitoclax in senescent cells. That has also been accomplished for other chemotherapeutics. Another evolution of navitoclax to reduce its harmful side-effects is to turn it into a PROTAC drug, a compound that removes target molecules by causing them to be degraded by the ubiquitin-proteasome system.

Vaccination against CD153 appears to be mildly senolytic, as are SYK inhibitors, through an as yet unknown mechanism of action. Researchers are still attempting to determine whether nutraceutical senolytics (including plant extracts such as fisetin or the senotherapeutic naringenin) can be effective enough to be interesting. In most cases, one suspects not. MYSM1 upregulation reduces the senescent cell burden in mice. Chimeric antigen receptor approaches can be used to produce senolytic immunotherapies, though not particularly cost-effective ones. Physical fitness, on the other hand, reduces inflammation, but isn't senolytic at all. Reversing cellular senescence by delivering new mitochondria or PDK1 inhibition is scientifically interesting, but sounds risky - some fraction of senescent cells are damaged in ways that may lead to cancer. Hormone therapy in women correlates with lower SASP expression, though it is unclear as to why this is the case. Researchers have started to examine the past use of long-approved drugs newly found to be senolytic, to see if there is any evidence for the degree of benefits. So far this is proving to be challenging.

Beyond senolytics, researchers continue to mine the biology of senescent cells in ever more depth. Any mechanism involved in the onset or maintenance of senescence might turn out to be a useful basis for therapies. The SASP Atlas is one of the results of this work, mapping the senescence associated secretory phenotype (SASP), potentially a rich source of ways to measure the burden of senescence. TGF-β is an important SASP component implicated in the transmission of senescence via the SASP, and so may be microRNAs miR-21 and miR-217. The SASP component CyPA may link hematopoietic cell senescence with cognitive decline. Some degree of suppression of the SASP can be achieved via a variety of approaches, including HDAC inhibition and inhibition of ATM kinase. G3BP1 is required for the SASP to exist, making it perhaps a more attractive potential point of intervention. Genetic databases are being used to identify genes involved in inhibition of cellular senescence - targeting those genes may be a basis for therapy. The genomic architecture of senescent cells is quite different from that of normal cells, and the details are being mapped in more detail. It is possible that non-replicating cells develop a senescence-like state in aged tissues.

Further research is ongoing. Astrocyte senescence kills neurons in cell culture, implicating these cells in neurodegenerative conditions. A better understanding has been developed of how senescent cells cause lung fibrosis (the target of one of the clinical trials for senolytic drugs). USP7 inhibition was shown to be senolytic. Vascular cellular senescence is increased by microRNA-34a. It is suggested that variability in outcomes in stem cell transplantation may be due to the presence of more or fewer senescent cells after expansion of the cells for transplant. Senescent cells contribute to declining NAD+ levels in aging.

Tissue by tissue data is finally arriving for senescent cell accumulation, for both mice and humans. A taxonomy of senescence is beginning to form, as researchers start to get a handle on how senescence can differ between cells. A senescent population for which removal might be problematic was identified in the livers of aged mice. Researchers are exploring roles for long non-coding RNAs in cellular senescence. Persistent CMV infection provokes greater senescent cell accumulation, perhaps

by causing immune dysfunction. AQP1 is involved in cellular senescence in tendons. Senescent cell accumulation may also be the primary mechanism by which cosmic radiation exposure produces detrimental health outcomes. T cell senescence increases with age and is quite harmful, forming part of an inflammatory feedback loop that can damage healthy tissue.

Cross-Links

Some researchers argue that cross-linking is a hallmark of aging that was overlooked by the authors of the noted Hallmarks of Aging paper. Stiffening of the extracellular matrix in tissues is a consequence of cross-linking, among other factors and is normally considered in skin and blood vessels, but researchers noted this year that it contributes to age-related loss of muscle function as well. A novel approach to breaking cross-links was discussed, the use of spiroligomers, carefully designed to interact in specific ways with cross-link molecules. The supporting work needed for projects focused on glucosepane cross-links, the most prevalent cross-links in humans, continued this year with the creation of anti-glucosepane antibodies. Researchers have also proposed inhibition of protein glycation as a way to reduce the creation of cross-links, though life-long therapy of this sort compares unfavorably with approaches that can be applied every few years to clean up existing cross-links. Measuring the cross-link burden in tissues remains challenging; more work will be needed here as targeted approaches to remove cross-links become viable.

Protein Aggregates

There are many forms of amyloid, misfolded proteins that replicate and aggregate in the body, beyond the few (amyloid-β, tau, α-synuclein) that are the focus of neurodegenerative research. This year, it was noted that medin amyloid causes cerebral vascular dysfunction. A good overview of transthyretin amyloidosis was alo published recently.

Microbiomes and Aging

The microbiomes of the body, particularly that of the gut, and their relationships with age are an area of growing research interest. Age-related changes in microbial populations take place, both caused by mechanisms of aging and causative of age-related dysfunctions, a two-way relationship. While most research focuses on the gut microbiome, the skin microbiome was given more attention of late, as are the varied microbiomes of the rest of the body. Researchers are in the process of cataloging specific gut microbial metabolites that harm or aid the body, and for which production changes with age: butyrate is beneficial, while trimethylamine is harmful to arterial function. Polyamine from gut microbes may mediate the relationship between higher environmental temperature and lower rates of osteoporosis. In general, aging results in larger inflammatory populations of gut microbes, and inflammation may be the primary way by which changes in the gut microbiome contribute to conditions such as Alzheimer's disease. In that context it is interesting that changing metabolite production by the microbiome correlates with amyloid burden in the brain. Transplanting gut microbes from old mice to young mice impairs cognitive function.

When it comes to addressing age-related changes in the gut microbiome, a wide range of strategies are being discovered and refined. Supplementation with IAP reduces gut inflammation. Delivery of cyclic peptides suppresses harmful populations to much the same end. Transplanting gut microbes from old rats to young rats produces inflammation and cognitive decline. The old standby of programs of physical activity may exert some of its beneficial effects on health via better maintenance of the gut microbiome.

Immune Aging and Chronic Inflammation

The immune system declines with age, in a complex and yet to be fully mapped fashion. Thus building better vaccines for older people is a poor alternative to rejuvenation of the immune system. We shouldn't need COVID-19 as a reminder in order to be able to argue for greater research into immune system rejuvenation. Yet a lot more work takes place on improving vaccines than there is on improving the immune system, more is the pity.

Immune aging isn't just the cause of increased mortality due to infectious disease. It is likely a major driver of many age-related conditions via chronic inflammation, the persistent unresolved activation of the immune response. This and other issues ensure that rejuvenation of immune function is vital to the treatment of aging. Sustained inflammation encourages cancer metastasis, and the progression of many other age-related conditions, including sarcopenia, vascular stiffness, and, ironically, dysfunction in the generation of new immune cells. It harms the blood-brain barrier, enabling the passage of damaging molecules and cells into the brain. In the brain, microglia become ever more inflammatory with age. It is thought that the evolutionary tradeoff that has produced this inflammatory aging of the immune system is between (a) protection against infection via greater immune activation versus (b) faster aging due to that immune activation.

Inflammation manifests in the actions of the immune system, but has its source in forms of molecular damage and cellular dysfunction in tissues throughout the body that provoke those actions. It is the failure of the immune system to clear senescent cells in later life that accounts for a great deal of that provocation. Skin tissue, being the largest organ provides a sizable contribution, but perhaps not as much as visceral fat tissue in overweight individuals, both tissues becoming laden with senescent cells in older people. Gum disease is another common contribution to raised inflammation, and a risk factor for inflammatory age-related conditions. Cortisol levels decline

with age, causing macrophages to become more inflammatory. Interestingly, some contributions to chronic inflammation are physical and structural, such as shear stress in the blood flow of the heart.

