CRYONICS

4th Quarter 2020 | Vol 41, Issue 4 www.alcor.org

How to Sustain an Organization for Over a Century, *Part Two*

page 3

The S-MIX: A Measure of Ischemic Exposure

page 12

***Dying To Be Frozen*: The Production of a Cryonics Documentary**

page 16

ALCOR
ALCOR LIFE EXTENSION FOUNDATION
The World's Leader in Cryonics

CRYONICS

Cryonics magazine is published quarterly.

Please note: If you change your address less than a month before the magazine is mailed, it may be sent to your old address.

Address correspondence to:
Cryonics Magazine
7895 East Acoma Drive, Suite 110
Scottsdale, Arizona 85260
Phone: 480.905.1906
Toll free: 877.462.5267
Fax: 480.922.9027

Letters to the Editor welcome:
aschwin@alcor.org

Advertising inquiries:
480.905.1906 x113
advertise@alcor.org
ISSN: 1054-4305

Visit us on the web at www.alcor.org

Alcor News Blog
http://www.alcor.org/blog/

Contents

How to Sustain an Organization for Over a Century. Part Two: Cryonics Organizations Built to Last

By Max More, Ph.D.

In my last article, I surveyed many forms of organization in a search for clues to organizational longevity. We saw that most of the century-plus organizations were universities and religious institutions. Profit-oriented organizations provide fewer examples but with interesting and instructive exceptions. Investment companies and trusts stood out in the relative number of survivors. So did the *shinese* of Japan and their counterparts in Europe including the Tercentenarians of England. A common factor in most of those exceptions was continuous ownership and control by a single family – even if fresh blood had to be adopted into the family.

Those long-lived organizations had to be both hard and somewhat flexible. Hard in the sense that they clung tenaciously to their original purpose or mission. Flexible in that they (commercial ones) either pivoted temporarily to survive economic disruptions – building coffins in war time instead of temples – or eagerly adopted new technologies that enhanced the pursuit of their mission. A paper in the October 22, 2020 issue of *Nature* brought to attention a naturalistic exemplar of hardness with sufficient flexibility.

The diabolical ironclad (*Nosoderma diabolicum*) is a flightless inch-long beetle discovered in 1851 but not well-understood until now. It boasts an impressive longevity. Whereas most beetles live only a few weeks, a diabolical ironclad can live for seven or eight years. That's equivalent to around 1,000 years for a human. A major reason they can live this long is due to their insanely strong exoskeleton. Any creature that tries to peck it, crunch it, or squash it will be frustrated. In their paper, the authors explain how the ironclad uses internal layers, tight joints and overall near-invulnerable shape to yield the golden combination of toughness and flexibility.

The ironclad's first bit of evolutionary fortune comes in its shape. It's both low and close to the ground and has a shell much flatter than those of other beetles. Crushing pressure is thereby distributed over the entire shell. Apparently, this diabolically tough bug can withstand a crushing force of 39,000 times its own weight. Scaled up to my level, that would come to 3,800 tons or – to use an odd unit – 38.3 whales.

The ironclad manages to combine stunning hardness with flexibility thanks to the ability of the top and bottom sections of its exoskeleton to move in relation to each other. When something heavy presses on the beetle, its internal stuff can move toward its back end, reducing pressure on the frontal internal organs. It also has a "jigsaw joint" that distributes pressure far more effectively rather than snapping at the thinnest point. Check out the paper for the whole mechanism.

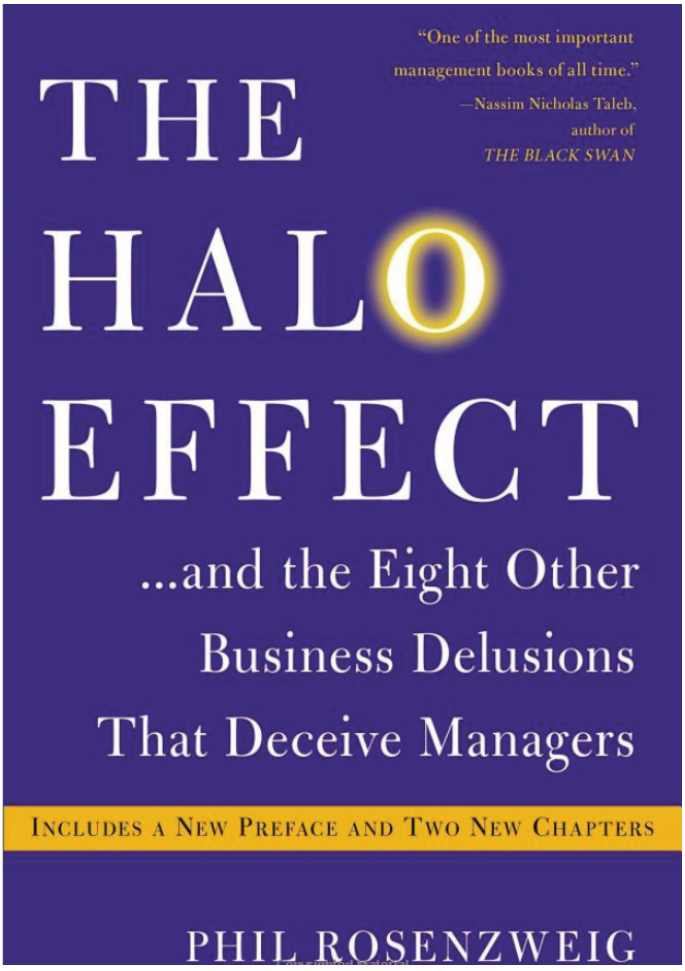
Since the paper came out, people have become excited about mimicking aspects of the diabolical ironclad to strengthen body armor, bridges, buildings, and aircraft. Perhaps organizations could learn something too? We already have the model of the "cryo-shinise." How about the model of diabolical ironclad cryonics organizations? Okay, we should drop the "diabolical" part. As you'll see below, we at Alcor can (and have) implemented a sort of equivalent of the principles of segmenting and distributing load.

Seduction by Management Literature

To shape Alcor's practices and structures for maximum organizational longevity, why not simply adopt the recommendations in management literature? There's no shortage of promising books, starting with the best-seller, *In Search of Excellence* by Thomas J. Peters and Robert H. Waterman. Jim Collins has built a career on writing books like this, including *Built to Last: Successful Habits of Visionary Companies, Good to Great: Why Some Companies Make the Leap... and Others Don't,* and *Great by Choice: Uncertainty, Chaos, and Luck—Why Some Thrive Despite Them All*, by Jim Collins and Morten T. Hansen.

Built to Last, for instance, tells us that the longest-lasting and most resilient corporations engage in "clock-building" rather

than relying on a charismatic leader; that they recognize the "genius of the 'and'"; that they are "more than profits"; and that they "preserve the core, stimulate progress". Collins advises us to have "big, hairy, audacious goals", "cult-like cultures", "experiment a lot and keep what works"; use "home-grown management"; and to live by the principle that "good enough never is". These may sound both plausible and impressive. They also come backed by large amounts of research.



However, as Phil Rosenzweig argues in *The Halo Effect*, much of business writing is what Richard Feynman called "cargo cult science", having the superficial trappings of science but operating at the level of storytelling. Many of the principles still hold up today, partly because some of them are so broad as to appear applicable to virtually everyone. The principles, while perhaps inspiring, are vague. That leads to a framework that explains everything but predicts nothing. That suggests that the future depends on much more subtle issues than can be captured with coarse-grained principles abstracted from the past.

The Halo Effect explains nine "delusions" or mistakes of reasoning that undermine these formulas for business success. For example:

- The Delusion of Connecting the Winning Dots: looking only at successful companies and finding their common features, without comparing them against unsuccessful companies. This is a common error in management literature.
- The Delusion of Rigorous Research: Some writers can show off the sheer amount of research they have done, as if that had any bearing on the validity of the conclusions.
- The Delusion of the Wrong End of the Stick: getting cause and effect the wrong way around. Many successful companies have a Corporate Social Responsibility policy. Should we then infer that CSR contributes to success, or that profitable companies have money to spend on CSR?
- The Delusion of Organizational Physics: the idea that business performance is non-chaotically determined by discoverable factors, so that there are rules for success out there if only we can find them.

Similar criticisms are made by Daniel Kahneman in *Thinking, Fast and Slow*. Kahneman argues that Collins overstates the importance of good practices relative to sheer luck. Previously excellent companies may not change their practices and yet fall on their face as they undergo a typical regression to the mean. Others have pointed out how many of these built-to-last companies went downhill not long after Collins' book was published. The bottom line is a rather pessimistic one: We cannot simply look at the most successful organizations and easily or reliably extract lessons to apply.

Measures Taken by Alcor

Having beaten up on *Built to Last*, we can acknowledge that many of the principles it proclaims are plausible – perhaps because they are vague enough to encompass our own views of what works. For instance, Collins talk of "clock-building." By this, he meant the companies that succeed over the long term are not built on a great idea or a charismatic, visionary leader. Instead, they succeed and endure because they build on strong foundations that carry them through the years and far beyond the active span of a generation of leaders. Alcor has continued to work on its organizational design, recognizing the value of strong foundations. That leads me to the first of six areas.

Governance

Self-perpetuating board: Alcor is governed by a "self-perpetuating Board." In such a Board, new Board members are elected to that position by existing Board members. This is the most common way of electing Board members in nonprofit organizations. The duties and authority of the Board are described in the Bylaws, Articles of Incorporation, and by applicable law. The Board seeks to achieve the fundamental goals of Alcor, as described by the Mission Statement.

A core reason for adopting the self-perpetuating structure was its ability to provide continuity of purpose over a long period of time. New Board members are selected by existing Board members based on who can best preserve Alcor's core values and carry out its mission. Importantly, all Board members are required by Alcor Bylaws to be Alcor members. Both conditions make it extremely difficult for hostile outsiders to take control of the Board as compared to a directly member-elected Board. In addition, it's something of a tradition to look for new Board members in the ranks of Alcor Advisors. These tend to be long-standing cryonicists who are well-known.

Sometimes Alcor's self-perpetuating Board is compared unfavorably to Cryonics Institute's member-elected board, which is said to be "more democratic." Even CI doesn't allow all members to vote without conditions. CI restricts voting to lifetime members or members of at least three years and they must have made arrangements to be cryopreserved. Even so, it would not take a particularly large group of determined outsiders long to take over a Board so constituted. Democracy, when not unlimited, is a valuable principle for the governing body of a country with its wide diversity of purposes. That does not suit it well to more focused organizations, whether non-profit or for-profit.

Internal leadership: When we looked at the Japanese *shinese*, we saw that these remarkably long-lived companies were run by the same family over many generations – with a little help from adoption into the family. We saw something very similar in the longest-lived European corporations. The self-perpetuating Board structure works a bit like this, allowing Alcor to enjoy the benefits of multi-generational families. Alcor presidents, too, must be Alcor members. We are also doing more succession planning for top positions, although we can do more as we grow. Succession planning and talent development are tough until you have enough people in the organization work with. The transition of the role of President and CEO from myself to Patrick Harris has been quite different from past transitions. This allows for richer transfer of knowledge and experience.

As Alcor has grown and the complexity of its operations increased, it has been developing its internal structures. While Alcor has always had committees, the number is growing while their structure is also becoming more sharply defined. There are special-purpose committees such as Deployment, and SST (Standby, Stabilization, and Transport), and a series of top-level committees such as Research, Legal & Regulatory, Fundraising, and Finance. Either spun off from these committees or operating independently are working groups, such as the recently formed Reintegration Working Group.

To further improve governance at the top level, in recent years the Board has adopted policies including a formal Conflict of Interest Policy, and the Advance Notice Policy. The latter policy is intended to prevent important motions from being pushed too quickly through the Board. It requires that the final wording of all proposed Board motions, clearly labeled as such and dated, must be distributed to all Board members, Board Advisors and staff at least 25 days prior to being voted on by the Board. This allows individual directors to delay a vote. The requirement can be waived only by agreement of all directors.

Openness and privacy: Related to core issues of governance, Alcor's internal behavior is regulated by two contrasting and yet complementary factors: Openness takes various forms, such as welcoming visitors on a frequent basis and publishing case reports. At the same time, Alcor strives to protect the privacy of members and patients who do not wish to be known publicly. Sometimes these two considerations are in tension, such as in deciding the level and amount of detail to include in published case reports.

Documentation

Alcor has always documented many of its most critical policies and procedures. In the Procedures section of the Library on Alcor's website, you can find both former and current examples, such as:

- General Introduction to Procedures for Alcor Transport Technicians
- Elements of a Transport
- Human Cryopreservation Stabilization Medications
- Field Cryoprotection
- Standby: End-Stage Care of the Human Cryopreservation Patient
- Case Reports in Cryonics [PDF]
- Calibration of Alcor Post-Cryopreservation CT Scans
- 1997 Manual – Stabilization and Transport
- Air Transportable Perfusion Kit Manual
- DuaLogR Manual (for temperature data logging in the field)
- Operating Room Tubing Assembly
- Isolation of the Brain
- 1990 Manual – Transport Protocol for Cryonic Suspension of Humans

The details of the crucial procedures for Alcor in cryopreserving people are laid out in the "Alcor Human Cryopreservation Protocol" and the 711-page "Human Cryopreservation Procedures Book."

Alcor Manuals and Standard Operating Procedures

The list of SOPs (standard operating procedures) continues to grow. These detail how to perform tasks in a way that both helps ensure consistency in practice and eases the way for new staff to step into a role. These are updated and revised periodically. We also have SOPs for contractors in the form of provider manuals.

A different form of documentation is seen in the "Red Books". These compile all available information on every Alcor patient. That includes membership information, any medical background, case report, revival preferences, and notes related to the case. These are locked away securely and all of them have been scanned and backed up in encrypted form in the cloud. (Exceptions to this practice are only made by special request.)

Financial management

Like the diabolical ironclad, Alcor's financial resources are segmented, with some being more heavily protected than others and with strict rules governing how they may be used. Unique to cryonics organizations, Alcor established a trust to protect patients over the long term. This began in 1997 with an irrevocable Patient Care Trust. This trust underwent further evolution in 2017, receiving tax-exempt status as a Type II supporting organization under the IRC Section 509(a)(3), becoming the Alcor Care Trust Supporting Organization.