Suppression of inflammation by interfering in cell signaling is a going concern, but present clinical strategies are blunt tools. The research community is in search of more sophisticated ways to achieve this goal, which would only suppress undesirable, excessive, long-term inflammation, while allowing useful, short-term inflammatory processes to proceed. The NLRP3 inflammasome is one potential target. The small molecule MW189 has been tested in patients and found to reduce inflammation in the brain. IGF-1R inhibition reduces inflammation in Alzheimer's disease mouse models, and delivery of BDNF reverses inflammatory microgial activity in the brains of old mice. MicroRNA-192 in extracellular vesicles suppresses inflammation, and so is a potential basis for treatments. Metformin can reduce liver inflammation. Glucosamine supplementation and TNFα blockade may reduce mortality by lowering inflammation. Alpha-ketogluarate may do much the same. The ketone body β-hydroxybutyrate and RAGE inhibition also inhibit inflammation. Eosinophil immune cells are anti-inflammatory and decline in number with age. Delivering eosinophil cells into visceral fat reduces chronic inflammation caused by that tissue.

The thymus atrophies with age, and evidence continues to accumulate to show this to be an important contributing cause of immune system decline. The thymus is where thymocytes, created in the bone marrow, go to become T cells of the adaptive immune system. Fewer new T cells means a growing loss of immune function. So why not rebuild a thymus? Recellularizing a rat thymus with human cells produces a functional thymus, only the latest of a range of tissue engineering approaches. Thymic atrophy is in part caused by loss of function in thymic epithelial progenitor cells. Cell therapy approaches to thymic regeneration are possible, and two were demonstrated in animal models this year using reprogrammed embryonic fibroblasts and T cell progenitors.

Other approaches exist - and are necessary - to address immune system aging. Replacing the hematopoietic stem cell population for example, as it becomes damaged and dysfunctional, or at the very least stop the signaling that degrades hematopoiesis. Introducing young hematopoietic stem cells extends life span while transplanting bone marrow improves measures of aging, both in old mice. Pharmacological approaches to improving the existing population are more widely considered, however.

Genetics of Aging

The study of genetic variants and their role on longevity is increasingly looking like a dead end from the point of view of discovering ways to meaningfully slow or reverse aging. Intensive and expanding analysis of data has found very few genetic influences on longevity, and the effect sizes are small. There are still those who think that very rare variants with large effects on longevity could exist, buried somewhere in the human data. The business as usual is still a matter of discovering variants with small effects on mechanisms connected to aging, however. A BPIFB4 variant affects inflammation and is found in long lived individuals. Overall, long-lived humans do not exhibit fewer harmful gene variants, perhaps suggesting that genetics has a small effect only on variations in life expectancy.

DNA Damage

Nuclear DNA damage of various types occurs progressively with age, and is certainly a cause of cancer. Beyond cancer, researchers are investigating the clonal expansion of mutations that occur in stem cells and progenitor cells in order to find out whether it contributes meaningfully to metabolic disarray in aging. This may or may not be the case, and isn't the only possible mechanism by which further harm may occur. An abnormal chromosome count, aneuploidy, is another form of damage, though it is argued that this can be beneficial in some circumstances, an adaptation that tries to resist some of the damage of aging. Repetitive elements that can copy themselves in the genome are yet another form of DNA damage. They are suppressed in youth, less so in old age. This can be used as the basis for a biomarker of aging, as illustrated by the fact that repetitive element activity is reduced by many interventions known to slow aging in mice.

Mitochondrial Function

Mitochondrial function declines with age, and disruption to mitochondrial structure and activities is noted in many specific age-related conditions, such as cardiovascular disease in general and heart failure and atherosclerosis specifically. Loss of mitochondrial function in T cells produces accelerated aging symptoms in mice. That same loss in monocytes contributes to chronic inflammation in aging. Low mitochondrial DNA copy number was shown this year to produce age-related epigenetic changes in the cell nucleus.

Heart issues are connected to failing mitophagy, the quality control mechanism responsible for removing worn and damaged mitochondria, and which falters in its operation with age. Loss of mitophagy is implicated in many age-related conditions, and upregulation of mitophagy is considered a good basis for therapies to improve age-related conditions. Some of this age-related decline in mitophagy is proximately caused by epigenetic changes that suppress mitochondrial function, while deeper causes remain debated.

Many groups are trying to find ways to slow or at least somewhat reverse mitochondrial decline with age. Mitochondrially targeted antioxidants have made their way into the supplement market,

or clinical trials and approval in some countries. It remains to be seen how they compare with exercise or NAD+ enhancement. SS-31 is an example yet to reach the clinic, still gathering data. Other approaches include downregulation of miR-155-5p, and delivery of whole new mitochondria to replace the old ones, shown to improve function in old mice. Photobiomodulation via near infrared light appears to modestly improve mitochondrial function, and visual function in older people, though how it does so remains to be determined. Long term low dose ethanol intake extends life modestly in mice and is suggested to do so via improved mitochondrial function.

Among the better approaches to mitochondrial aging under development, the SENS Research Foundation is one of the few groups presently working on allotopic expression. This is the copying of mitochondrial genes into the cell nucleus in order to avoid the negative consequences of mitochondrial DNA damage. At present the consensus on the cause of mitochondrial DNA damage is leaning towards it occuring during DNA replication rather than by interaction with reactive molecules. Not that all mitochondrial DNA damage is equal, as point mutations are well tolerated. It is more disruptive mutational damage that causes issues. Repair of that damage - or potentially allotopic expression to make the damage irrelevant - is a potential treatment for the aging of the heart.

NAD+ levels decline with age, and NAD+ upregulation improves mitophagy and mitochondrial function. For example, it reduces the burden of point mutations in mitochondrial DNA and slows female reproductive aging in mice. Loss of NAD+ is implicated in circadian rhythm dysfunction. There are many approaches to NAD+ upregulation, some dating back through decades of sporadic clinical trials, and none of which have yet been shown to increase NAD+ any more than is the case for structured exercise programs. This year saw new data for nicotinamide mononucleotide supplementation to improve neurovascular function and fertility in mice. Animal data on nicotinamide riboside supplementation also continues to be published: it improves the generation of immune cells in mice. Additionally, CD38 is becoming a target of interest related to NAD+ metabolism due to is role in degrading NAD, but it is a little early to say what sort of therapies might emerge to target CD38.

Age-Related Deafness

There is some debate over whether age-related hearing loss is caused by damage to sensory hair cells or via loss of the connections between those cells and the brain. Chronic inflammation is shown to be a significant factor in the risk and development of age-related hearing loss, as is loss of mitochondrial function. Hearing loss may contribute to the onset of dementia by depriving the brain of stimulation necessary for normal operation.

Blood Vessels and Blood Pressure

A reduction in the capacity to grow new blood vessels, and consequent loss of blood vessel density, takes place throughout the body with age, reducing blood supply, with negative consequences that are most noticeable in energy-hungry tissues such as the brain, muscles, and especially the heart. It is noted that a better blood supply to the brain slows cognitive decline with age. Exercise can increase blood vessel density, at least in mice. Other approaches to achieve this goal presently under study focus on BMP6 and VEGF-B.

Raised blood pressure, hypertension, is one of the more harmful downstream consequences of the underlying molecular damage of aging. It causes structural damage to tissues, and aggressive control of blood pressure – without addressing the causes of hypertension – can rein in further downstream harm such as damage to the brain that accelerates cognitive decline. Indeed, early control of hypertension in later life reduces risk of dementia and atrial fibrillation. More intensive blood pressure reductions lead to a few years' increase in life expectancy. This increase holds even in the most frail of elderly people. Further, gene variants associated with risk of hypertension also associate with reduced life expectancy.

Atherosclerosis is probably the worst thing to happen to blood vessels with age, in that it kills a sizable fraction of the population. By the time they are in their 40s, many people already have preclinical atherosclerosis, a study revealed this year. Atherosclerosis is driven by inflammation, and reducing chronic inflammation is as effective as lowering blood cholesterol in the treatment of the condition. There are numerous ways in which macrophages might be manipulated to slow or reverse atherosclerosis, given their role in clearing up damage to blood vessel walls. Some approaches published this past year include adjusting their polarization or encouraging them to greater clearance of debris in atherosclerotic plaque. Other approaches don't directly target macrophages, but do benefit them, such as cyclodextrin-containing nanoparticles that sequester harmful oxidized cholesterol. CD9 blockade appears to prevent senescence in endothelial cells, and was demonstrated to reduce progression of atherosclerosis in mice.

Parabiosis Research

Heterochronic parabiosis is the joining of two circulatory systems, an old and young animal. The young animal exhibits signs of accelerated aging, while the old animal exhibits signs of rejuvenation. Research initially focused on potential factors in young blood that might be producing benefits. Now however, evidence continues to emerge for the dilution of harmful factors in old blood to be the primary cause of benefits resulting from parabiosis. A few months ago, researchers demonstrated that plasma dilution reduces inflammation and improves cognitive function in old mice, and shortly thereafter self-experimenters

ran a small human test based on this work, with intriguing signs of benefits.

Regenerative Medicine

The regenerative medicine community is focused on cell therapies to provoke greater regeneration, largely through signals secreted by the transplanted cells, rather than any significant integration of those cells. This is an area of research and development too large to do more than point out a few highlights and reviews, such as a discussion of the present state of mesenchymal stem cell therapies, reversal of photoaging via stem cell transplantation, or replacement of microglia or dopaminergenic neurons in the brain. Reprogramming is an interesting topic, when used to produce, say, patient-matched photoreceptor cells for transplantation to treat retinal degeneration, or neurons for transplantation as a stroke treatment. Reprogramming has of late been delivered in vivo, changing cells in living animals. This has been shown to improve cognitive function.

A great many stem cell therapies can in principle be replaced with the delivery of extracellular vesicles secreted by those stem cells. This is logistically easier to take to the clinic, is as effective where compared head to head, and thus an area of considerable activity at the moment. Examples of the potential of this approach are accumulating: stroke recovery via neural stem cell exosomes; a treatment for neurodegenerative conditions; a treatment for sarcopenia; a treatment of skin aging; a way to suppress senescent cell signaling.

Further, many regenerative therapies might in principle be replaced with treatments that restore native stem cell activity, which declines with age, or due to chronic inflammation. This is at least the case in people whose stem cell populations are not very damaged by aging. Such potential therapies are largely based on manipulation of cell signaling, such as Wnt signaling. A variety of such approaches were reviewed in the context of restoring muscle stem cell activity, a population known to largely retain its capabilities into later life, even while becoming quiescent. Secreted stem cell factors are proposed as a treatment for male pattern baldness. Lin28 upregulation and electrical stimulation can spur nerve regeneration. Lef1 upregulation enables skin regeneration without scarring, while protrudin gene therapy provokes regeneration in optic nerve.

There are other approaches, such as the guide nerve regrowth or heart tissue regrowth that would not normally have occurred. More cells survive for longer following transplantation if supported by a scaffold such as a heart patch, or if treated before transplantation with strategies such as mitochondrial transfer. Decellularization is another approach, using donor organs stripped of their cells. This can be done between species, as demonstrated by the production of tiny human livers from decellularized rat livers. Other unrelated work includes improving transplanted stem cell function via tethered signal molecules, improving mitochondrial function in neurons to cause greater regrowth, or using small bioprinters to print structured tissue directly into wounds.

Neurodegeneration

Neurodegeneration is a blend of many forms of damage and symptoms, not nice neat categories of disease. This is another area in which a great deal of work takes place, making any selection of that research something of a sampler plate. The risk of dementia is falling for any given individual, but total incidence is increasing because the population is increasingly older. The integrity of the blood-brain barrier declines with age, allowing harmful molecules and cells into the brain, where they can cause issues such as chronic inflammation. Other forms of vascular dysfunction also contribute, and are often reviewed in the literature. Inflammation due to the aging of the immune system is very much associated with neurodegenerative conditions such as Alzheimer's disease. Targeting mechanisms of inflammation to suppress it in brain tissue is considered a basis for the development of therapies, and is shown to slow the onset of neurodegeneration in animal models. Additionally, the presence of bacterial DNA appears to promote tau aggregation through mechanisms independent of the inflammation of infection. Persistent infection is hypothesized to contribute to Alzheimer's disease.

Mitochondrial decline led by a progressive disruption of the quality control mechanism of mitophagy is implicated in numerous neurodegenerative conditions. Impairment of the ubiquitin-proteasome system responsible for recycling proteins also appears relevant. Loss of myelin seems to have some negative effect in aging, as illustrated by the connection between declining oligodendrocyte production and failing memory, oligodendrocytes being the cells responsible for maintaining myelin. Thus it is interesting to note potential strategies to spur greater remyelination, such as PAR1 inhibition, theophylline use, and glial progenitor cell therapy. Researchers are looking for ways to improve mitochondrial function in neurons, to reverse the age-related loss that is linked to neurodegeneration. Activating ILC2 immune cells results in signaling that improves cognitive function, involving IL-5 and other yet to be identified molecules. HDAC1 activation improves DNA repair in neurons and slows cognitive decline. PTB inhibition converts astrocytes into neurons, reversing Parkinson's symptoms in mice. A fisetin variant, CMS121, has slowed disease progress in Alzheimer's mice. Parkinson's disease is splitting into two distinct conditions that converge on the same outcome. ISRIB treatment in old mice quickly restored youthful cognitive function, suggesting a large role for reversible cell signaling and cell state in neurodegeneration.

Amyloid-β remains an important target in the development of Alzheimer's therapies. The failure of immunotherapies targeting amyloid-β are not stopping the expansion of efforts

to test immunotherapies targeting both amyloid-β and tau - tau being more harmful than amyloid-β. Not all amyloid plaques are the same; those containing nucleic acids may be worse and more inflammatory, thus potentially explaining differences between individuals who appear to have similar levels of plaque. Enhancing a natural process by which cells ingest and break down misfolded extracellular proteins might be a basis for treating neurodegenerative conditions in which protein aggregates are important. TREM2 antibodies are explored as a way to encourage greater microglia activity to clear molecular waste and treat Alzheimer's disease. Other groups are looking into sequestration of amyloid-β into nanoparticles.

While Leucadia Therapeutics and EnClear Therapies continue to progress towards their respective approaches to dealing with the clearance of molecular waste from cerebrospinal fluid, more evidence continues to arrive in support of the role of reduced cerebrospinal fluid drainage (and thus reduced removal of waste products from the brain) in the development of neurodegenerative conditions. It isn't just cerebrospinal fluid; blood drainage from the brain also slows with age, with consequences to brain structure.

Biomarkers of Aging

The assessment of biological age is a growing concern. It is widely recognized that some way of reliably testing biological age is necessary to speed development of therapies capable of rejuvenation, to separate the wheat from the chaff, and direct resources to the best outcomes. Setting aside a few initiatives to construct biomarkers of aging from simple assessments of frailty, much of the present focus is on clocks derived from epigenomic, transcriptomic, metabolomic, and proteomic data gathered from populations at different ages. There are even clocks based on protein glycosylation, antibody binding, and ionomic (elemental composition of tissue) patterns.

These clocks are proliferating and specializing but it remains the case that there is no connection between the clock and the underlying damage processes that it reflects. Thus there is no assurance that any given clock will in fact accurately measure the outcome of a therapy: each would have to be calibrated for each type of intervention, using life span studies. There is every reason to expect these clocks to only partially represent the full portfolio of age-related mechanisms, or exhibit odd quirks, such as an underestimation of age in later life, or heart tissue showing up younger than other tissues. Nonetheless, clocks are starting to be used in clinical trials.

Meanwhile, the research continues. Pulmonary aging correlates with epigenetic age acceleration. A clock was developed for skeletal muscle tissue, two more using metabolomics and the plasma proteome, then the RNAAgeCalc transcriptional clock, and yet another new transcriptomic clock. Many of the clocks have been compared head to head in large study populations, and the GrimAge clock is coming out ahead in such comparisons. Recently the more accurate DeepMAge clock was developed using machine learning approaches.

Mitochondrial DNA copy number correlates with epigenetic age. Exceptionally long-lived individuals exhibit slower epigenetic aging. Blood metabolites can be used as a marker of frailty. Work on protein biomarkers overlaps with work on senescent cells, as the SASP contains many molecules that might be used to mark the progression of aging, as represented by an increased burden of senescent cells. The rate of germline mutations and certain molecular changes in the lens of the eye may also potentially provide a way to assess the pace of aging. Circular RNAs may be a useful basis for a biomarker of aging.

Muscle Function

Follistatin gene therapy is still under investigation in animal models, and still shown to double muscle mass in mice. A more recent approach is DOK7 gene therapy, which regrows neuromuscular junctions to improve aged muscle function. Inhibition of mTORC1 also slows muscle aging via preservation of neuromuscular junctions. Further, CCR2 inhibition reduces inflammatory signaling to promote muscle regeneration in old mice, while upregulation of unacetylated ghrelin and 15-PGDH inhibition slows loss of muscle with age. Resistance training reliably improves muscle mass and strength in old people, and there are many ways to optimize this approach by combining training with various other interventions. Aerobic exercise boosts muscle stem cell activity. Molecular signals released by damaged muscle fibers promote muscle stem cell activity, for example.