The Alcor Care Trust is exclusively for providing care for cryopreserved patients until such future time as it may be possible to repair and revive them to such a condition as will allow them to be considered legally alive, functional, and independent. The ACT is charged with investing its funds so as to maximize growth while minimizing risk. In addition to covering the expenses of keeping the patients in biostasis, the ACT attempts to accumulate enough funds in the ACT Trust Estate to eventually pay for the successful resuscitation and rehabilitation of the Patients once that becomes possible. Using a conservative estimate, the funds should generate more than enough money to cover patient maintenance indefinitely and grow over time – even without the influx of new funds.

Alcor strongly supports the ACT by requiring that the full amount of the ACT's allocation be provided, even if a patient

is underfunded. As of 2020, that means putting $25,000 into the Trust for each neuropatient and $115,000 for each whole-body patient. These minimum allocations (members may provide funding over the minimum) are calculated to suffice for capital preservation and growth despite patient care costs and inflation.

Understanding the value of having extra funds available for events beyond the norm, Alcor has a Reserve Account. Reserve funds cannot be spent without approval by the Board of Directors. These funds play a crucial role when legal expenses are high or when an unusual opportunity for improvement appears. Two other segregated accounts are the Underfunding Fund and the Hardship Fund. The former is used to pay for cryopreservation expenses of underfunded members (who joined the plan by 2013) while the latter is available to help members who are struggling financially but want to maintain their membership.

Another major pot of money is the Endowment Fund, as described briefly in Part One. Essentially, the maximum draw is 2% with a modest yearly adjustment up or down, depending on the performance of the investments. As I noted then, contributions to the endowment produce a smaller immediate benefit but generate a reliable income for operations. This helps to slow increases in membership dues despite inflation.

One area where Alcor could continue to do better is helping members plan for inflation. We implemented the Underfunding Plan because members had not increased their funding over time. Contrary to what some have said, Alcor's publications *did* communicate the need for this. However, more frequent and directed communications are needed. At time of sign-up, we are now emphasizing the need for inflation planning and directing new members to calculations that show what to expect over the years. We hope to tackle this issue at a more fundamental level by changing the way membership is priced, and by doing more to encourage additional funding through means other than life insurance.

Security measures

Many of these relate to physical security of the Alcor facility and safety of the staff and patients. Some years ago, we replaced regular locks with high security locks and electronic logging of those who enter and exit. Different staff members have differing levels of access, with the highest limitation being on access to the Patient Care Bay. The PCB itself is physically secured also from outside access by force by various means that I will not describe here.

The hardware that goes with the dewars includes a level monitor to alert us in the remote eventuality of a sudden and major drop in liquid nitrogen levels. The outer perimeter is strengthened and monitored. We have further security upgrades in mind. It's always possible for a determined intruder to get inside and then threaten staff to give further access. We have other measures for such eventualities. Police response time in our area is brief.

A different form of security is bolstered by universal use of non-disclosure agreements by anyone working for, consulting with, advising, or contracting with Alcor. Although background checks had typically been done before a new president, the practice was otherwise little used. Several years ago, I urged that these be run for all new directors and the practice is now applied also to candidates for all major positions in the organization.

Information security is maintained by redundant storage of crucial member and patient information, including off-site, encrypted cloud storage. Finally, Alcor recognizes the importance of being as secure as possible against threats from legislation. We have had to deal with such threats both in California and Arizona. One valuable resource in this area involves keeping a well-connected legislative consultant on retainer to keep track of potentially threatening litigation. Most recently, this gave us early warning of restrictive legislation sparked by problems at a company that supplied human body parts to medical schools. Our consultant contacted the authors of the bill who immediately agreed to rewrite it to exclude us.

On a financial level, security and correctness is maintained through GAAP accounting, independent reviews and audits, and the lack of signing authority on the part of the Finance Director.

Periodic Reevaluations of Procedures

When I came onboard as president in 2011, I sent out a memo challenging everyone involved to "Question Everything." A motto, of course, is not enough. Continuous improvement is not just a program or process improvement. It needs to be an institutionalized habit, an integral part of the organizational culture, a way of life. We are in the habit of doing after-action reviews/debriefings following every cryopreservation. In a future report, you will learn about a major meta-analysis project that uses huge amounts of performance data and extracts actionable lessons for improvement. We will continue to practice "evidence-based cryonics" by measuring objectively, wherever possible, our performance in all areas of operation.

Scalability

Finally, a brief word about a big topic. Some organizations initially flourish and grow rapidly but eventually reach a point where they are unable to generate increased output from increased resources. This might be because they depend on a specific leader or management team that is unwilling to cede any control. Or there might be a bottleneck in the system that further growth will only break. Organizational longevity through a period of growth requires administrative, functional, geographic, and load scalability.

Alcor has been and will continue building our capacity to scale. We have grown at faster and slower rates over the years. We will be aiming for greatly accelerated growth once the infrastructure to scale is further developed. One obvious area to tackle here is the ability of staff to process a multiplying number of membership applications. We plan to develop a simplified and largely automated sign-up process. This will both reduce the difficulty on the part of applicants and enable each membership administrator to handle more applications.

We also face a need to be able to scale in the way we handle financial transactions. We have already made some moves in this direction by upgrading our IT infrastructure and will continue to use IT along with revised business processes to handle higher transaction volume.

Part of being scalable is not just scaling up but scaling down. We hope and expect to grow constantly but need to be able to survive periods of stagnation or membership decline. Contrary to the "must grow or die" view, I believe Alcor must be able to endure without growing. That means avoiding huge structures that take vast amounts of money and effort to maintain.

In the second part of this two-part article, I have surveyed practices, processes, and values that Alcor is using and can continue to improve upon in order to maximize our chances of sustaining the organization long enough to one day revive and reintegrate our patients. These are some of the building blocks that cryonics organizations can use to combine the strengths of the diabolical ironclad beetle, the *shinise*, and the Tercentenarians and family firms. One day, organizational historians will point to Alcor as an exemplar of organizational architecture for longevity – if we build a culture that continues to focus relentlessly on these core factors. ■

References

Built to Last: Successful Habits of Visionary Companies.
Jim Collins and Jerry I. Porras
Collins Business; 3rd edition, September 1, 2002

Good to Great: Why Some Companies Make the Leap... and Others Don't
Jim C. Collins, HarperCollins October 16, 2001

Great by Choice: Uncertainty, Chaos, and Luck—Why Some Thrive Despite Them All
Jim Collins and Morten T. Hansen, Oct 11, 2011

Daniel Kahneman, Thinking, Fast and Slow
Farrar, Straus and Giroux; 1st edition, April 2, 2013

In Search of Excellence: Lessons from America's Best-Run Companies.
Thomas J. Peters and Robert H. Waterman, Jr.
HarperTrade, New York, NY, U.S.A. January 1, 1982

The Halo Effect: ... and the Eight Other Business Delusions That Deceive Managers
by Phil Rosenzweig
Free Press, February 6, 2007

Rivera, J., Hosseini, M.S., Restrepo, D. et al. Toughening mechanisms of the elytra of the diabolical ironclad beetle. Nature 586, 543–548 (2020). https://doi.org/10.1038/s41586-020-2813-8

CryoBio: Why Cryonics?

By David Harker

A CryoBio is a recently coined term referring to text provided by public members for publication before they are cryopreserved. These differ from the biographies of still-living members although they may be constructed from the text of a regular biography if the member or their family has not provided text. We encourage members to provide CryoBio text in advance since they may wish to include different information than they would in a living biography. For instance, members may want to include more genealogical information in a CryoBio, or publicly express wishes for revival. Once we have the long-planned Member Portal set up, members will be able to easily supply Alcor with text both for CryoBios and regular Member Bios. The CryoBio will be linked to the List of Patients.

David Harker, Napa High School Yearbook Photo, 1970 (courtesy of Ancestry.com)

As I lie here on my hospice bed after a seven year struggle with cancer, I am struck by how perfectly my life experiences have coalesced towards this final chapter of my existence – ensuring a good death. Soon I intend to avail myself of my legal right to end my life under the provisions of Washington State's Death With Dignity Act. In doing so I hope to achieve the dual goals of avoiding unnecessary suffering while making my body available to Alcor while my brain is still in top form. Considering the ephemeral nature of all things, it seems to me that achieving a good death is secondary in importance only to that of springing into existence in the first place. My life achievements will doubtless prove inconsequential. I will hold no significant mention in the annals of History, but perhaps a few highlights from my life's story will bring into focus why I think a good death is a worthy goal.

I was born an only child in Redding, California on September 18th, 1952. My father was a right-of-way appraiser for the State of California. My mother was a grade school teacher. I was the inquisitive type of child enthralled with my chemistry set, microscope, home-made weather station (hair hygrometer anyone?) and a vast menagerie of pets. I did well in school and there was never any doubt in the dreams of my parents that their only child was destined for college, graduate school, and beyond. On my 12th birthday I received a 5-gallon aquarium from my grandmother. Aquatic biology soon became my all-abiding passion and I've identified myself as a "scientist" ever since. At one time I believe I was the youngest NAUI certified scuba diver in the state of California. When I left home for college, no less than 16 aquariums full of aquatic organisms and a tidy row of lab notebooks in my parent's rec room remained behind. In 1974 I was awarded a Bachelor of Science degree in biology with honors at the University of California Santa Cruz. The next fall I packed all my worldly possessions into my Ford Pinto and drove to the University of Washington School of Oceanography to pursue advanced degrees in biological oceanography. I was awarded a Master of Science degree biological oceanography, however during my academic pursuits I discovered much to my chagrin that I was extremely susceptible to seasickness which made pursuing an academic career in oceanographic research impractical.

Fortunately, I discovered two new loves in my advanced degree program, statistical analysis and computer programming. After working a few years as an un-degreed consultant in these areas a good friend and I launched a software startup in 1983 we named Precedent Systems, Inc. It was the dawn of the microcomputer revolution – a fortuitous time for two young lads to embark on the development of electronic billing and medical charting software for private practice physical therapy offices. The company did well reaching 20 employees. My true passion was designing elegant and efficient algorithms. Unfortunately, as the company grew I found my time as CEO and President consumed by essential administrative tasks which I did not enjoy. Also during this time I met my lovely wife Susan, a high tech executive, and began to devote more time to raising a family. I remember how my first born son would cry every morning when I left for work. It was heartbreaking. When Susan became pregnant a few years later with my daughter I resolved to sell my company and retire.

In 2013 I was diagnosed with an extremely rare cancer called Follicular Dendritic Cell Sarcoma (FDCS). Only 1 in 25,000 cancer cases is FDCS. This disease is so rare that there are no FDA approved standards of care. Few oncologists have ever seen a single case. Ironically this rarity provided the perfect opportunity to integrate my diverse skill set (biologist, statistician, medical data analyst, and software engineer) into one final grand project. Over the next seven and a half years

I traveled the country visiting experts at all the top cancer research centers, I read hundreds and hundreds of cancer research publications, I collected extensive biometrics about the slowly deteriorating condition of my own body, and I developed computer models to direct the course of my own therapy. The treatments were all mainstream, but often novel applications in the context of standard cancer care. Many oncologists resisted prescribing the treatments I requested, but generally I either found an accommodating oncologist or clinical trial to achieve my goals.

Stage 4 cancer is an implacable foe and the best I could hope for was to buy more time. However, I did have the satisfaction of extending my life 50% beyond the typical prognosis for FDCS. The subject matter was rather grim, but in many ways this research was the culmination of my life's work and a great source of personal joy.

Obviously, I am not a person who treats the miracle of existence cavalierly. Although my life will have legally ended by the time you read this, I don't consider my existence to be irrevocably ended by this event. I've believed that science is the way forward for humanity since I was 12 years old. I believe that future science may yet save the day and allow my existence to continue. Cryonics is currently the only possible bridge to the future for me. As my final day draws near, I tell my children, "Don't think of me as dead and gone forever. Instead think of me as a lightbulb whose electrical current is switched off and no longer shines." I tell them, "Someday maybe, just maybe, science will figure out a way to flip that switch back on." ■

David Harker was cryopreserved by Alcor in September 2020

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. ■

The S-MIX: A Measure of Ischemic Exposure*

By R. Michael Perry and Aschwin de Wolf

Abstract

The S-MIX is a quantitative cryonics cases outcome metric to calculate the total ischemic exposure of a patient. In this brief exposition, R. Michael Perry and Aschwin De Wolf introduce this metric and the issues involved in calculating it for a cryonics case involving several distinct procedures.

Introduction

An ever-present unknown in cryonics is evaluating the quality of a cryonics case. Until more is known, in fact, we will have no good assessment of case quality in terms of what we would really like to know: how well memory and other identity-critical elements are preserved in cryopreserved patients. Meanwhile we are interested in whatever reasonable indicators of cryopreservation quality it may be feasible to compute, while acknowledging these are imperfect.

One such possible indicator would be a "measure of ischemic exposure" intended to assess the amount of normal body temperature ischemic exposure a patient experiences, mainly in the early stages of a cryonics procedure before the start of cryogenic cooling. Basically, this measure would tally up how long a patient has been at a given temperature, with a heavier weighting used for higher temperatures, since more damage is occurring at these temperatures. According to a rule of thumb in wide use (the so-called Q_{10} rule), each decrease of 10°C is supposed to halve the amount of damaging activity per unit time. More generally, we can assume that each drop of 10° reduces (divides) the activity by a factor Q_{10}. At least it is considered roughly accurate for $Q_{10} \approx 2$, though it must not be pressed very far. Here we adopt this "exponential rule," with the understanding that it is only a starting point.

In 2003, Dr. Steve Harris also developed a measure aimed at estimating the total duration of normothermic ischemia during initial cooling named the E-HIT. In this article we present a closely related measure called the S-MIX (**S**tandardized **M**easure of **I**schemic E**x**posure) to express the total ischemic exposure prior to the start of cryogenic cooling as the equivalent duration of normothermic ischemia. Two special cases are considered in detail: (1) where the rate of temperature descent is constant with time. For this case we obtain the "linear" S-MIX or S-MIX_L, which, it turns out, is proportional to the total exposure time. (2) A second case considered is Newtonian cooling, S-MIX_N, in which the rate of cooling is proportional to the difference between a starting temperature and a final temperature T_∞ which is never reached but approached more and more closely with increasing time. For the Newtonian case one must also know a "characteristic time" t_C which is the amount of time it takes to cool the subject by (1-1/*e*) or about 63% of the difference between the starting and the final temperature. It turns out that S-MIX_L is a limiting case of S-MIX_N in which the final temperature T_∞ is very low and the characteristic time t_C is very large. S-MIX can also be attenuated to express a lower ischemic exposure when the patient is oxygenated.