Telomeres and Telomerase

Telomerase gene therapy is under development by a number of groups. It is considered a potential treatment for heart disease, among other age-related conditions. It may treat fibrosis via reducing the burden of senescent cells in old tissues. Other approaches to lengthening telomeres are under investigation, such as the use of small molecules to disrupt the balance of mechanisms in favor of more telomere lengthening activity in stem cells.

Cancer

Cancer research is a vast field, and there is always far too much to note. Mortality rates continue to fall. The most important areas of cancer research are those that are likely to give rise to treatments that can impact many or nearly all cancers with little to no per-cancer adjustment required. They must target universal mechanisms that cancers cannot evade. There are simply too many cancer types, and too much evolution within any given cancer, to make meaningful progress otherwise. This year, researchers have suggested targeting lipid metabolism to suppress metastasis, MR1 as a signature of cancerous cells, use

of the small molecule NU-1 to inhibit telomerase activity, lipid nanoparticles carrying calcium phosphate and citrate, inhibition of mitochondrial DNA transcription, and TREM2 antibody therapy.

In other parts of the cancer field, chimeric antigen receptor immunotherapies are expanding to use in macrophages as well as T cells. The immune response to cancer changes with age in ways that are far from fully understood, making the development of immunotherapies a more complex proposition than would otherwise be the case. Researchers have shown that cancer treatment increases cancer risk for cancer survivors. This may be mediated by the creation of excess senescent cells.

Stress Response Mechanisms

In this age of comfort, low-cost calories, and machineries of transport, all too few people are as fit as they might be. Yet fitness and activity is one of the most reliable interventions to reduce age-related disease and mortality, in this world still lacking widespread and proven anti-aging therapies. Even light physical activity is significantly better than a sedentary lifestyle when it comes to mortality risk. Being sedentary raises the risk of cancer mortality. A healthier lifestyle at age 50 increases healthspan by nearly a decade. The data keeps on arriving to reinforce this point, year after year. Training for a marathon reverses some age-related vascular stiffness and hypertension. Exercise improves memory via increased blood flow, and also correlates with improved functional connectively in the brain. Exercise acts through Wnt signaling to slow brain aging and also helps T cells kill cancer cells. Physical activity is a treatment for frailty, can actually reverse frailty to some degree, and produces beneficial metabolic adaptations mediated by myokine signaling, such as increasing ubiquitination to clear damaged proteins from cells. Physical fitness correlates with a lesser decline in gray matter with age.

Calorie restriction is, of course, the other long-standing and well proven existing intervention that can reduce age-related disease and mortality. A great deal of thought has gone into why the calorie restriction response evolved early in the history of life. Data arrives every year to reinforce the small mountain of evidence that already exists in support of the health benefits. Calorie restriction reduces the harmful chronic inflammation of aging, perhaps largely by suppressing the inflammatory SASP of senescent cells. Intermittent fasting is also shown to be beneficial in human patients, improving biomarkers in metabolic syndrome, and improving chemotherapy effectiveness while reducing side effects. In mice, it increases neurogenesis and accelerates wound healing. Calorie restriction slows muscle aging in non-human primates, and reverses gene expression changes in old rats, even when started late. Calorie restriction also slows the aging of microglia in the brain and improves intestinal stem cell and intestinal barrier function.

Most, and I would say too much, of present research and development related to the treatment of aging is focused on upregulation of stress response mechanisms, in attempts to mimic the benefits of calorie restriction and exercise. This cannot have a large enough beneficial outcome to be worth the effort. It won't add decades to healthy life spans. Nonetheless, it is the largest portion of the field today. Upregulation of autophagy is arguably the most important of these stress responses. Indeed, if autophagy is inhibited, then accelerated aging results, such as increased T cell inflammatory activity. Impairment of autophagy occurs with aging, for reasons that include the presence of protein aggregates, and is implicated in loss of stem cell function. It contributes to osteoporosis.

Strategies noted in this past year to upregulate stress response mechanisms engaged by calorie restriction or exercise include sestrin upregulation, use of the small molecule nilotinib, cyclin D1 upregulation, injection of metformin rather than oral administration, mTORC2 activation, TAT peptide delivery, increased levels of β-hydroxybutyrate, intermittent treatment with rapamycin, which some feel should be widely prescribed, HNF4α inhibition, use of metolazone, and overexpression of Gpld1. Other approaches that boost stress responses include PASK deficiency, cAMP upregulation, lowered body temperature, and induction of mitochondrial uncoupling, given a safe way to achieve that goal. It is also possible to create many of the effects of calorie restriction by restricting intake of only one essential amino acid, such as threonine. Aspirin, of course, is also a calorie restriction mimetic drug that improves health via autophagy.

Self-Experimentation

There is a small but energetic community of self-experimenters, interested in assessing the outcomes of various strategies. I published a few notes on this topic over the past year. Firstly, an analysis as to why sex steroid ablation isn't a viable approach to thymus regeneration, at least not without a great deal more work on the part of the research community. Secondly, an outline for recreating a flagellin immunization study that was carried out in mice and noted to favorably adjust the gut microbiome. Other groups are trying to raise the bar on information for self-experimenters. Forever Healthy Foundation published a conservative risk-benefit analysis for the use of the dasatinib and quercetin senolytic combination.

Slowing Aging in Animal Models

Brd2 inhibition, astaxanthin based drugs, CDC42 inhibition via CASIN, low dose PPARγ agonist treatment, and overexpression of humanin have been found to slow aging in laboratory species for reasons that are either unclear, or involve many distinct mechanisms with little evidence for which are more or less important. In a case that is a little more cut and dried, mifepristone reduces innate immune driven inflammation in flies, slowing aging as a result.

Odds and Ends

There are always areas of research, some quite ambitious, some of it not, but nonetheless interesting, that don't quite fit into any of the usual buckets. This is a barnstorming era in biotechnology, in which it is possible to try all sorts of adventurous options to see if they can work, at least in principle. A selection follows. Increased expression of DICER has been suggested as a treatment for age-related macular degeneration as well as a way to improve the metabolic benefits of exercise in later life. Aging can be divided into "ageotype" categories based on how the common mechanisms develop into distinct patterns in different individuals. ELOVL2 upregulation reverses vision decline in aging eyes. Researchers have speculated that a downward trend in body temperature over the past few centuries reflects a lower burden of infection-driven inflammation, and thus is a feature linked to increased life expectancy.

Amyloid-β aggregation may be more than just a mechanism of Alzheimer's disease, but also a contributing cause of cardiovascular disease. Klotho is an area of interest because of its effects on aspects of aging. Recently delivery of soluble α-klotho was shown to reduce cardiac fibrosis in mice. The effects of klotho on life span may take place in part due to increased resistance to hypertension. Plasma transfer is an area of interest, in that transfer from young rats to old rats reduces measures of aging and senescent cell burden. A lower socioeconomic status correlates with faster age-related decline. Researchers have devised a way to provide photoreceptors with near-infrared sensitivity, as a way to restore light sensitivity in degenerating retinas that have lost their normal visible light sensitivity, but retain cells able to function.

There is an age-related increase in CD47 expression that impairs vascular function, and inhibiting CD47 reverses this effect. Hyperbaric oxygen treatment may have some benefits, such as improved cerebral blood flow, but it doesn't seem likely that it truly reverses aging, such as via strong senolytic effects. Transcranial magnetic stimulation might be getting to the point of showing some reliable benefits to cognitive function in old people; the precise details of the technique used may be important, and thus few approaches will actually work. Thermoregulation is impaired by aging for reasons yet to be comprehensively explored. Despite failures of past years, some researchers continue to be interested in the use of laser light to break down harmful protein aggregates. Something like 30% to 40% of dementia might be avoided through better lifestyle choices. Increased insulin receptor expression improves memory in old rats. The story of C60 in olive oil came to a sad but predictable end. It is not in fact a viable was to slow aging, and the original study that suggested it was and should be discarded.