S-MIX; General Case

We normalize our measure so that 1 corresponds to 1 hour at body temperature B (B = 37°C for a human). With this assumption and the Q_{10} rule, with $Q_{10} = 2$, 1 hour at B-10°C or 27°C would be 0.5 hours by S-MIX, and for 1 hour at 17°C, 0.25 hours, etc. The measure for a fixed temperature would also scale linearly with time – twice as much exposure at a given temperature would give twice as much expected damage, consequently, twice as big a contribution. 2 hours at 37°C, then, would yield a measure of 2. At 27°C, however, in view of the exponential rule, 1-hour exposure would give a result of 0.5, and 2 hours a result of 1. Mathematically, at temperature T, by the Q_{10} rule, the rate of ischemic damage for the general case of Q_{10} is given by

$$\text{Rate of damage} = Q_{10}^{-(B-T)/10} = \exp(qT\text{-}qB), \quad (1)$$

where

$$q = (\ln Q_{10})/10 \quad (2)$$

The total ischemic damage the patient experiences, at a fixed temperature, equals the rate of damage at that temperature times the amount of time spent at that temperature, assuming the temperature is constant over the time interval. For the general case, however, the temperature varies with time, so we divide the time interval into small subintervals, for each of which we can assume the temperature is constant, and add up all the small contributions to obtain the total estimate of ischemic injury. Mathematically, the temperature is now a non-constant function $T(u)$ of time parameter u, and we must integrate the rate of ischemic damage between two time limits, t_0 and t_1, to obtain the total estimate of ischemic injury:

$$\text{S-MIX}(t_0, t_1) = \int_{t_0}^{t_1} \exp(qT(u) - qB)du. \quad (3)$$

In most of what follows it simplifies the treatment to normalize the start time t_0 to 0 and designate the finish time t_1 as t. We further simplify S-MIX(0, t) to S-MIX(t). Eq. (3) then becomes

$$\text{S-MIX}(t) = \int_0^t \exp(qT(u) - qB)du. \quad (4)$$

S-MIX linear case (S-MIX$_L$)

For this case we start at time 0 with temperature T_0 and end at time t with temperature T_1. For intermediate times $0 < u < t$ the temperature $T(u)$ varies linearly with the time according to

$$T(u) = T_0(1\text{-}u/t) + T_1(u/t) \quad (5)$$

Applying eq. (4) then gives

$$\text{S-MIX}_L(t) = t\exp(-qB)[\exp(qT_0) - \exp(qT_1)]/[qT_0 - qT_1]. \quad (6)$$

So, we see, in particular, that S-MIX$_L(t)$ is just proportional to time t, the proportionality constant depending on the starting and ending temperatures T_0 and T_1. The assumption of a linear cooling rate has only limited applicability, however. For example, during the final stages of cardiopulmonary support (CPS) and blood washout the cooling generally slows considerably as the target temperature is approached. A more accurate approximation of the cooling profile is Newtonian cooling which we now consider.

S-MIX$_N$ (NEWTONIAN)

In its "pure" or idealized form the basic assumption about Newtonian cooling is that we start at temperature T_0 as before, but the final temperature T_∞ is never reached but only approached in the limit of infinite time. Instead, the temperature $T(u)$ at time u is given by

$$T(u) = T_0\exp(-u/t_C) + T_\infty(1 - \exp(-u/t_C))$$
$$= T_\infty + (T_0 - T_\infty)\exp(-u/t_C), \quad (7)$$

where t_C in this case is the time needed to cool to $1 - 1/e = 1 - \exp(-1)$ of the distance between T_0 and T_∞. (For a human body, a good rough estimate of t_C is about 7 hours. This means, for example, that if a postmortem body initially at 37°C is placed in a 0° cooler, so $T_\infty = 0°$, and left for 7 hours it will cool to a temperature of 63.2% = 1-1/e of the way from 37° to 0°, or 13.6°C.) The measure in this case is determined by substituting the expression for temperature $T(u)$, eq. (7), into eq. (4).

In practice we start as before with temperature T_0 and reach temperature T_1 at time t. We can then determine T_∞ as needed for the calculations from eq. (7):

$$T(t) = T_1 = T_\infty + (T_0 - T_\infty)\exp(-t/t_C), \quad (8)$$

from which it follows that

$$T_\infty = (T_1 - T_0\exp(-t/t_C))/(1 - T_0\exp(-t/t_C)). \quad (9)$$

To obtain an expression for the integral, eq. (4), for the Newtonian case, two additional quantities need to be defined:

$$s = q(T_0 - T_\infty), \quad (10)$$

and the "mainsum function" ms given by

$$\text{ms}(x) = \sum_{k=1}^{\infty} \frac{x^k}{k\,k!} = x\,{}_2F_2(1,1;2,2;x) = \text{Ei}(x) - \ln(|x|) - \gamma, \quad (11)$$

where Ei is the exponential integral function given (for real-valued, nonzero x) by

$$\text{Ei}(x) = \int_{-\infty}^{x} \frac{\exp(u)}{u} du, \quad (12)$$

and γ is the Euler-Mascheroni constant, 0.5772156649…. With these conventions, then, we can express the Newtonian S-MIX$_N$ by

$$\text{S-MIX}_N(t) = \exp(qT_\infty - qB)[t + t_C(\text{ms}(s) - \text{ms}(s\exp(-t/t_C))]. \quad (13)$$

Using eqs. 10-13 it is straightforward to show that S-MIX$_N$ reduces to S-MIX$_L$ in the limiting case that t_C is large and the ratio t_C/T_∞ is fixed ($|T_\infty|$ is also large), so effectively the cooling rate does not change with time but is still appreciable. (In practice, of course, T_∞ cannot be colder than absolute zero but this physical limit is not important for the mathematical properties considered here.)

Lessening the S-MIX through metabolic support

So far, in our consideration of possible variants of S-MIX (linear, Newtonian) we have not recognized the benefits of providing metabolic support to the tissues during CPS and blood washout. To remedy this, we propose that we decrease the ischemic "hit" when the patient is ventilated during CPS. Since the cerebral blood flow during artificial chest compressions (manual or mechanical) falls short of what is observed during normal circulation we only allow a 50% reduction of ischemic exposure. During blood washout, when physiological perfusion pressure is possible, the ischemic hit can be allowed to be non-existent for the duration of the blood washout, *provided that ventilation was present during CPS as well*. The presence or absence of oxygen is reflected in an ischemia weight function that can have 0 (physiological oxygenation), 0.5 (oxygenation during CPS), or 1 (no oxygenation). In this way the original S-MIX, of whatever form, linear, Newtonian or more general, is transformed in a simple way to a weighted form, S-MIX$_W$ according to:

$$\text{S-MIX}_W(t) = w\text{S-MIX}(t), \quad (14)$$

where

$$w = \begin{cases} 0, \text{physiological oxygenation} \\ 0.5, \text{oxygenation during CPS} \\ 1, \text{no oxygenation.} \end{cases} \quad (15)$$

We have assumed that weighting parameter w is constant during the time interval of the cooling (from start time 0 to end time t). It is expected that otherwise Newtonian rather than linear (or more general) cooling will be assumed, in absence of frequent temperature measurements. So from eqs. (13-15) we obtain an explicit expression for a weighted, Newtonian version of S-MIX,

$$\text{S-MIX}_{W,N}(t) = w\text{SMIX}_N(t). \quad (16)$$

There will also be a succession of time intervals each with its own weighting w, along with start time (normalized to 0) and end time t, and different values of both T_0 and T_∞ (and possibly t_C). The total S-MIX will be the sum of all the values obtained for the different time intervals; see discussion below.

Cryonics case S-MIX calculation

The $\text{S-MIX}_{W,N}$ formula is easy to apply for a time interval in which conditions are stable (presence or absence of oxygenation, parameters for Newtonian cooling). However, we run into a major practical problem when we consider that a cryonics case consists of several procedures. A typical cryonics procedure employs several distinct cooling methods to induce hypothermia. In ideal cryonics cases a patient is immediately placed in a portable ice bath for vigorous external cooling. Then, at 20°C, external cooling is followed by *internal* cooling with an organ preservation solution until a temperature is reached that is safe for cryoprotective perfusion (between 5°C and 0°C). In non-remote cases there is additional complication that a patient spends a considerable period at a *fixed* temperature (~ 0°C) before the start of cryoprotection. A typical case also shows different kinds of oxygenation modalities (or the absence thereof).

An accurate calculation that incorporates those elements entails that we calculate the measure from a comprehensive set of cooling data. If such comprehensive data is not available (or can only be estimated or inferred), a more accurate measure can be obtained by breaking down the cooling data in distinct segments that correspond to typical cryonics procedures. For example, we can calculate the S-MIX for a total case by adding up the S-MIX scores for:

1. The time between circulatory arrest and completion of cardiopulmonary support (37°C to 20°C)
2. The time between the start and completion of internal cooling (20°C to 5°C)
3. The time between the start of cryoprotection and the start of cryogenic cooling (5°C to 0°C) [local]

OR

The time between the start of cold transport and the start of cryogenic cooling (5°C to 0°C) [non-local]

In practice, the difference for segment 3 for a local or non-local case is relatively minor for the purpose of calculating the S-MIX because the cold transport temperature approximates the (ideal) temperature for conduct of cryoprotectant perfusion. In both scenarios the temperature of the patient is in the 5°C to 0°C range but with additional S-MIX time for a patient transported on water ice.

Calculating the S-MIX by adding up the segments for these distinct cryonics procedures renders a more accurate equivalent normothermic ischemia exposure time and also allows for scenarios in which a patient spends a considerable period at a fixed temperature (in the case of cold transport or a mortuary cooler). In principle, the number of segments that is chosen for calculating the total S-MIX depends on the specifics of a case and how much precision one wants to see in the calculations. To make comparison of S-MIX values between cases meaningful, it is important to describe the segments along with the calculations.

Conclusion

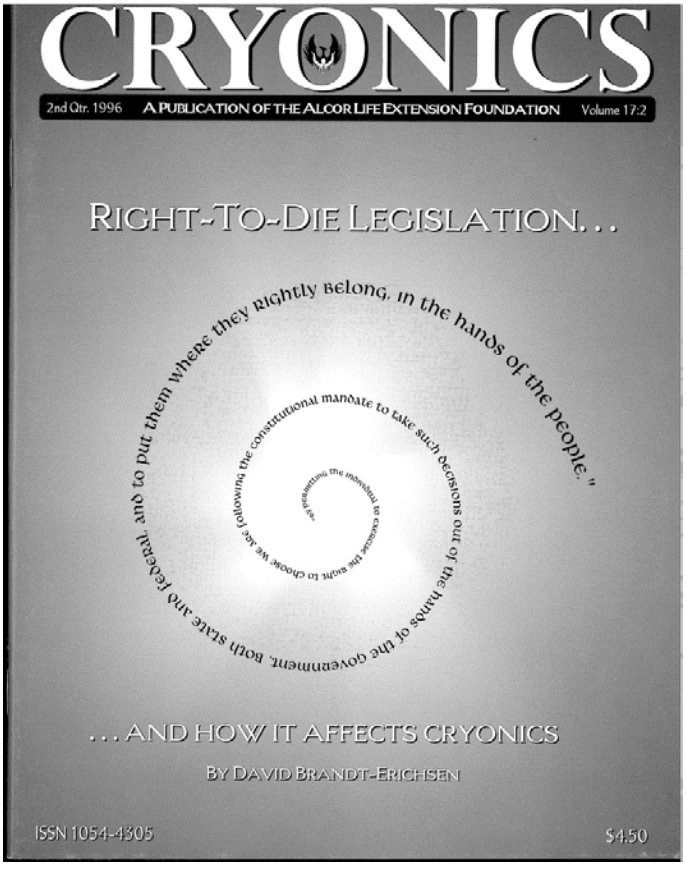
In this article we present a quantitative measure to calculate the equivalent normothermic ischemic time for a cryonics case. We assume a Q_{10} rule with a cooling factor of 2 throughout. (So reaction rates, including ischemic damage, are halved by a 10°C drop in temperature.) The S-MIX_L (linear case) assumes additionally that there is a constant cooling rate, or in effect, identical time spent at each small, fixed-width temperature interval, until the start of deep cooling. The S-MIX_N (Newtonian) measure is then derived by allowing Newtonian cooling. Degrees of oxygenation are modeled by weighting the version of S-MIX that is assumed (in particular, S-MIX_N) by quantities ranging between 0 (perfect oxygenation) and 1 (no oxygenation). Guidelines are provided to calculate an overall S-MIX by summing the total contributions from distinct segments to reflect typical cryonics procedures.

It is hardly necessary to add that these ideas can be further refined. As stated before, in an ideal case the S-MIX would be derived from detailed temperature data instead of adding up distinct segments. In fact, the lack of such temperature data is itself indicative of compromised case work. The assumption that cryogenic cooling starts at 0°C is not always realistic and may over- or understate the situation. It may not be known exactly when the patient reaches a temperature of 0°C and this will need to be estimated.

There can also be cases where the temperature rises again due to poor compliance with cold transport protocol or compromises during perfusion. Is it realistic to assume that a patient did not suffer some degree of cerebral ischemia prior to circulatory arrest? Should a more sophisticated measure incorporate the administration of neuroprotective medications? Are there circumstances in which oxygenation aggravates ischemic injury?

It is inevitable that calculating an ischemic exposure measure for some cases (i.e. missing data) may entail educated inferring of times and temperatures. However, we think the above could be a starting point to *one* useful indicator of cryopreservation quality as it allows us to identify trends and correlate duration of ischemia to case outcomes. ■

*This article is a revision of R. Michael Perry's "Toward a Measure of Ischemic Exposure" (*Cryonics* Magazine, 2nd Quarter, 1996). The most fundamental change is to calculate the S-MIX$_L$ as the duration of equivalent normothermic ischemia and to present a measure that incorporates Newtonian cooling and metabolic support. We thank Hugh Hixon and Steve Harris for their contribution to developing these outcome metrics.



Dying To Be Frozen: The Production of a Cryonics Documentary

By Jake McCurdy

After a 7-year odyssey, the film *Dying To Be Frozen* is now available on digital streaming platforms. This 72-minute documentary is the most comprehensive look at cryonics on film to date. The film retells some of the most controversial events in the history of cryonics through the lens of Kim Suozzi, a 23 year old who died of brain cancer after fighting to raise the funds for her cryopreservation. I was its unwitting and naïve director.

The story of how *Dying To Be Frozen* was made is similar to the story of so many cryonics projects where good intentions were waylaid by inexperience and overconfidence. I made nearly every mistake I could directing and producing this film, and this is the story of how it came to fruition in spite of me.

Background

In the spring of 2011, Kim had been diagnosed with brain cancer. She was a highly intelligent and vibrant young woman and she knew that her diagnosis was likely a death sentence. Over the next two years she set off on a journey that would eventually lead her to where she is today: in 'suspension,' floating in liquid nitrogen at Alcor.

She embraced cryonics as a means to possibly extend her shortened life and have some hope for the future. The cryonics community would return that embrace and help her fulfill her last wishes. I believe she faced her death with bravery but sought cryonics with the pragmatism of someone with nothing left to lose.

But this isn't a story about Kim. You'll have to watch the film to see her journey retold along with the history and controversies that make cryonics so fascinating. This is the story of how I set off to tell that story with little experience, scant resources and the blind self-assurance that ensured I'd recognize neither.

A Tragic Beginning

One morning in January of 2013 I received a call from Bill Faloon of the Life Extension Foundation.

Kim Suozzi was in hospice care and would likely die within days if not hours. The Life Extension Foundation was looking for a producer in the area to help capture her story before it was too late. I had a wealth of experience as an interviewer and that's all I thought this would take. Neither Bill nor I could imagine that this would eventually become a feature length documentary. All I expected was what Bill had asked for, a way to capture some of Kim's last words for posterity.

That afternoon I arrived at Kim's hospice and met her friends, family, and Josh Schisler, her boyfriend and caregiver. I knew that this was going to be difficult as I set out to convince as many of them as possible to step away from her bedside to give an interview in the coming hours. They had all been living her journey for the last two years and here I was, a complete stranger stepping in to ask for immediate trust at their most vulnerable moment.

And perhaps that was my first mistake…

The next day, my crew and I had the bittersweet task of filming Kim's last interview and the last wishes and thoughts of her family and friends who had gathered to see her off. A week later she succumbed to her illness and was transported to Alcor to have her head cryopreserved.

A Larger Story to tell

After that series of interviews, I waited for a week or two as the first word of her death, then cryopreservation procedure, came. Bill Faloon had asked me to do some additional interviews with those involved in her procedure and other prominent cryonicists with thoughts on her case but we waited as the family grieved and the cryonicists involved recovered from the long standby. As I waited I began to think about what a huge story this really was.

All I saw was the opportunity to tell a wider story on this fascinating topic. I couldn't find any feature length documentaries

on cryonics at the time which should have given me a clue but didn't. Obviously there would be interest and how hard could it be? Kim's story was a great way to explore this controversial topic in a hopeful yet tragic way.

At the time, I had no idea that almost all of the most prominent voices in cryonics and their opponents had long ago grown tired of the controversies. After decades of people seeking to exploit what are deeply personal stories about death, most of the people I needed to help tell this story were either dead or uninterested. But it would take many months and years for me to come to that realization.

So it was with no reservations, and a healthy dose of misplaced optimism, that I reached back out to Bill to ask for his help in turning Kim's story into the comprehensive cryonics documentary that it would become.

Doors Open, Doors Close

Bill and the Life Extension Foundation (LEF) helped me to secure interviews with prominent cryonicists. I interviewed Max More and filmed a tour of Alcor. I went to southern California and interviewed Dr. Steven Harris who was instrumental in cryonics research in the '80s and '90s and a player in some of the controversial events of the past. I filmed an interview and tour with Dr. Greg Fahy whose biomedical research facility was being supported by LEF and whose work in organ preservation was being applied to cryonics practices.

The first few months of work trying to weave Kim's story into a larger narrative were optimistic. I wanted secure interviews with some of the historically prominent voices from the cryonics community, but I knew that a balanced approach was the only way to tell the story with credibility. I set out to find whoever could speak with authority against the practice of cryonics and that's where I got my first sense of how hard telling this story would be.

I knew from stories I had found in old cryonics publications, that the Society for Cryobiology was likely the best source of dissent on the subject. Several members of the Society had spoken out vociferously against cryonics throughout the '90s.

I tried to get Art Rowe to speak first. He was a previous president of the Society and had made a famous quote comparing cryonics to trying to turn hamburger back into a cow. I thought he would be the perfect counter-viewpoint. Calls and emails were not returned.

I reached out to Steve Novella who is a Yale Neurology professor and ostensible head of the modern Skeptics movement. I had heard him debating the existence of God on NPR and decided that he might make a great skeptical voice in the film. He was interested and came with a bonus: his brother, a software developer and skeptic in his own right, was signed up with Alcor. I traveled to Connecticut to interview them and they turned out to be fantastic.

I still didn't have a strong dissenting voice though. Steve turned out to be more pragmatic about it and Jay was a passionate proponent who mixed his responses with jokes and empathy. Good material but not what the film needed to create drama. I turned back to the history where I knew there would surely be drama.

The History Unfolds

It was now mid-2014. Things were moving slowly mostly due to my inexperience in stitching so many different story elements together into something comprehensive.

I was struggling to marry Kim Suozzi's story to cryonics in general in the edit. That's when I realized that Kim must have done the same research that I was doing and likely came across the same controversies. I knew that I could recreate that by just turning the camera onto a Google search. This was a way to weave in the fractured artifacts of cryonics past with modern cryonics and Kim's story.

I started by spending a day at David Pizer's ranch where at the time he maintained a huge collection of cryonics documents. His collection contained nearly every publication in cryonics history along with most of the print media accounts of various cryonics activities from inception through the nineties and beyond. I already knew about Bob Nelson's exploits and the Dora Kent case and this gave me a treasure trove of materials to tell those stories.

I had narrowed my scope to three events or time periods: Bob Nelson's time as president of the Cryonics Society of California, The Dora Kent case, and the 'Cold War' between cryonicists and cryobiologists that took place largely in the 1990s. I spent the next two years chasing the people involved with these periods, begging them to speak on camera with varying success.

Bob Nelson was easy to get on camera. He was always happy to speak and I was able to track him down at a cryonics conference. Bob had performed the first cryopreservation on Dr. Bedford but finances and fantasy quickly became intertwined and most of his patients were allowed to thaw in a vault in the Chatsworth cemetery in California. Dr. Bedford, however, was protected from these early calamities and is cryopreserved at Alcor as part of Alcor's charitable mission.

Most of the people involved with Bob and his exploits had already passed, so I relied on his story and the news accounts of the time to create the drama. I was also able to convince Linda Chamberlain, a co-founder of Alcor, to speak about what she knew of those early days and the failures.

Next, I turned to the Dora Kent case, in which a number of cryonicists were arrested for performing a cryopreservation.

Dora's cryonicist son, Saul Kent, was unwilling to go on camera, having given so many filmed accounts over the years, but he was willing to give me his perspective by phone. He told me about going on the Larry King show during that time which I thought might make a nice stand-in along with footage of the interviews.

My attempts to get any other cryonicists involved in the Dora Kent Case to go on camera were futile. Mike Darwin was uninterested. Steven Harris had already given me an interview on cryonics and didn't want to delve into this incident. Most of the rest involved were either minor players or had died. This was the most important story in cryonics history; the incident that largely put cryonics on the map and actually helped to grow Alcor's membership, but all those involved had long ago grown tired of talking about it.

With so many of the players in that drama unwilling or unable to go on camera I rolled the dice and reached out to Larry King himself. I had a friend who had produced a doc that featured Larry, so I was able to get to his contact info and he agreed to give an interview covering both the Dora Kent case and his own cryopreservation wishes. He turned out to be a great addition. He talked about his recollection of interviewing Saul and the few details that he remembered.

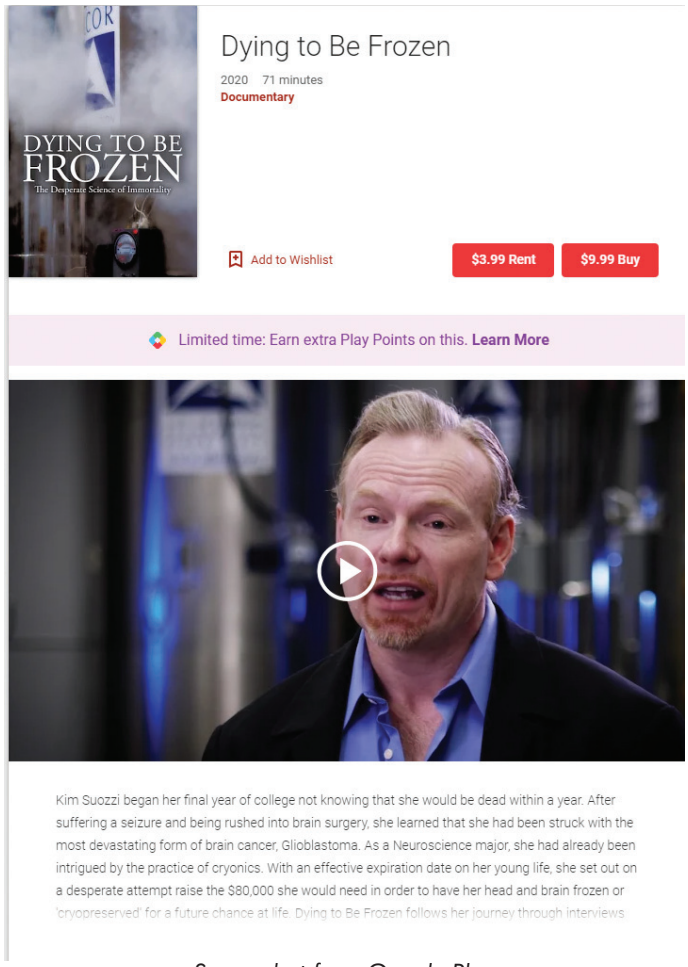
Next I tried to find someone from the Coroner's office and came across Alan Kunzman. He had been a deputy corner and one of the first to arrive on the scene. Some years later he had written a rather scathing account titled *Mothermelters*. He agreed to give his side of the story and I secured an embalming room at a mortuary near his home to film the interview in.

Finally, I turned to the tumultuous relationship between cryonicists and cryobiologists in what was first dubbed "The Cold War" in this publication nearly three decades ago. Cryonicists had made inroads into the Society For Cryobiology throughout the '70s and '80s. However, after decades of bad press, unfortunate incidents, and charlatans delving into cryonics, it seems the Society came to view the entire practice as quackery.

Jason Acker was one of the few Society for Cryobiology officers who agreed to even speak with me about the film. At the time he was the president elect of the Society and would become the president shortly. After some conversations, he agreed to an interview and I flew to his lab in Canada to film him – at the time it felt like a coup. His interview turned out to be exactly what I needed. While he wasn't vitriolic as Art Rowe had been, he made no qualms about sharing his views on cryonics as being desperate and misguided at best.

Bringing it all together

By 2017 I finally had all the interviews I needed but the film was still missing something to make the material more accessible. Around this time I had a conversation with Bill Faloon who asked me why I thought cryonics was so fascinating to the public, yet still a tiny niche. I didn't have a good answer but he had made me start to think about all the various accounts of resurrection and cryonics on film and how that might give the film some much needed punch. I hired an archival consultant and we searched out clips from *Frankenstein* to *Star Trek* and everything in between.



Screenshot from Google Play

Bringing that material into the edit made the film more accessible. But it also complicated things. Now I had to get legal clearances on everything I used, signed off on by a fair use legal expert, in what is called a "Fair Use Opinion Letter." That process would become a drawn out negotiation that lasted nearly a year. I can't tell you how frustrating it became to be negotiating with someone you are paying by the hour. Eventually, after a few concessions I received the legal blessing and had what I needed to release the film.

Distribution Nightmare(s)

It turns out that making a film is much easier than getting it released. It would take another year and a half and bring us to

where I am as I write this: two days before publication of this article with one platform still in limbo.

The biggest mistake I made was only thinking about the film through the process and not the marketing of it, which, in many respects, is much more important.

When the film was complete I reached out to a few friends with distribution connections but the distributors they knew declined to view the film. The film industry has changed significantly in the last decade. As the larger studios consolidated, smaller distributors were swallowed up or folded leaving only aggregators to fill the gap. I spent months emailing trailers and screener links to the remaining distributors but not a single link was opened.

After spending nearly five years making this film I was done. I was sick of knocking on doors that didn't want to be opened and knew that we just had to release it. In mid-2019 I sent the film to Distribber, the largest aggregator with the most films accepted by the major platforms. Even though going with an aggregator meant that I wouldn't have any marketing support, I thought coinciding the release with a festival screening and some interest from the cryonics community would be enough.

The film sat at Distribber for three months until I and thousands of other filmmakers found out in October 2019 that Distribber had gone bankrupt. Next I turned to a smaller aggregator who accepted the film after about a month only to tell me they had lost their iTunes partnership. Finally I found Quivver, one of the last remaining reputable aggregators. They accepted the film and started processing it for release.

Around this time I had received news that the film was accepted into the Arizona Film Festival and would premiere there just a month before Quivver was slated to release on all platforms. This was great news. While we hadn't found a traditional distributor willing to consider the film, now I had a release date on iTunes, Amazon and Google just after our festival premiere in March 2020.

Then some bats started coughing in China and soon the whole world was coughing. The festival was cancelled. Quivver pushed release windows out 90 days and started taking a week to respond to any emails (when they responded at all).

The film was finally released in September for rental on iTunes. Amazon released the film through Prime video shortly after but as I write this, Google and Quivver are still pointing fingers at each other but assure me the film will be available shortly.