Looking Ahead

Achieving healthy human longevity, a life that is vigorous and youthful in old age, is the challenge of our era. Work on the treatment of aging is expanding, but even though the old are becoming functionally younger, these are early years yet. Aging remains the largest and brightest unexplored new therapeutic frontier. Aging research should be a higher priority and enjoy far more funding given the prospects to improve the human condition - we should be trying to treat aging, and thereby improve many diseases, not continue treating the symptoms of aging on a disease by disease basis. Further, the future should involve a great deal more experimentation with combinations of therapies for aging. This is an underexplored area. Despite the promise of the field, a great deal of education and advocacy remains necessary: the public, and indeed many investors, cannot yet distinguish between scientific, unscientific, likely good and likely bad approaches to longevity. Those of us with a better idea of the nature of the field have a responsibility to spread our knowledge.

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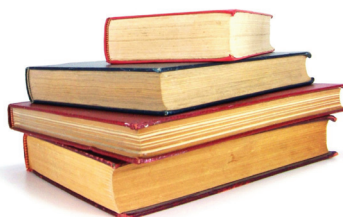

No one knows better than you what you will want to have with you.

Alcor makes available to every member and patient, without charge, one acid free Memory Box about the size of a standard banker's box (H10" x W12" x L15") for memorabilia to be stored underground at a commercial storage site called Underground Vaults and Storage (UGVS) in Kansas. Additional Boxes are a one-time charge of $250 each for perpetual storage.

Some of the most popular items that have been placed into storage are such things as letters, cards, photographs, diaries, journals, notebooks, books, clippings, army records, directories, recipes, video tapes, cassettes, medical records, flash drives, and external drives.

If you would like to begin working on your own Memory Box, or perhaps contribute items to a Box for an Alcor Member already in stasis, or if you have any questions, please contact **Linda Chamberlain at linda.chamberlain@alcor.org**.

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Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

MP-Pt(IV): A MAOB-sensitive mitochondrial-specific prodrug for treating glioblastoma.

Sudhir Raghavan, David S Baskin and Martyn A Sharpe

***Molecular Cancer Therapeutics*, 8 Oct. 2020, DOI: 10.1158/1535-7163.MCT-20-0420, https://mct.aacrjournals.org/content/early/2020/10/06/1535-7163.MCT-20-0420, accessed 13 Oct 2020**

Abstract

We previously reported the in vitro and in vivo efficacy of N,N-bis(2-chloroethyl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)propenamide, a prodrug that targeted the mitochondria of glioblastoma (GBM). The mitochondrial enzyme monoamine oxidase B (MAOB) is highly expressed in GBM and oxidizes an uncharged methyl-tetrahydropyridine (MP-) moiety into the mitochondrially-targeted cationic form, methyl-pyridinium (P+-). Coupling this MAOB-sensitive group to a nitrogen mustard produced a prodrug that damaged GBM mitochondria and killed GBM cells. Unfortunately, the intrinsic reactivity of the nitrogen-mustard group and low solubility of MP-MUS precluded clinical development. In our second generation prodrug, MP-Pt(IV) we coupled the MP-group to an unreactive cisplatin precursor. The enzymatic conversion of MP-Pt(IV) to P+-Pt(IV) was tested using recombinant human MAOA and rhMAOB. The generation of cisplatin from Pt(IV) by ascorbate was studied optically and using mass-spectroscopy. Efficacy toward primary GBM cells and tumors was studied in vitro and in an intracranial patient-derived xenograft mice GBM model. Our studies demonstrate that MP-Pt(IV) is selectively activated by MAOB. MP-Pt(IV) is highly toxic toward GBM cells in vitro. MP-Pt(IV) toxicity against GBM is potentiated by elevating mitochondrial ascorbate and can be arrested by MAOB inhibition. In in vitro studies, sub-lethal MP-Pt(IV) doses elevated mitochondrial MAOB levels in surviving GBM cells. MP-Pt(IV) is a potent chemotherapeutic in intracranial patient-derived xenograft mouse models of primary GBM and potentiates both temozolomide (TMZ) and TMZ-chemoradiation therapies. MP-Pt(IV) was well tolerated and is highly effective against GBM in both in vitro and in vivo models.

From: Experimental Glioblastoma Therapy Shows Curative Powers in Mice Models

Patti Muck, Houston Methodist Hospital Newsroom, 8 Oct. 2020, https://www.houstonmethodist.org/newsroom/experimental-glioblastoma-therapy-shows-curative-powers-in-mice-models/, accessed 13 Oct 2020.

Houston Methodist researchers found that mice harboring human glioblastoma tumors in their brains had greatly enhanced survival and weight gain when given a newly developed prodrug. This mitochondrial-targeted prodrug - an inactive compound that cancer cells selectively metabolize to produce an active toxic drug – also greatly improves outcomes when coupled with standard therapies of radiation and/or chemotherapy. The drug selectively targets and destroys the DNA inside the glioblastoma cell mitochondria (the energy factory of the cancer cell) leaving normal cells intact.

In an Oct. 8 study published online in *Molecular Cancer Therapeutics*, a journal of the American Association for Cancer Research, investigators used a second generation prodrug called MP-Pt(IV) to target the deadly cells of glioblastoma tumors, a brain cancer that is almost always fatal and has no cure. Life expectancy in humans with glioblastoma ranges from a few months to two years.

Human glioma cells were removed from patients during surgical excision and isolated within 10 minutes after removal. The glioblastoma cells were injected into the brains of 48 female mice for a 300-day study. The prodrug was well tolerated, and, when given on its own, extended survival by more than a factor of three. However, when combined with standard chemotherapy and radiotherapy, the drug was curative in nature, allowing 90% of mice to survive, thrive and gain weight during the 10 months of observation.

"This study tells us that adding MP-Pt(IV) to a chemoradiotherapy protocol could address a critical need in glioblastoma treatment," said David S. Baskin, M.D., FACS, FAANS, corresponding author and director of the Kenneth R. Peak Center for Brain and Pituitary Tumor Treatment in the Department of Neurosurgery at Houston Methodist. "We now know that MP-Pt(IV) is an excellent candidate for preclinical development."

eIF2α Controls Memory Consolidation via Excitatory and Somatostatin Neurons

Vijendra Sharma, Rapita Sood, Abdessattar Khlaifia, Mohammad Javad Eslamizade, Tzu-Yu Hung, Danning Lou, Azam Asgarihafshejani, Maya Lalzar, Stephen J. Kiniry, Matthew P. Stokes, Noah Cohen, Alissa J. Nelson, Kathryn Abell, Anthony P. Possemato, Shunit Gal-Ben-Ari, Vinh T. Truong, Peng Wang, Adonis Yiannakas, Fatemeh Saffarzadeh, A. Claudio Cuello, Karim Nader, Randal J. Kaufman, Mauro Costa-Mattioli, Pavel V. Baranov, Albert Quintana, Elisenda Sanz, Arkady Khoutorsky, Jean-Claude Lacaille, Kobi Rosenblum & Nahum Sonenberg

Nature **586, 412–416 (7 Oct. 2020), Chttps://www.nature.com/articles/s41586-020-2805-8, accessed 15 Oct. 2020.**

Abstract

An important tenet of learning and memory is the notion of a molecular switch that promotes the formation of long-term memory. The regulation of proteostasis is a critical and rate-limiting step in the consolidation of new memories. One of the most effective and prevalent ways to enhance memory is by regulating the synthesis of proteins controlled by the translation initiation factor eIF211. Phosphorylation of the α-subunit of eIF2 (p-eIF2α), the central component of the integrated stress response (ISR), impairs long-term memory formation in rodents and birds. By contrast, inhibiting the ISR by mutating the eIF2α phosphorylation site, genetically and pharmacologically inhibiting the ISR kinases, or mimicking reduced p-eIF2α with the ISR inhibitor ISRIB, enhances long-term memory in health and disease. Here we used molecular genetics to dissect the neuronal circuits by which the ISR gates cognitive processing. We found that learning reduces eIF2α phosphorylation in hippocampal excitatory neurons and a subset of hippocampal inhibitory neurons (those that express somatostatin, but not parvalbumin). Moreover, ablation of p-eIF2α in either excitatory or somatostatin-expressing (but not parvalbumin-expressing) inhibitory neurons increased general mRNA translation, bolstered synaptic plasticity and enhanced long-term memory. Thus, eIF2α-dependent mRNA translation controls memory consolidation via autonomous mechanisms in excitatory and somatostatin-expressing inhibitory neurons.