I could have pushed this article off until the film was released on all platforms but I think telling the story now, and hopefully putting an end to its futility, will be a poignant ending to this chapter in my life, and in the life of this film. Perhaps it will find an audience on its own. Perhaps Kim and all the patients at Alcor will be revived someday. Perhaps, perhaps, perhaps. ■

To view the film:

Amazon Prime: https://amzn.to/35SUBCK

iTunes on Apple Devices: https://apple.co/3kNS6Ig

Google Play: https://play.google.com/store/movies/details/Dying_to_Be_Frozen?id=6WnKdRK3E4s.P

ABOUT THE AUTHOR

Jake McCurdy is a freelance commercial producer based out of Chandler Arizona. He can be contacted through his company at www.cinemastersind.com. He can make 20 minute brownies in 9.5 minutes, write a call to action for anything immediately on demand and above all, he's humble. He also wrote this... in the third person.

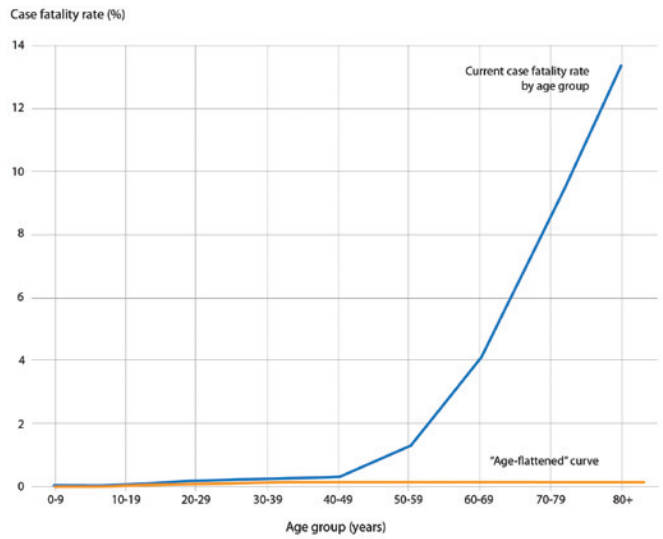
Why is the novel coronavirus so deadly to the elderly?

By the SENS Research Foundation

A pandemic has swept the globe, leaving more than a million dead. In response, many wait in isolation, while health workers face the disease head-on in our hospitals, fighting to save patients from "drowning on dry land."

All wait in anticipation for the scientists, who labor at a pace that is both record-breakingly rapid yet frustratingly slow to bring us a way out: a drug, a vaccine — a hope.

Through all the updates on the sick and the dead, on testing and public health guidance, there remains one constant: by far the greatest predictor of death from this plague is ***age***. The so-called comorbidities predisposing patients to death from COVID-19 — chronic lung diseases, damaged kidneys and hearts, high blood pressure, diabetes — are themselves aspects of aging, erupting in their distinctive ways in particular tissues. Flattening this "demographic curve" of degenerative aging would reduce COVID-19 to a disease similar in impact to an average recent flu season (and make future flu seasons less deadly), while also putting an end to the staggering toll of age-related death and debility that ticks on in the background even now, day in and day out, pandemic or none.

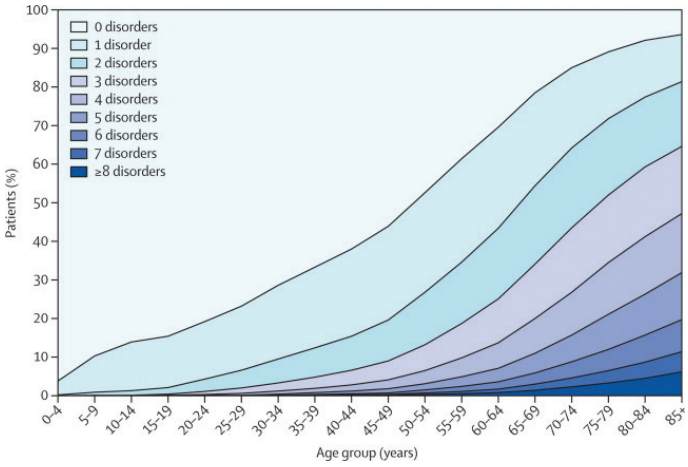


Aging's effect on COVID-19 mortality rate, and the anticipated effects of future rejuvenation biotechnologies. Data taken from Lancet Infect Dis 2020 Mar 30. pii: S1473-3099(20)30243-7

Ending that toll is our mission. At SENS Research Foundation (SRF), we develop rejuvenation biotechnologies: new therapies that will repair the accumulated cellular and molecular damage in our tissues and restore youthful function.

The SARS-CoV-2 pandemic is both an immediate, pressing danger, and a call to action. It demonstrates the critical need for better long-term strategies for addressing threats to human life. As members of the global scientific community, all of us at SRF acknowledge the need to adapt and apply our expertise and experience to the current crisis. *(SARS-CoV-2 is the coronavirus that causes the disease called SARS-2 or COVID-19.)*

Below, we outline some of the ways in which specific forms of aging damage are relevant to diseases like COVID-19 – and how some of our research programs may help render this and other viruses far less dangerous in the future.



Comorbidity by age group. Image credit: Lancet 380(9836):37-43.

Rejuvenate the Immune System

The most obvious link between aging and COVID-19 is the aging of the immune system, or immunosenescence. Older people mount a much weaker and less complete immune response to both infection and vaccine, even as they suffer increasingly from overactive parts of the immune response, including autoimmunity and chronic inflammation.

A key part of the aging of the immune system is the loss of naïve T-cells, due to a combination of waning production by the aging thymus and damage to the lymph nodes such that they are no longer able to keep them alive and functional so that they are ready for future threats. Scientists have now discovered that pre-existing T-cell populations that were originally raised to fight the coronaviruses that cause the common cold appear to offer some protection against SARS-CoV-2; and diverse, strong, and early T-cell responses appear to be critical to successfully fighting off the virus — whereas, surprisingly, antibody levels did not in a study where the two were evaluated together. SENS Research Foundation has sponsored several projects aimed at developing damage-repair technologies to restore aging T-cell numbers and function, including pilot studies of a T-cell scrubber that might clear out a specific class of dysfunctional T-cells and early-stage work toward a tissue-engineered thymus, along with a pilot animal study to simulate the effects of both of these interventions.

In today's pandemic, COVID-19 patients suffer from an exhaustion of *natural killer (NK)* and *CD8+ ("killer") T-cells*. Whereas T-cells and B-cells are specialists, focused on eliminating specifically-identified threats (such as cells infected with specific viruses), NK cells are sentinels patrolling the perimeter of a military camp, on the lookout for anything that looks like it doesn't belong. Thus, NK cells attack abnormal cell types such as cancer cells, cells infected by viruses like SARS-CoV-2, and senescent cells — that is, cells that have undergone changes that prevent them from replicating, and that spew out a witches' brew of inflammatory signaling molecules, growth factors, and enzymes that break down proteins. This brew is called the senescence-associated secretory phenotype, or SASP.

Long before the pandemic hit, we knew that NK cells lose much of their effectiveness with age, meaning that aging people already come into the fight against infections like SARS-CoV-2 with these critical early responders weakened. At our Research Center, Dr. Amit Sharma and Elena Fulton have been developing strategies to rejuvenate and reinforce NK cells in aging people. They recently collected preliminary data showing that the proportion of NK cells exhibiting markers of strong cell-killing ability declines sharply with age. To confirm this preliminary finding, they will look for an age-related reduction in NK cells' ability to kill senescent cells, using NK cells freshly isolated from young adult, middle-aged, and older people. They will run parallel tests on NK cells from the spleens of young (6 months) and old (24 months) mice. Moving from basic research to anti-aging intervention, the team is developing strategies to enhance senescent-cell-killing ability in old NK cells. They will test rejuvenation strategies including adoptive transfer of young NK cells into aging mice, and agents that sidestep the protective shielding that senescent cells throw up to defend themselves against NK cells.

If transferring young NK cells works as a proof of concept, it would support moving forward by adapting immune transfer biotechnologies already in use for cancer therapies to instead selectively target senescent cells. In CAR-T cell therapy for some cancers, a patient's T-cells are drawn out with the blood, expanded in number, and engineered to express artificial CAR receptors. These receptors specifically target proteins found on the surface of the cancer cells, and the T-cells can also still attack cancer cells that are no longer displaying markers that T-cells normally need to identify and attack. These CAR-T cells are then re-infused into the patient to attack the cancer aggressively.

Recently, CAR-T cells were engineered to target senescent cells, zeroing in on a receptor that scientists tentatively identified as commonly displayed by them. At the same time, CAR engineering of cancer patient cells has been used with NK cells. This CAR-NK cell technology is very new, but has already revolutionized immunotherapy for some cancers at MD Anderson and elsewhere, and thirteen clinical trials are underway in other cancers, including some against which CAR-T therapy has not (or has not yet) proven effective. And NK cells — not T-cells — are the natural immunological enemies of senescent cells. So by combining NK cells' intrinsic senescent cell-stalking abilities with CAR receptors laser-focused on markers displayed on the senescent cell surface, the SRF team expects to generate a remarkable chimeric predator specialized in eliminating these cells.

Purge Senescent Cells

For Younger Lungs...

Some of the rejuvenation strategies being tested by Elena and Dr. Sharma will likely enhance aging NK cells' ability to eliminate any kind of abnormal cell, including those infected by SARS-CoV-2. But the SENS lab is focused on rejuvenating the capacity of NK cells to eliminate senescent cells because of their broad role in driving aging pathology, and it's not a coincidence that many of their ill effects directly impact a person's vulnerability to COVID-19.

First is senescent cells' role in driving fibrosis in our tissues. Multiple aspects of lung function decline with age, while fibrosis increases. Accordingly, diseases of the lung — including chronic obstructive pulmonary disease, lung cancer, and most especially idiopathic pulmonary fibrosis (IPF) — are profoundly age-related. Preliminary evidence suggests that the lung is one of the organs most burdened with senescent cells in aging in humans — a burden further exacerbated by IPF.

We've known for a while that the age-related loss of lung function is a massive driver of risk of death from pneumonia. Aging people not only have fewer functional alveoli available, but progressively lose the ability to inhale and exhale deeply to compensate for alveoli taken offline by the infection. Continuing research suggests that eliminating senescent cells in the lung may preserve and restore youthful lung function, leaving the

lungs better prepared to endure the attack of the SARS-CoV-2 virus and other causes of pneumonia.

Senolytic drugs, which selectively kill senescent cells, have been shown to reverse lung fibrosis and other tissue fibrosis in aging mice. Studies in aging mice with inbuilt "suicide genes" demonstrate that ablating senescent cells in aging mice restores youthful lung compliance, suggesting an opportunity to do the same with other senescent-cell elimination strategies, such as restoring the ability of NK cells to eliminate them from tissues. Further supporting this, lung fibrosis is partially reversed by two different senolytic drugs in mouse models of IPF, and a third senolytic partially reversed lung fibrosis in mice whose lungs have suffered radiation damage.

... and a Rejuvenated Signaling Environment...

In addition to lung damage, another way that senescent cells may exacerbate COVID-19 involves the SASP cocktail of inflammatory factors and proteins that degrade the network of proteins that support the organs in which they're embedded. Some researchers have argued that inflammatory factors in the SASP may also suppress the immune response to the virus underlying COVID-19 (SARS-CoV-2). This hypothesis is based on a number of previous studies showing that chronic inflammation caused by numerous different conditions interferes with the immune response to multiple other viruses, including blunting the immune system's response to vaccines against influenza, yellow fever, and hepatitis B. Moreover, inflammation driven by macrophages in the lesions of patients with atherosclerosis suppresses the activation of T-cells, and this is associated with the failure of T-cells from these patients to mount an effective T-cell response against the virus that causes chickenpox in children and shingles (herpes zoster) in older adults. In one study, damping down the release of inflammatory factors in the skin before administering a shingles vaccine virus boosted the T-cell response to the vaccine.

Inflammation is complicated, however: *acute* inflammatory responses to injury or infection are essential to wound repair and successful immune response, respectively, whereas the *chronic* inflammation of aging impairs both, drowning out the local ramp-up when immune cells are actually needed and instead dispersing those cells all over the body to sites riddled with aging damage, futilely trying to repair microscopic injuries they cannot resolve. This is why drugs and antibody therapies that simply force down the inflammatory response lead to vulnerability to infection.

The solution here is not to attack the inflammation, but to remove and repair the underlying damage of aging, thereby eliminating the source of chronic inflammatory stimulus while freeing up the rejuvenated tissues' ability to mount an effective inflammatory response to acute threats.

A surprising example of this has emerged in the context of aging and COVID-19. As a result of the pandemic, people worldwide have become familiar with the "cytokine storm" — a severe inflammatory response that leads to immune derangement and the deadly acute respiratory distress syndrome (ARDS) that directly kills so many COVID patients. Cytokine storms are also involved in many other viral fatalities, and the fact that young people can mount aggressive cytokine storms is thought by many scientists to be the reason why so many middle-aged people were killed by the 1918 influenza epidemic, which normally stalks the elderly and extremely young infants and children while leaving middle-aged people alone.

But there's a wrinkle on cytokine storms and aging in COVID-19. Chinese researchers have found that a *delayed* immune response to the virus, as much as the strength of it, predicts death from COVID-19, accompanied by higher levels of inflammatory factors at death and depleted levels of multiple immune cell types. A study in aging monkeys suggests reasons why. The researchers found *young* monkeys infected with SARS-CoV-2 quickly mounted a savage immune response, complete with extensive attack of macrophages and T-cells and high levels of inflammatory factors within the first week of infection, but were quickly able to recover after that. By contrast, the immune response was *delayed* in old monkeys — and this seemed to have cost them. Having gotten started late, the old animals' immune systems seem to have attempted to make up for lost time, mounting a more severe cytokine storm that recruited even higher levels of infiltrating macrophages and drove a more persistent T-cell attack. Yet those aged T-cells were also less effective at actually fighting the virus, making the inflammation and immune cell attack on the tissues purely self-destructive — a story we have seen play too often in our hospitals.