From: Discovery of a New Key Player in Long-Term Memory

(unattributed), McGill University News, 07 Oct. 2020, https://www.mcgill.ca/newsroom/channels/news/discovery-new-key-player-long-term-memory-325183, accessed 15 Oct. 2020.

A McGill-led multi-institutional research team has discovered that during memory consolidation, there are at least two distinct processes taking place in two different brain networks – the excitatory and inhibitory networks. The excitatory neurons are involved in creating a memory trace, and the inhibitory neurons block out background noise and allow long-term learning to take place.

The team, led by McGill University Professors Nahum Sonenberg and Arkady Khoutorsky, Université de Montréal Professor Jean-Claude Lacaille, and University of Haifa Professor Kobi Rosenblum, senior authors on the paper published today in *Nature*, also found that each neuronal system can be selectively manipulated to control long-term memory. The research, which answers a long-standing question about which neuronal subtypes are involved in memory consolidation, has potential implications for novel targets for medication for disorders such as Alzheimer's disease and autism, which involve altered memory processes.

How do short-term memories (which last just a few hours) transform into long-term memories (which may last years)? It's been known for decades that this process, called memory consolidation, requires the synthesis of new proteins in brain cells. But until now, it hasn't been known which subtypes of neurons were involved in the process.

To identify which neuronal networks are essential in memory consolidation, the researchers used transgenic mice to manipulate a particular molecular pathway, eIF2α, in specific types of neurons. This pathway had already been shown to play a key role in controlling the formation of long-term memories and regulating protein synthesis in neurons. Moreover, earlier research had identified eIF2α as pivotal for both neurodevelopmental and neurodegenerative diseases.

"We found that stimulation of protein synthesis via eIF2α in excitatory neurons of the hippocampus was sufficient to enhance memory formation and modification of synapses, the sites of communication between neurons", says Dr. Kobi Rosenblum.

However, interestingly, "we also found that stimulation of protein synthesis via eIF2α in a specific class of inhibitory neurons, somatostatin interneurons, was also sufficient to augment long-term memory by tuning the plasticity of neuronal connections", says Dr. Jean-Claude Lacaille.

"It is fascinating to be able to show that these new players - inhibitory neurons – have an important role in memory consolidation," added Dr. Vijendra Sharma, a research associate in Prof. Sonenberg's lab and the first author on the paper. "It had been assumed, until now, that eIF2α pathway regulates memory via excitatory neurons."

"These new findings identify protein synthesis in inhibitory neurons, and specifically somatostatin cells, as a novel target for possible therapeutic interventions in disorders such as Alzheimer's disease and autism," concluded Dr. Nahum

Sonenberg. "We hope that this will help in the design of both preventative and post-diagnosis treatments for those who suffer from disorders involving memory deficits."

Quantum Circuit for the Fast Fourier Transform

Ryo Asaka, Kazumitsu Sakai & Ryoko Yahagi

***Quantum Information Processing* volume 19, Article number: 277 (2020), online 07 Aug. 2020, https://link.springer.com/article/10.1007/s11128-020-02776-5, accessed 16 Oct. 2020.**

Abstract

We propose an implementation of the algorithm for the fast Fourier transform (FFT) as a quantum circuit consisting of a combination of some quantum gates. In our implementation, a data sequence is expressed by a tensor product of vector spaces. Namely, our FFT is defined as a transformation of the tensor product of quantum states. It is essentially different from the so-called quantum Fourier transform (QFT) defined to be a linear transformation of the amplitudes for the superposition of quantum states. The quantum circuit for the FFT consists of several circuits for elementary arithmetic operations such as a quantum adder, subtractor and shift operations, which are implemented as effectively as possible. Namely, our circuit does not generate any garbage bits. The advantages of our method compared to the QFT are its high versatility, and data storage efficiency in terms, for instance, of the quantum image processing.

From: Bringing a Power Tool from Math into Quantum Computing

(unattributed), Tokyo University of Science Media Relations, 14 Oct. 2020, https://www.tus.ac.jp/en/mediarelations/archive/20201014_0900.html, accessed 16 Oct. 2020.

The Fourier transform is an important mathematical tool that decomposes a function or dataset into its constituting frequencies, much like one could decompose a musical chord into a combination of its notes. It is used across all fields of engineering in some form or another and, accordingly, algorithms to compute it efficiently have been developed – that is, at least for conventional computers. But what about quantum computers?

Though quantum computing remains an enormous technical and intellectual challenge, it has the potential to speed up many programs and algorithms immensely provided that appropriate quantum circuits are designed. In particular, the Fourier transform already has a quantum version called the quantum Fourier transform (QFT), but its applicability is quite limited because its results cannot be used in subsequent quantum arithmetic operations.

To address this issue, in a recent study published in *Quantum Information Processing*, scientists from Tokyo University of Science developed a new quantum circuit that executes the "quantum fast Fourier transform (QFFT)" and fully benefits from the peculiarities of the quantum world. The idea for the study came to Mr. Ryo Asaka, first-year Master's student and one of the scientists on the study, when he first learned about the QFT and its limitations. He thought it would be useful to create a better alternative based on a variant of the standard Fourier transform called the "fast Fourier transform (FFT)," an indispensable algorithm in conventional computing that greatly speeds things up if the input data meets some basic conditions.

To design the quantum circuit for the QFFT, the scientists had to first devise quantum arithmetic circuits to perform the basic operations of the FFT, such as addition, subtraction, and digit shifting. A notable advantage of their algorithm is that no "garbage bits" are generated; the calculation process does not waste any qubits, the basic unit of quantum information. Considering that increasing the number of qubits of quantum computers has been an uphill battle over the last few years, the fact that this novel quantum circuit for the QFFT can use qubits efficiently is very promising.

Another merit of their quantum circuit over the traditional QFT is that their implementation exploits a unique property of the quantum world to greatly increase computational speed. Associate Professor Kazumitsu Sakai, who led the study, explains: "In quantum computing, we can process a large amount of information at the same time by taking advantage of a phenomenon known as 'superposition of states.' This allows us to convert a lot of data, such as multiple images and sounds, into the frequency domain in one go." Processing speed is regularly cited as the main advantage of quantum computing, and this novel QFFT circuit represents a step in the right direction.

Moreover, the QFFT circuit is much more versatile than the QFT, as Assistant Professor Ryoko Yahagi, who also participated in the study, remarks: "One of the main advantages of the QFFT is that it is applicable to any problem that can be solved by the conventional FFT, such as the filtering of digital images in the medical field or analyzing sounds for engineering applications." With quantum computers (hopefully) right around the corner, the outcomes of this study will make it easier to adopt quantum algorithms to solve the many engineering problems that rely on the FFT.

A novel quantum circuit that calculates the Fourier transform in a much quicker, versatile, and more efficient way (credit: Tokyo University of Science)

Tailoring Magnetic Fields in Inaccessible Regions

Mach-Batlle, Rosa, Bason, Mark G, Del-Valle, Nuria and Prat-Camps, Jordi

Physical Review Letters, 125 (17). a177204. ISSN 0031-9007, 27 Oct 2020, https://doi.org/10.1103/PhysRevLett.125.177204, accessed 28 Jan. 2021.

Abstract

Controlling magnetism, essential for a wide range of technologies, is impaired by the impossibility of generating a maximum of magnetic field in free space. Here, we propose a strategy based on negative permeability to overcome this stringent limitation. We experimentally demonstrate that an active magnetic metamaterial can emulate the field of a straight current wire at a distance. Our strategy leads to an unprecedented focusing of magnetic fields in empty space and enables the remote cancellation of magnetic sources, opening an avenue for manipulating magnetic fields in inaccessible regions.

From: Physicists Circumvent Centuries-Old Theory to Cancel Magnetic Fields

Alice Ingall, University of Sussex News, 29 Oct. 2020, https://www.sussex.ac.uk/research/full-news-list?page=6&id=53701, accessed 27 Jan. 2021.

A team of scientists, including two physicists at the University of Sussex, has found a way to circumvent a 178-year old theory which means they can effectively cancel magnetic fields at a distance. They are the first to be able to do so in a way which has practical benefits.