One important component of the SASP is an inflammatory factor called *IL-6*, which rises with age and predicts the risk of frailty and death even without SARS-CoV-2 infection. A report suggests that a hospitalized COVID-19 patient's IL-6 level is a strong risk factor for eventually requiring a ventilator, suggesting that senescent cells make aging people more vulnerable to the disease, and that senescent cell ablation could shore up this vulnerability. These findings are so compelling that some clinical centers treating critically ill COVID-19 patients are making experimental use of monoclonal antibody therapies such as tocilizumab and sarilumab, which block IL-6's access to its receptors. But if we restore NK cells' ability to eliminate senescent cells, people infected with SARS-CoV-2 would start off with lower IL-6 levels more characteristic of a young person, and thus better prepared for the fight.

In addition to IL-6, it's recently been discovered that there is a network of factors emitted in the SASP that trigger the formation of blood clots and impede the countervailing factors that dissolve them. It's long been known that an imbalance in these factors becomes increasingly common as people age, especially if they

have risk factors for cardiovascular disease. The discovery that the SASP could tip the balance toward excessive coagulability, combined with the fact that aging people's tissues become increasingly riddled with senescent cells over time, suggests that senescent cells and their SASP may be a key driver of this process.

Senescent cells' possible culpability in the pro-clotting bias in aging people's blood was already an important avenue for research before the rise of COVID-19, since the excessive tendency to form and maintain clots puts them at greater risk of heart attack, stroke, and venous thromboembolism (VTE) — abnormal clots forming in the veins. But it becomes a matter of acute focus in the face of multiple reports that high levels of markers of excessive clotting are common in COVID-19 patients at hospitalization, and foreshadow admission to the ICU and death from or with COVID-19 (in Holland and in Wuhan). Indeed, despite receiving prophylactic anti-clotting medication, nearly a third of Dutch patients with COVID-19 suffered from dangerous blood clots, including very commonly VTE that work their way up to cut off the lung tissue's own blood supply, starving the lung itself of oxygen even as it is under attack by the virus and the patient's own immune system.

Medical researchers have suggested a number of possible causes of excessive clotting specific to COVID-19, but as usual, the role of *aging itself* has been almost entirely ignored, despite the powerful influence of age in one's risk of dying of the disease. Older people's burden of senescent cells, the recent research suggests, may be predisposing them to a clotting crisis if infected by SARS-CoV-2.

Fortunately, the same research that originally identified the pro-clotting cocktail in the SASP also suggests that rejuvenation biotechnology could eliminate the associated risk of dangerous blood clots. Mice, like people, suffer a rise in senescent cell burden when given the chemotherapy drug *doxorubicin*, and the cells release SASP factors that favor the formation and stability of blood clots. In response, the mice produce higher levels of clot-initiating platelets, and those platelets are placed on a hair trigger. Activating a senescent-cell-destroying suicide gene prevented all of these things from happening, suggesting that purging aging cells from aging people could also leave them better prepared to survive an infection with SARS-CoV-2. Conversely, researchers at the Mayo Clinic have discovered that proteins from the SARS-CoV-2 virus exacerbate the SASP in human senescent cells, creating a vicious cycle of inflammation consistent with the ravages of the virus in older people.

***... and Now in Human Trial*s**

Work is already underway to translate these exciting results into human rejuvenation therapies. Mayo Clinic researchers last year conducted a very early-stage clinical trial of drugs that trigger self-destruction of senescent cells in human patients with IPF. Although there were few clearly apparent benefits to senolytic therapy in this study, it was too short-term and involved too few patients (just 14) to expect anything obvious: happily, the researchers are working to expand this pilot study into a larger clinical trial, and other such trials are underway in patients with kidney disease and osteoarthritis, diseases also driven by senescent cells. We will soon begin seeing what these therapies can do to maintain our health and resilience against the forces of degenerative aging and COVID-19.

In fact, there's now proof-of-concept evidence that eliminating senescent cells can protect the body against mouse beta-coronavirus — the same subgroup of coronaviruses to which SARS-CoV-2 belongs. Mayo Clinic scientists recently found that administering a senolytic agent allows mice to survive infection with mouse beta-coronavirus. The evidence is so compelling — and the intensity of the pandemic so threatening — that the FDA has green-lit them to initiate a clinical trial of a senolytic for older people hospitalized with COVID-19, aiming to keep them from drowning in the abnormal age-related cytokine storm.

Trigger Self-Destruction of Mutation-Prone Cells

More than half of the human genome is invasive genetic data left behind by viruses, including millions of *retrotransposons*. Retrotransposons are "dead" DNA, but their long- and short-interspersed virus-like repetitive elements (LINEs and SINEs) encode machinery that —under certain circumstances — allows them to reactivate, replicate, and spread through the genome. These reactivation events can cause mutations in our functional genes and even disrupt the normal expression of non-mutated genes, leading to cancer, cellular self-destruction (apoptosis), and cellular senescence.

To develop a proof of concept for a new class of "retrolytic" drugs that would ablate these cells before they can further damage the body, SENS Research Foundation is sponsoring work by Dr. Andrei Gudkov and his team at the Roswell Park Comprehensive Cancer Center for a suicide-gene system similar to the groundbreaking INK-ATTAC system that paved the way for the senolytic revolution. As a side-benefit, the gene whose expression will activate the retrolytic suicide gene is also activated in cells with active viral infection (such as SARS-CoV-2), which may eliminate such cells before they are hijacked by the virus to replicate itself.

Transplant Mitochondria to Rescue Critical Lung Cells

Recent gene-expression and protein distribution studies demonstrate that the ACE2 receptor — the critical loophole through which the SARS-CoV-2 virus slips into our cells — is more enriched in a type of lung cell known as *AT2 cells*, and COVID-19 patient autopsy reports indicate that these cells are subject to a terrible assault during the disease. AT2 cells are

critical support cells for type I alveoli — the tiny air sacs that expand and contract to effect gas exchange and respiration. AT2 cells produce the pulmonary surfactant that allows type I alveoli to expand again after contraction by reducing alveolar surface tension. This surfactant also facilitates the exchange of gases between the oxygen-poor, CO_2-enriched venous blood and the relatively oxygen-rich air in the lungs; we believe the virus's assault on these cells is a major contributor to respiratory failure.

It's these same AT2 cells that fail in an animal model of septic pneumonia, and these mice are rescued by transplanting bone marrow stem cells that donate their mitochondria to the failing AT2. Dr. Amutha Boominathan and Nana Anti of our mitochondrial mutation rescue team have been developing our mitochondrial transplantation protocol. Their initial target is different, but we hope it will treat many conditions of acute energy depletion, as is already being done in small open clinical trials for babies with heart damage from ischemia-reperfusion injury.

A New Generation of SENS Scientists in a New Model System

Over the summer, SRF partnered with Dr. Evan Snyder at the Sanford Consortium for Regenerative Medicine to learn more about COVID-19. Under the expert mentorship of the Snyder lab, six SRF Summer Scholars successfully established innovative lung and brain organoid models as well as a lung epithelium model to uncover how SARS-CoV-2 infects these organs, investigate drugs that might treat or ameliorate the disease, and look for clues about what makes aging people more vulnerable. These models contain blood vessels, since abnormal clotting and damage to blood vessels are critical vulnerabilities in COVID-19. The lung epithelial model also offers the potential to identify age-related or virus-induced damage to specialized lung cells' ability to produce the critical surfactant needed to keep lung air sacs functional. Our Scholars demonstrated that these systems could be infected with the virus and that they could use them to test drugs that might thwart that infection and to profile aspects of COVID-19 that might make the elderly so vulnerable (including increased inflammation, compromised vasculature, loss of critical lung proteins, and aging brain cells). These studies establish systems that may accelerate progress toward novel therapies against COVID-19 and against lung and brain aging.

Conclusion

Like the pandemic, aging touches all of us. It creeps silently through our tissues, progressively crippling our minds and bodies, and eventually killing us if we don't die first of accident, violence, or other abrupt age-independent causes. In COVID-19, the damage caused by aging is the largest factor in determining who lives and who dies, even if the trigger was pulled by a virus spread by globalization. The need for rejuvenation biotechnologies as part of medicine has never been clearer, and so we strengthen our resolve. Restoring our cells and tissues to youthful vigor will allow us to step out of our ancient lockdown and into a bright future. ■

The 2019 World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease

By Ben Best

Background

Insulin is the primary hormone causing the storage of energy as fat and glycogen. Blood sugar (glucose) rises after eating carbohydrates, causing insulin to be released from the pancreas. Insulin stimulates the formation of fat in fat tissue, while inhibiting the breakdown of fat. In the liver, insulin causes glucose to be stored as **glycogen**, while inhibiting the breakdown of glycogen already stored in the liver. Insulin facilitates the entry of glucose into muscle cells.

In obesity, the capacity of fat cells to store fat is exceeded, causing excess fat to be released into the bloodstream.[1] The excess fat enters muscle and liver, causing those organs to become resistant to the effects of insulin (**insulin resistant**).[1] Because fat storage capacity has been exceeded, fat tissue becomes inflamed, which worsens insulin resistance.[1]

In insulin resistance muscle cells require more insulin for the uptake of glucose. The pancreas compensates by secreting more insulin. In the liver, insulin resistance increases the synthesis of fat from glucose,[2] but insulin fails to suppress the release of glucose from glycogen.[3] Insulin resistance therefore results in excessively high blood levels of glucose, insulin, and fat. The excess fat not only worsens insulin resistance, but causes fatty liver (non-alcoholic fatty liver disease, NAFLD), and impairs the ability of beta cells in the pancreas to produce insulin, eventually leading to type 2 diabetes.[4]

This report is based primarily on presentations made at the 2019 World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease.

Therapies for Non-Alcoholic Fatty Liver Disease

Arun Sanyal, MD

Arun Sanyal, MD (Professor of Medicine, Virginia Commonwealth University, Richmond) is interested in finding treatments for **Non-Alcoholic Fatty Liver Disease (NAFLD)**. Approximately one-quarter of the population has NAFLD, more than ten times as many people as have fatty liver disease due to alcoholism.[5] Both forms of fatty liver disease can lead to fibrotic scarring of the liver (cirrhosis).[5] The main cause of NAFLD is obesity,[5] although in most cases there are no obvious symptoms of NAFLD.[6] Patients with NAFLD typically consume three times more fructose than average, causing the liver to manufacture more fat,[7] possibly because fructose cannot be stored as glycogen.

There are no approved drug therapies for NAFLD, although pioglitazone[8] and liraglutide[9] have shown promise. Weight loss is the therapy that has the most proven benefit for NAFLD,[10] although most patients are unable to exercise or diet sufficiently to lose weight. Dr. Sanyal cited a study in which patients achieved significant weight loss by consuming an oral hydrogel.[11] Probiotics have been shown to be of benefit in treating NAFLD.[12]

SGLT2 Inhibitors for Type 2 Diabetes

Volker Vallon, MD

Volker Vallon, MD (Professor of Medicine, University of California San Diego) is interested in the treatment of diabetic kidney disease. Almost 40% of persons with diabetes develop kidney disease in their lifetime.[13] **Sodium GLucose coTransporters (SGLTs)** are transport proteins in the kidney that reabsorb nearly all of the filtered glucose.[14] SGLT2 reabsorbs most of the glucose, whereas SGLT1 reabsorbs most of the remaining glucose that has not been reabsorbed by SGLT2.[15] Drugs inhibiting kidney glucose reabsorption target SGLT2, not only because this SGLT reabsorbs most of the glucose, but because it also reabsorbs sodium and uric acid.[15]

The high blood sugar associated with diabetes causes the size of the kidney to increase in order to increase glucose reabsorption.[15] Glycation, inflammation, free radicals, and blood vessel injury, all contribute to kidney damage in diabetes.[16]

Patients treated with SGLT2 inhibitors not only benefit from reduced blood glucose, but the elimination of calories in the form of glucose in the urine is associated with a 5 to 10 pound weight loss.[13] And the increased loss of sodium results in reduced blood pressure.[13] Cardiovascular disease is also decreased.[13] The main side effects of SGLT2 inhibitors are an increase in genital and urinary tract infections associated with the increased glucose in the urine.[14]

Fat Cell Size and Insulin Resistance

Tracey McLaughlin, MD

Tracey McLaughlin, MD (Professor of Medicine, Stanford University, Stanford, California) is interested in the relationship between diet, fat cell size, and type 2 diabetes. With obesity, increased fat mass can be either due to more numerous small fat cells, or due to increased size of fat cells.[17] When fat cells become too large, they have less access to blood circulation,[18] becoming more vulnerable to dying in a way that results in inflammation.[19] Overweight adults can lose weight on either a low fat or a low carbohydrate diet.[20] Dr. McLaughlin has shown, however, that with weight loss insulin sensitivity increases in proportion to reduced fat cells size, rather than in proportion to reduced body weight.[21] Dr. McLaughlin suggests that a low carbohydrate diet will increase insulin sensitivity more than a low fat diet because the higher insulin levels on the low fat (high non-fiber carbohydrate) diet will increase fat cell size.

Restriction of Non-Fiber Carbohydrates for Type 2 Diabetes

Sarah J. Hallberg, DO, MS

Sarah J. Hallberg, DO, MS (Medical Director, Indiana University Health, West Lafayette, Indiana) has been involved in clinical trials on type 2 diabetes comparing low (non-fiber) carbohydrate with low fat diets. Overweight subjects on a 12-week low carbohydrate diet have shown a 50% drop in plasma insulin and a 12% drop in plasma glucose.[22] A 2-year trial of type 2 diabetics randomized to either a low carbohydrate diet or a low fat, high carbohydrate, low glycemic index diet, showed comparable reductions in weight, glycated hemoglobin (HbA1c) and blood pressure, but the low carbohydrate group showed greater reduction in blood glucose and less required use of anti-diabetic medications.[23] Dr. Hallberg showed similar medication reduction use in a 1-year low carbohydrate clinical trial she ran on type 2 diabetics.[24] In a longer (2-year) clinical trial she participated in, type 2 diabetics were carbohydrate restricted, but otherwise personally supervised to ensure good nutrition. Most of the subjects (53.5%) became non-diabetic as a result of the intervention.[25]

Exercise for Diabetes

Nikolaos Perakakis, MD (Instructor in Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts) has studied exercise therapy in persons with diabetes and metabolic syndrome. For better insulin sensitivity, type 2 diabetics are recommended to get at least 150 minutes of exercise per week, with no more than two days between exercise sessions.[26] For people with metabolic syndrome, aerobic exercise is best for reducing body mass and diastolic blood pressure, whereas the combination of aerobic and resistance exercise is best for reducing waist circumference (abdominal fat) and systolic blood pressure.[27] Despite the benefits of exercise for type 1 diabetes, most type 1 diabetics do not get adequate exercise, at least partially because of their fear of getting blood glucose dangerously low.[28]

Nikolaos Perakakis, MD

Because exercise can be uncomfortable and boring, Dr. Perakakis has sought a chemical treatment that could provide the benefits of exercise. Reducing the levels of the natural protein **follistatin** in mice has been shown to increase insulin sensitivity.[29] Obese patients who have undergone bariatric surgery show a 22%-33% reduction in follistatin associated with improved insulin sensitivity, reduced blood glucose, and reduced HbA1c.[29] Although follistatin reduction has not yet been proven to be a substitute for exercise in humans, Dr. Perakakis thinks more research on follistatin is merited.

Sarcopenia and Type 2 Diabetes

Elena Volpi, MD, PhD

Elena Volpi, MD, PhD (Director of the Sealy Center on Aging, Galveston, Texas) has studied the effect of sarcopenia on cardiovascular disease and death. **Sarcopenia** refers to low levels of muscle strength, muscle quantity and quality, and physical performance.[30] Older adults lose muscle faster if they have type 2 diabetes.[31] Persons with insulin resistance (including type 2 diabetics) have reduced blood flow to muscle, which reduces protein synthesis in muscle.[32] Cardiovascular disease is more common in persons having obesity or metabolic syndrome in combination with sarcopenia than when not combined with sarcopenia.[33] Slow walking speed is an easy and widely used means of determining sarcopenia.[30] Walking speed over a distance of 66 feet was the strongest predictor of heart failure in a 10-year study of death rates in elderly adults.[34] Dr. Volpi has shown that aerobic exercise increases muscle formation,[35] with even greater benefit, for muscles in elderly adults, when aerobic exercise is combined with supplements of essential amino acids.[36]

Hormone Replacement for Menopause and Type 2 Diabetes

Franck Mauvais-Jarvis, MD, PhD (Professor of Medicine, Tulane University, New Orleans, Louisiana) is concerned with the effects of menopause and hormone replacement on metabolic syndrome and type 2 diabetes. Menopause roughly doubles the incidence of metabolic syndrome, and increases the incidence

Franck Mauvais-Jarvis, MD, PhD

of type 2 diabetes by about an additional 50%.[37] Estrogen replacement can reduce accumulation of visceral fat (reducing type 2 diabetes and atherosclerosis), increase insulin sensitivity, reduce the size of fat cells, and protect insulin-producing cells in the pancreas.[38]

The Women's Health Initiative (WHI) study on hormone replacement that ended in 2002 concluded that menopausal hormone replacement increased the risk of coronary heart disease, breast cancer, and stroke.[39] However, the hormones used in the study were urine from pregnant horses (**Premarin**) and synthetic progesterone (**MedroxyProgesterone Acetate**, **MPA**). Dr. Mauvais-Jarvis noted that Premarin contains only 1% 17β-estradiol compared to 7% 17β-estradiol in human estrogen.[40] MPA was responsible for the increased cardiovascular disease in the WHI study.[41] Human levels of 17β-estradiol and natural progesterone should protect against breast cancer.[41] Dr. Mauvais-Jarvis notes that transdermal application of 17β-estradiol results in more natural blood levels of estrogen, avoiding excessive estrogen levels in the liver caused by oral dosing.[40]

Hazards of Statins Greater than Benefits

David Diamond, PhD

David Diamond, PhD (Professor, Department of Psychology, University of South Florida, Tampa) challenges the belief that general lowering of LDL cholesterol prevents cardiovascular disease. He argues that the hazards of statin drugs to lower LDL cholesterol are greater than the claimed benefits. In reviewing studies claiming to establish the benefits of statin drugs, Dr. Diamond says that the benefits are often exaggerated by describing relative risk rather than absolute risk. Lipitor (atorvastatin) advertised a 36% reduction in heart attacks on the basis of a study showing 3% heart attacks in the placebo group compared to 1.9% in the Lipitor group.[42] Dr. Diamond also notes that about one-fourth of those in statin trials drop out, and that the benefit of LDL cholesterol in preventing cancer or infections is ignored.[42,43] Statins increase insulin resistance.[44] Muscular pains upon exercise are frequent with the use of statins, which is why most athletes stop taking statins.[45,46] Small, dense LDL cholesterol particles are easily oxidized and thereby contribute to atherosclerosis, but whether statins reduce small, dense LDL has not been determined.[47] A study of reports on statin trials indicated that authors often had undisclosed ties to pharmaceutical companies.[48]

Treating Diseases due to Oxidized LDL Cholesterol

Matthew O'Conner, PhD

Matthew O'Conner, PhD (Co-Chief Executive Officer, Underdog Pharmaceuticals Mountain View, California) is concerned with the atherosclerosis and other diseases caused by oxidized LDL cholesterol. Unlike unoxidized LDL cholesterol, oxidized LDL cholesterol is pro-inflammatory and readily crosses cell membranes.[49] The **7-ketocholesterol** form of oxidized cholesterol is highly concentrated in atherosclerotic plaques, and can be used as a biomarker for coronary artery disease and cerebrovascular disease (stoke).[50] 7-ketocholesterol can also accumulate in the eye, leading to macular degeneration, and in neurons (as lipofuscin) leading to diseases of the brain.[51,52] The compound 2-hydroxypropyl-β-cyclodextrin was shown in 2016 to remove cholesterol from atherosclerotic plaques.[53] Dr. O'Conner has co-founded a company dedicated to using cyclodextrins to reverse many of the diseases of aging, including atherosclerosis, macular degeneration, and diseases of the brain.

Concluding Remarks

Insulin resistance primarily affects fat, liver, and muscle. Insulin resistance usually begins in fat tissue, where obesity causes fat tissues to become inflamed and to release fat. Fat and inflammatory proteins (cytokines) in the bloodstream then cause insulin resistance in muscle and liver. But the insulin resistance is not uniform.

Insulin resistance in muscle results in higher blood levels of glucose, causing the pancreas to produce more insulin. The resulting high blood levels of insulin cause tissues that remain insulin sensitive to become hyperactive.[54] Insulin overstimulation of SGLT2 reabsorption in the kidney increases blood levels of glucose and sodium, elevating blood pressure.[54,55] The liver becomes insulin resistant to suppression of glucose production (further elevating blood glucose), but remains insulin sensitive to fat formation (elevating blood fat).[56]

Insulin resistance is a much greater risk factor for cardiovascular disease than LDL cholesterol.[57] To the extent that LDL cholesterol may contribute to cardiovascular disease, more attention should be paid to reducing LDL oxidation rather than to simply reducing all LDL. Even passive exposure to tobacco smoke (which increases LDL oxidation[58]) can raise the risk of cardiovascular disease by one-quarter.[59] Claims that statins do not cause muscle symptoms[60,61] are not relevant if statins are a distraction from insulin resistance, inflammation, and oxidation of LDL cholesterol as the primary causes of cardiovascular disease. ■

References

1. Morigny P, Houssier M, Mouisel E, Langin D. Adipocyte lipolysis and insulin resistance. *Biochimie.* 2016;125:259-266.
2. Song Z, Xiaoli AM, Yang F. Regulation and Metabolic Significance of De Novo Lipogenesis in Adipose Tissues. *Nutrients.* 2018;10(10).
3. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev.* 2018;98(4):2133-2223.
4. Saponaro C, Gaggini M, Carli F, Gastaldelli A. The Subtle Balance between Lipolysis and Lipogenesis: A Critical Point in Metabolic Homeostasis. *Nutrients.* 2015;7(11):9453-9474.
5. Younossi Z, Henry L. Contribution of Alcoholic and Nonalcoholic Fatty Liver Disease to the Burden of Liver-Related Morbidity and Mortality. *Gastroenterology.* 2016;150(8):1778-1785.
6. Tran NL, Sitia G. New players in non-alcoholic fatty liver disease induced carcinogenesis: lipid dysregulation impairs liver immune surveillance. *Hepatobiliary Surg Nutr.* 2016;5(6):511-514.
7. Marjot T, Moolla A, Cobbold JF, Hodson L, Tomlinson JW. Nonalcoholic Fatty Liver Disease in Adults: Current Concepts in Etiology, Outcomes, and Management. *Endocr Rev.* 2020;41(1).
8. Cusi K, Orsak B, Bril F, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. *Ann Intern Med.* 2016;165(5):305-315.
9. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* 2016;387(10019):679-690.
10. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology.* 2015;149(2):367-378. e365; quiz e314-365.
11. Greenway FL, Aronne LJ, Raben A, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss. *Obesity (Silver Spring).* 2019;27(2):205-216.
12. Xiao MW, Lin SX, Shen ZH, Luo WW, Wang XY. Systematic Review with Meta-Analysis: The Effects of Probiotics in Nonalcoholic Fatty Liver Disease. *Gastroenterol Res Pract.* 2019;2019:1484598.
13. Bonora BM, Avogaro A, Fadini GP. Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence. *Diabetes Metab Syndr Obes.* 2020;13:161-174.
14. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med.* 2015;66:255-270.
15. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia.* 2017;60(2):215-225.
16. Barrera-Chimal J, Jaisser F. Pathophysiologic mechanisms in diabetic kidney disease: A focus on current and future therapeutic targets. *Diabetes, obesity & metabolism.* 2020;22 Suppl 1:16-31.
17. Hoffstedt J, Arner E, Wahrenberg H, et al. Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. *Diabetologia.* 2010;53(12):2496-2503.
18. Catalan V, Gomez-Ambrosi J, Rodriguez A, Fruhbeck G. Adipose tissue immunity and cancer. *Front Physiol.* 2013;4:275.
19. Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res.* 2005;46(11):2347-2355.
20. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. *Jama.* 2018;319(7):667-679.
21. McLaughlin T, Abbasi F, Lamendola C, Yee G, Carter S, Cushman SW. Dietary weight loss in insulin-resistant non-obese humans: Metabolic benefits and relationship to adipose cell size. *Nutr Metab Cardiovasc Dis.* 2019;29(1):62-68.
22. Volek JS, Phinney SD, Forsythe CE, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids.* 2009;44(4):297-309.
23. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes, obesity & metabolism.* 2018;20(4):858-871.
24. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-

Label, Non-Randomized, Controlled Study. *Diabetes Ther.* 2018;9(2):583-612.

25. Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-randomized Clinical Trial. *Front Endocrinol (Lausanne).* 2019;10:348.
26. Colberg SR, Sigal RJ, Yardley JE, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care.* 2016;39(11):2065-2079.
27. Ostman C, Smart NA, Morcos D, Duller A, Ridley W, Jewiss D. The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2017;16(1):110.
28. Ostman C, Jewiss D, King N, Smart NA. Clinical outcomes to exercise training in type 1 diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2018;139:380-391.
29. Perakakis N, Kokkinos A, Peradze N, et al. Follistatins in glucose regulation in healthy and obese individuals. *Diabetes, obesity & metabolism.* 2019;21(3):683-690.
30. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019;48(1):16-31.
31. Park SW, Goodpaster BH, Lee JS, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care.* 2009;32(11):1993-1997.
32. Timmerman KL, Lee JL, Fujita S, et al. Pharmacological vasodilation improves insulin-stimulated muscle protein anabolism but not glucose utilization in older adults. *Diabetes.* 2010;59(11):2764-2771.
33. Chin SO, Rhee SY, Chon S, et al. Sarcopenia is independently associated with cardiovascular disease in older Korean adults: the Korea National Health and Nutrition Examination Survey (KNHANES) from 2009. *PLoS One.* 2013;8(3):e60119.
34. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *Jama.* 2011;305(1):50-58.
35. Timmerman KL, Dhanani S, Glynn EL, et al. A moderate acute increase in physical activity enhances nutritive flow and the muscle protein anabolic response to mixed nutrient intake in older adults. *Am J Clin Nutr.* 2012;95(6):1403-1412.
36. Markofski MM, Jennings K, Timmerman KL, et al. Effect of Aerobic Exercise Training and Essential Amino Acid Supplementation for 24 Weeks on Physical Function, Body Composition, and Muscle Metabolism in Healthy, Independent Older Adults: A Randomized Clinical Trial. *J Gerontol A Biol Sci Med Sci.* 2019;74(10):1598-1604.
37. Slopien R, Wender-Ozegowska E, Rogowicz-Frontczak A, et al. Menopause and diabetes: EMAS clinical guide. *Maturitas.* 2018;117:6-10.
38. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev.* 2013;34(3):309-338.
39. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama.* 2002;288(3):321-333.
40. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. *Endocr Rev.* 2017;38(3):173-188.
41. Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med.* 2009;121(1):73-85.
42. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol.* 2015;8(2):201-210.
43. Magulick JP, Frei CR, Ali SK, et al. The effect of statin therapy on the incidence of infections: a retrospective cohort analysis. *Am J Med Sci.* 2014;347(3):211-216.
44. Cederberg H, Stancakova A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia.* 2015;58(5):1109-1117.
45. Redberg RF, Katz MH. Statins for Primary Prevention: The Debate Is Intense, but the Data Are Weak. *JAMA Intern Med.* 2017;177(1):21-23.
46. Ravnskov U, de Lorgeril M, Diamond DM, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. *Expert Rev Clin Pharmacol.* 2018;11(10):959-970.
47. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. *Oxid Med Cell Longev.* 2017;2017:1273042.
48. Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in

Canada and United States: cross sectional study. *Bmj.* 2011;343:d5621.