The work is hoped to have a wide variety of applications. For example, patients with neurological disorders such as Alzheimer's or Parkinson's might in future receive a more accurate diagnosis. With the ability to cancel out 'noisy' external magnetic fields, doctors using magnetic field scanners will be able to see more accurately what is happening in the brain.

The study "Tailoring magnetic fields in inaccessible regions" is published in *Physical Review Letters*. It is an international collaboration between Dr Mark Bason and Jordi Prat-Camps at the University of Sussex, and Rosa Mach-Batlle and Nuria Del-Valle from the Universitat Autonoma de Barcelona and other institutions.

"Earnshaw's Theorem" from 1842 limits the ability to shape magnetic fields. The team were able to calculate an innovative way to circumvent this theory in order to effectively cancel other magnetic fields which can confuse readings in experiments.

In practical terms, they achieved this through creating a device [consisting] of a careful arrangement of electrical wires. This creates additional fields and so counteracts the effects of the unwanted magnetic field. Scientists have been struggling with this challenge for years but now the team has found a new strategy to deal with these problematic fields. While a similar effect has been achieved at much higher frequencies, this is the first time it has been achieved at low frequencies and static fields – such as biological frequencies – which will unlock a host of useful applications.

Other possible future applications for this work include:

- Quantum technology and quantum computing, in which 'noise' from exterior magnetic fields can affect experimental readings
- Neuroimaging, in which a technique called 'transcranial magnetic stimulation' activates different areas of the brain through magnetic fields. Using the techniques in this paper, doctors might be able to more carefully address areas of the brain needing stimulation.
- Biomedicine, to better control and manipulate nanorobots and magnetic nanoparticles that are moved inside a body by means of external magnetic fields. Potential applications for this development include improved drug delivery and magnetic hyperthermia therapies.

Dr Rosa Mach-Batlle, the lead author on the paper from the Universitat Autonoma de Barcelona, said: "Starting from the fundamental question of whether it was possible or not to create a magnetic source at a distance, we came up with a strategy for controlling magnetism remotely that we believe could have a significant impact in technologies relying on the magnetic field distribution in inaccessible regions, such as inside of a human body."

Small Molecule Cognitive Enhancer Reverses Age-Related Memory Decline in Mice

Karen Krukowski, Amber Nolan, Elma S Frias, Morgane Boone, Gonzalo Ureta, Katherine Grue, Maria-Serena Paladini, Edward Elizarraras, Luz Delgado, Sebastian Bernales, Peter Walter, Susanna Rosi

***eLife*, 1 Dec. 2020, https://elifesciences.org/articles/62048, accessed 28 Jan. 2021.**

Abstract

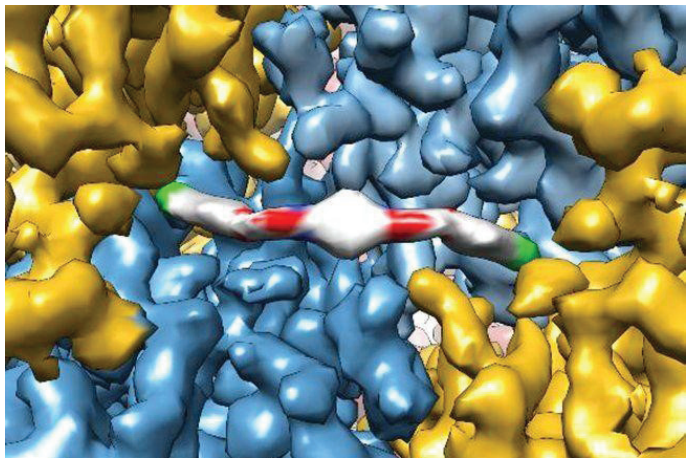
With increased life expectancy, age-associated cognitive decline becomes a growing concern, even in the absence of recognizable neurodegenerative disease. The integrated stress response (ISR) is activated during aging and contributes to age-related brain phenotypes. We demonstrate that treatment with the drug-like small-molecule ISR inhibitor ISRIB reverses ISR activation in the brain, as indicated by decreased levels of activating transcription factor 4 (ATF4) and phosphorylated eukaryotic translation initiation factor eIF2. Furthermore, ISRIB treatment reverses spatial memory deficits and ameliorates working memory in old mice. At the cellular level in the hippocampus, ISR inhibition (i) rescues intrinsic neuronal electrophysiological properties, (ii) restores spine density and (iii) reduces immune profiles, specifically interferon and T cell-mediated responses. Thus, pharmacological interference with the ISR emerges as a promising intervention strategy for combating age-related cognitive decline in otherwise healthy individuals.

From: Drug Reverses Age-Related Mental Decline Within Days

Nicholas Weiler, UCSF News, 1 Dec. 2020, https://www.ucsf.edu/news/2020/12/419201/drug-reverses-age-related-mental-decline-within-days, accessed 29 Jan. 2021.

Just a few doses of an experimental drug can reverse age-related declines in memory and mental flexibility in mice, according to a new study by UC San Francisco scientists. The drug, called ISRIB, has already been shown in laboratory studies to restore memory function months after traumatic brain injury (TBI), reverse cognitive impairments in Down Syndrome, prevent noise-related hearing loss, fight certain types of prostate cancer, and even enhance cognition in healthy animals.

In the new study, published Dec. 1, 2020, in the open-access journal *eLife*, researchers showed rapid restoration of youthful cognitive abilities in aged mice, accompanied by a rejuvenation of brain and immune cells that could help explain improvements in brain function.



A cryo-electron microscope rendering of an ISRIB molecule. Image by the Adam Frost lab

"ISRIB's extremely rapid effects show for the first time that a significant component of age-related cognitive losses may be caused by a kind of reversible physiological 'blockage' rather than more permanent degradation," said Susanna Rosi, PhD, Lewis and Ruth Cozen Chair II and professor in the departments of Neurological Surgery and of Physical Therapy and Rehabilitation Science.

"The data suggest that the aged brain has not permanently lost essential cognitive capacities, as was commonly assumed, but rather that these cognitive resources are still there but have been somehow blocked, trapped by a vicious cycle of cellular stress," added Peter Walter, PhD, a professor in the UCSF Department of Biochemistry and Biophysics and a Howard Hughes Medical Institute investigator. "Our work with ISRIB demonstrates a way to break that cycle and restore cognitive abilities that had become walled off over time."

Could Rebooting Cellular Protein Production Hold the Key to Aging and Other Diseases?

Walter has won numerous scientific awards, including the Breakthrough, Lasker and Shaw prizes, for his decades-long studies of cellular stress responses. ISRIB, discovered in 2013 in Walter's lab, works by rebooting cells' protein production machinery after it gets throttled by one of these stress responses – a cellular quality control mechanism called the integrated stress response (ISR; ISRIB stands for ISR InhiBitor).

The ISR normally detects problems with protein production in a cell — a potential sign of viral infection or cancer-promoting gene mutations — and responds by putting the brakes on cell's protein-synthesis machinery. This safety mechanism is critical for weeding out misbehaving cells, but if stuck in the on position in a tissue like the brain, it can lead to serious problems, as cells lose the ability to perform their normal activities, Walter and colleagues have found.

In particular, recent animal studies by Walter and Rosi, made possible by early philanthropic support from The Rogers Family Foundation, have implicated chronic ISR activation in the persistent cognitive and behavioral deficits seen in patients after TBI, by showing that, in mice, brief ISRIB treatment can reboot the ISR and restore normal brain function almost overnight.

The cognitive deficits in TBI patients are often likened to premature aging, which led Rosi and Walter to wonder if the ISR could also underlie purely age-related cognitive decline. Aging is well known to compromise cellular protein production across the body, as life's many insults pile up and stressors like chronic inflammation wear away at cells, potentially leading to widespread activation of the ISR.

Variational Fast Forwarding for Quantum Simulation Beyond the Coherence Time

Cîrstoiu, Cristina; Holmes, Zoë; Iosue, Joseph; Cincio, Lukasz; Coles, Patrick J.; Sornborger, Andrew

npj Quantum Information, Volume 6, article id. 82, 18 Sep. 2020, https://www.nature.com/articles/s41534-020-00302-0, accessed 29 Jan. 2021.

Abstract

Trotterization-based, iterative approaches to quantum simulation (QS) are restricted to simulation times less than the coherence time of the quantum computer (QC), which limits their utility in the near term. Here, we present a hybrid quantum-classical algorithm, called variational fast forwarding (VFF), for decreasing the quantum circuit depth of QSs. VFF seeks an approximate diagonalization of a short-time simulation to enable longer-time simulations using a constant number of gates. Our error analysis provides two results: (1) the simulation error of VFF scales at worst linearly in the fast-forwarded simulation time, and (2) our cost function's operational meaning as an upper bound on average-case simulation error provides a natural termination condition for VFF. We implement VFF for the Hubbard, Ising, and Heisenberg models on a simulator. In addition, we implement VFF on Rigetti's QC to demonstrate simulation beyond the coherence time. Finally, we show how to estimate energy eigenvalues using VFF.

From: Fast-Forwarding Quantum Calculations Skips Past the Time Limits Imposed By Decoherence, Which Plagues Today's Machines

Unattributed, SciTechDaily, 27 Jan. 2021, https://scitechdaily.com/new-fast-forward-algorithm-could-unleash-the-power-of-quantum-computers/, accessed 29 Jan. 2021.

A new algorithm that fast forwards simulations could bring greater use ability to current and near-term quantum computers, opening the way for applications to run past strict time limits that hamper many quantum calculations.

"Quantum computers have a limited time to perform calculations before their useful quantum nature, which we call coherence, breaks down," said Andrew Sornborger of the Computer, Computational, and Statistical Sciences division at Los Alamos National Laboratory, and senior author on a paper announcing the research. "With a new algorithm we have developed and tested, we will be able to fast forward quantum simulations to solve problems that were previously out of reach."

Computers built of quantum components, known as qubits, can potentially solve extremely difficult problems that exceed the capabilities of even the most powerful modern supercomputers. Applications include faster analysis of large data sets, drug development, and unraveling the mysteries of superconductivity, to name a few of the possibilities that could lead to major technological and scientific breakthroughs in the near future.

Recent experiments have demonstrated the potential for quantum computers to solve problems in seconds that would take the best conventional computer millennia to complete. The challenge remains, however, to ensure a quantum computer can run meaningful simulations before quantum coherence breaks down.

"We use machine learning to create a quantum circuit that can approximate a large number of quantum simulation operations all at once," said Sornborger. "The result is a quantum simulator that replaces a sequence of calculations with a single, rapid operation that can complete before quantum coherence breaks down."

The Variational Fast Forwarding (VFF) algorithm that the Los Alamos researchers developed is a hybrid combining aspects of classical and quantum computing. Although well-established theorems exclude the potential of general fast forwarding with absolute fidelity for arbitrary quantum simulations, the researchers get around the problem by tolerating small calculation errors for intermediate times in order to provide useful, if slightly imperfect, predictions.

In principle, the approach allows scientists to quantum-mechanically simulate a system for as long as they like. Practically speaking, the errors that build up as simulation times increase limits potential calculations. Still, the algorithm allows simulations far beyond the time scales that quantum computers can achieve without the VFF algorithm.

One quirk of the process is that it takes twice as many qubits to fast forward a calculation than would make up the quantum computer being fast forwarded. In the newly published paper, for example, the research group confirmed their approach by

implementing a VFF algorithm on a two-qubit computer to fast forward the calculations that would be performed in a one qubit quantum simulation.

In future work, the Los Alamos researchers plan to explore the limits of the VFF algorithm by increasing the number of qubits they fast forward, and checking the extent to which they can fast forward systems.

A Roadmap to Revival

Successful revival of cryonics patients will require three distinct technologies: (1) A cure for the disease that put the patient in a critical condition prior to cryopreservation; (2) biological or mechanical cell repair technologies that can reverse any injury associated with the cryopreservation process and long-term care at low temperatures; (3) rejuvenation biotechnologies that restore the patient to good health prior to resuscitation. OR it will require some entirely new approach such as (1) mapping the ultrastructure of cryopreserved brain tissue using nanotechnology, and (2) using this information to deduce the original structure and repairing, replicating or simulating tissue or structure in some viable form so the person "comes back."

The following is a list of landmark papers and books that reflect ongoing progress towards the revival of cryonics patients:

Jerome B. White, "**Viral-Induced Repair of Damaged Neurons with Preservation of Long-Term Information Content**," Second Annual Conference of the Cryonics Societies of America, University of Michigan at Ann Arbor, April 11-12, 1969, by J. B. White. Reprinted in *Cryonics* 35(10) (October 2014): 8-17.

Michael G. Darwin, "**The Anabolocyte: A Biological Approach to Repairing Cryoinjury**," *Life Extension Magazine* (July-August 1977):80-83. Reprinted in *Cryonics* 29(4) (4th Quarter 2008):14-17.

Gregory M. Fahy, "**A 'Realistic' Scenario for Nanotechnological Repair of the Frozen Human Brain**," in Brian Wowk, Michael Darwin, eds., *Cryonics: Reaching for Tomorrow*, Alcor Life Extension Foundation, 1991.

Ralph C. Merkle, "**The Molecular Repair of the Brain**," *Cryonics* 15(1) (January 1994):16-31 (Part I) & *Cryonics* 15(2) (April 1994):20-32 (Part II).

Ralph C. Merkle, "**Cryonics, Cryptography, and Maximum Likelihood Estimation**," First Extropy Institute Conference, Sunnyvale CA, 1994, updated version at http://www.merkle.com/cryo/cryptoCryo.html.

Aubrey de Grey & Michael Rae, "**Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime**." St. Martin's Press, 2007.

Robert A. Freitas Jr., "**Comprehensive Nanorobotic Control of Human Morbidity and Aging**," in Gregory M. Fahy, Michael D. West, L. Stephen Coles, and Steven B. Harris, eds, *The Future of Aging: Pathways to Human Life Extension*, Springer, New York, 2010, 685-805.

Chana Phaedra, "**Reconstructive Connectomics**," *Cryonics* 34(7) (July 2013): 26-28.

Robert A. Freitas Jr., "**The Alzheimer Protocols: A Nanorobotic Cure for Alzheimer's Disease and Related Neurodegenerative Conditions**," *IMM Report* No. 48, June 2016.

Ralph C Merkle, "**Revival of Alcor Patients**," *Cryonics*, 39(4) & 39(5) (May-June & July-August 2018): 10-19, 10-15.

What is Cryonics?

Cryonics is an attempt to preserve and protect human life, not reverse death. It is the practice of using extreme cold to attempt to preserve the life of a person who can no longer be supported by today's medicine. Will future medicine, including mature nanotechnology, have the ability to heal at the cellular and molecular levels? Can cryonics successfully carry the cryopreserved person forward through time, for however many decades or centuries might be necessary, until the cryopreservation process can be reversed and the person restored to full health? While cryonics may sound like science fiction, there is a basis for it in real science. The complete scientific story of cryonics is seldom told in media reports, leaving cryonics widely misunderstood. We invite you to reach your own conclusions.

How do I find out more?

The Alcor Life Extension Foundation is the world leader in cryonics research and technology. Alcor is a non-profit organization located in Scottsdale, Arizona, founded in 1972. Our website is one of the best sources of detailed introductory information about Alcor and cryopreservation (www.alcor.org). We also invite you to request our FREE information package on the "Free Information" section of our website. It includes:

- A fully illustrated color brochure
- A sample of our magazine
- An application for membership and brochure explaining how to join
- And more!

Your free package should arrive in 1-2 weeks. (The complete package will be sent free in the U.S., Canada, and the United Kingdom.)

How do I enroll?

Signing up for cryopreservation is easy!

Step 1: Fill out an application and submit it with your $90 application fee.
Step 2: You will then be sent a set of contracts to review and sign.
Step 3: Fund your cryopreservation. While most people use life insurance to fund their cryopreservation, other forms of prepayment are also accepted. Alcor's Membership Coordinator can provide you with a list of insurance agents familiar with satisfying Alcor's current funding requirements.
Finally: After enrolling, you will wear emergency alert tags or carry a special card in your wallet. This is your confirmation that Alcor will respond immediately to an emergency call on your behalf.

Not ready to make full arrangements for cryopreservation? Then *become an Associate Member* for $5/month (or $15/quarter or $60 annually). Associate Members will receive:

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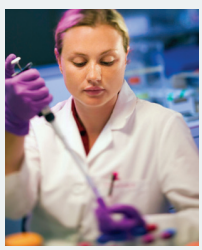

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