49. Poli G, Biasi F, Leonarduzzi G. Oxysterols in the pathogenesis of major chronic diseases. *Redox Biol.* 2013;1:125-130.
50. Khatib S, Vaya J. Oxysterols and symptomatic versus asymptomatic human atherosclerotic plaque. *Biochemical and biophysical research communications.* 2014;446(3):709-713.
51. Anderson A, Campo A, Fulton E, Corwin A, Jerome WG, 3rd, O'Connor MS. 7-Ketocholesterol in disease and aging. *Redox Biol.* 2020;29:101380.
52. Gaspar J, Mathieu J, Alvarez P. 2-Hydroxypropyl-beta-cyclodextrin (HPbetaCD) reduces age-related lipofuscin accumulation through a cholesterol-associated pathway. *Sci Rep.* 2017;7(1):2197.
53. Zimmer S, Grebe A, Bakke SS, et al. Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming. *Sci Transl Med.* 2016;8(333):333ra350.
54. Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. *Arterioscler Thromb Vasc Biol.* 2012;32(8):1754-1759.
55. Nakamura N, Matsui T, Ishibashi Y, Yamagishi S. Insulin stimulates SGLT2-mediated tubular glucose absorption via oxidative stress generation. *Diabetol Metab Syndr.* 2015;7:48.
56. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med.* 2012;18(3):363-374.
57. Bertsch RA, Merchant MA. Study of the Use of Lipid Panels as a Marker of Insulin Resistance to Determine Cardiovascular Risk. *Perm J.* 2015;19(4):4-10.
58. Devaraj S, Jialal I. Oxidized low-density lipoprotein and atherosclerosis. *Int J Clin Lab Res.* 1996;26(3):178-184.
59. Khoramdad M, Vahedian-Azimi A, Karimi L, Rahimi-Bashar F, Amini H, Sahebkar A. Association between passive smoking and cardiovascular disease: A systematic review and meta-analysis. *IUBMB Life.* 2020;72(4):677-686.
60. Zhou Z, Albarqouni L, Curtis AJ, Breslin M, Nelson M. The Safety and Tolerability of Statin Therapy in Primary Prevention in Older Adults: A Systematic Review and Meta-analysis. *Drugs Aging.* 2020;37(3):175-185.
61. Schweitzer AM, Gingrich MA, Hawke TJ, Rebalka IA. The impact of statins on physical activity and exercise capacity: an overview of the evidence, mechanisms, and recommendations. *Eur J Appl Physiol.* 2020.

PROFESSIONAL SST. ANYWHERE IN THE WORLD.

THE I.C.E. TEAM IS YOUR PREMIER PROVIDER FOR STANDBY, STABILIZATION, AND TRANSPORTATION.

As a global leader in the Cryonics industry, International Cryomedicine Experts (I.C.E.) is the trusted name to know for Standby, Stabilization, and Transportation. With a team of world-renowned Cryomedics, I.C.E. provides cryonicists with peace of mind by offering the highest potential for cryopreservation success, irrespective of location.

I.C.E. incorporates Field Cryoprotectant (FCP) capabilities to offer international SST services without time constraints for transportation. Any location that has available dry ice is eligible for services.

Having responded to more cases than any other SST provider worldwide, I.C.E.'s Cryomedics embody the highest levels of hands-on experience within the cryonics industry.

I.C.E.

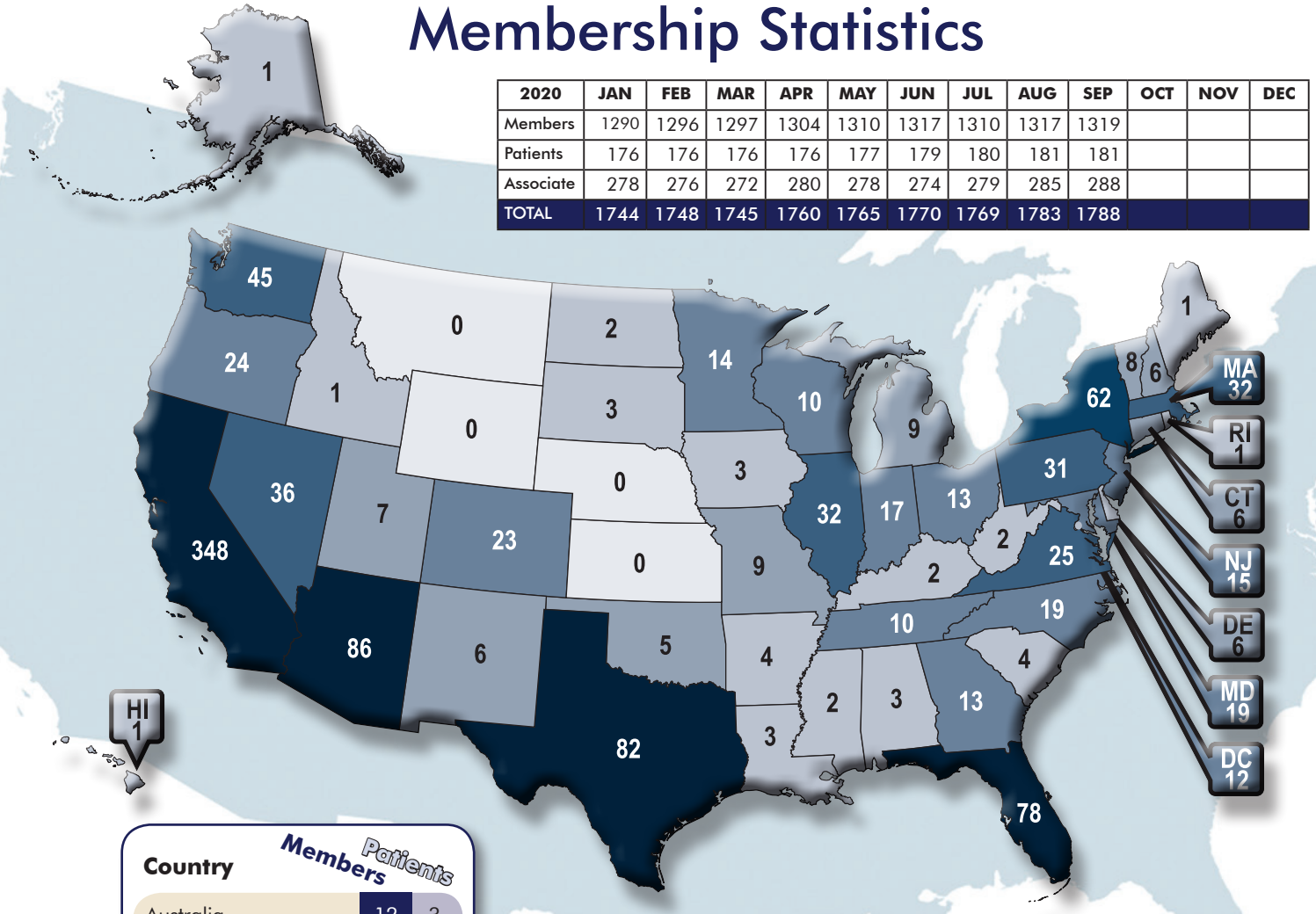
International Cryomedicine Experts

I.C.E. today for the best chance at tomorrow.

Contact us at **info@cryomedics.org**
844-INTL-CRYO (468-5279) • www.cryomedics.org

Membership Statistics

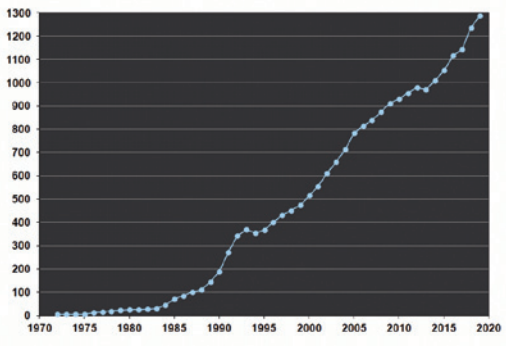
2020	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1290	1296	1297	1304	1310	1317	1310	1317	1319			
Patients	176	176	176	176	177	179	180	181	181			
Associate	278	276	272	280	278	274	279	285	288			
TOTAL	1744	1748	1745	1760	1765	1770	1769	1783	1788			



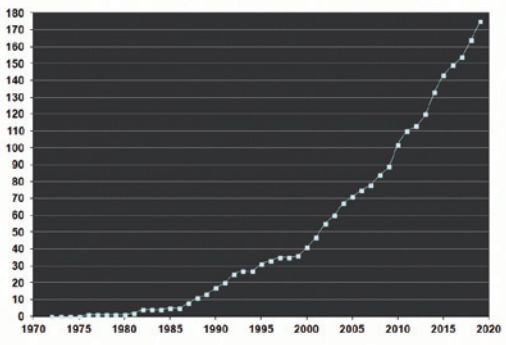
International Members & Patients

Country	Members	Patients
Australia	12	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	62	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	40	3
TOTAL	179	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

Some Thoughts on "Coming Back"

By R. Michael Perry

Introduction

Those of us in cryonics have hopes that future technology will bring substantial improvements in the quality of life, and possibly clarify and deepen its meaning as well. In particular, we are hoping for medical or physiological innovations that will free us from aging and diseases so that, radically lengthened, happy lives will be possible, and possibly open doors for still greater advances.

Our revival from cryopreservation could take several forms. Many cryonicists envision a return to life in a biological body similar to what they had before, with aging and diseases reversed and otherwise like their previous healthy state. Another possibility would be a technologically enhanced body, part biological and part artificial, or perhaps entirely artificial. For the latter possibility it would be necessary to "upload" the personality of the patient into something that could function like a brain. An artificial brain could offer advantages ranging from clearer and faster thinking and remembering to imperviousness to such natural brain disorders as stroke or dementia. A further extension of the uploading scenario would place several or many individuals in one large, brainlike device so that a community could be sustained. A version of this scenario is elaborated in Robin Hanson's book, *The Age of Em*, where many whole-brain emulations (WBEs) occupy an "em city."[1]

Em cities are mainly viewed as places on Earth which must make the usual environmental concessions to persist. Managers of an em city might be concerned about such issues as power input, a power grid, pollution, or climate change. Another, and, I think, far more favorable and hopeful setting would place the em city on an orbiting platform in space, directly powered by solar energy, without the intervention of weather or the necessity to compete with a biosphere or other ecological challenges. It is in such settings that individual uploaded personalities could persist for many centuries of tranquil, happy existence, ever developing in both capabilities and sensitivities, so that something approaching ancient concepts of a blissful afterlife is achieved. If such a happy state is realized, there should be a strong incentive, for at least some of the participants, to ensure the continuance of the society which treats the individual as a worthy object of perpetuation and regards an individual's death as unacceptable.

Here we consider possible future scenarios under several headings: (1) getting there in the first place; (2) what life might be like when we do, with emphasis on the period when are still recognizably much as we are now, (3) some details relevant to maintaining em cities in space, (4) special and longer-term issues. A fictional setting is used to explore ideas of what future life might be like, which takes up several sections. Overall, there seem reasons for optimism, based in part on the abundance of resources (energy, materials) in the solar system for sustaining the future habitations that are envisioned. Historical precedents, notably the futuristic forecasting of Nikolai Fedorov, can help motivate us in our quest for a future of long-term meaning, betterment, and enjoyment.

Informed speculation such as we are considering has its hazards and is not guaranteed to be close to what is really going to happen. It is worthwhile, though, to suggest possible reasons to seek such a future (through cryonics, for instance) and as a counterweight to the dystopic projections one frequently finds in fiction and elsewhere.

Getting There

There are widely differing opinions on what is likely to be involved in reviving cryonics patients. To illustrate, in *Cryonics* magazine we find these two opinions in "A Roadmap for Revival" that is now reprinted in the "Revival Updates" section of each issue:

> 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."[2]

As it happens, Aschwin de Wolf is the author of the first opinion, the "medical approach," focusing on revival as basically a medical problem involving a biological body like what we have today.

I in turn take credit (blame?) for the second opinion, the "cyber approach," in which I imagine a very different method that could bypass the medical/biological scene altogether, instead working in an advanced computational environment. There, you would start with information extracted from the preserved remains, mainly the brain, and create a type of program that embodies the personality of the person to be revived, and "wake it up" in a virtual reality setting as a WBE.

It can be asked whether there is any reason to favor the one approach over the other. My feeling is that the task of revival will be difficult enough that, by the time it is possible, technology will have advanced to the point that the cyber approach will be possible, or at least clearly attainable, and thus will be used to guard against mishaps and obtain the best possible results.

That persons would thus end up as "software bots" may be disconcerting to some, but are we not that already, in hardware we call the brain? In this case our sensory apparatus keeps us informed about the outside world, which is just beyond the contours of our body (or sometimes within it). When we sleep, though, nature manufactures a virtual reality for us, in the state we call dreaming. In the future we might upload into a robot body whose onboard computer would in effect become our new "brain." Such an existence need not differ greatly from our present one in which our biological brain is our "onboard computer." Or, our uploading could be as suggested above, with many personalities "running" in one device to make up an em city.

There are those who view the prospect of, in effect, being one day replaced by a software bot with dread because, they say, at best it will be "just a copy" not *them*. Instead they may insist on reactivation of their original bodies with fully functioning, healthy brains housing "them." Such people, though, might still be helped if their equivalent personalities are reactivated temporarily as WBEs so they could become familiar with their new existence and be better positioned to make choices about how they wished to continue it. (And they might do some rethinking and decide to continue as WBEs; otherwise, experiences acquired as WBEs could be added to those already present in the "meat" version of the brain before it is reactivated.) Granted, some may not want to ever be expressed as WBEs, fearing certain metaphysical difficulties, but in what follows we will assume that our subjects are comfortable with the idea of at least temporarily existing in that form.

Being There

A fictional scenario will help illustrate what revival might be like. Kirsten, we imagine, was an aging cryonicist living alone in a nice house in Anytown, USA, when she was diagnosed with terminal cancer. Her golden retriever named Peach, a beloved companion of many years, had been cryopreserved not long before, and she hadn't yet gotten another pet. Before that her father had also been cryopreserved, after a severe stroke that left him mentally impaired. As the end approached, Kirsten herself was fortunate in having good support from her cryonics service provider and her cryopreservation went well.

A long time went by. Space stations were established at various locations in the solar system, many of them directed by robot crews or onboard computers. AI greatly advanced, along with quantum computing, nanotechnology, materials science, and other supporting technology. A "quickening" event occurred when artificial, conscious systems were created with substantial "free will" – as much as natural minds could be said to have of this philosophically elusive quality. Finally, it became possible to emulate natural brains in artificial systems. An emulated mouse in a virtual setting would show behavior entirely consistent with its biological counterpart in a maze of wire and wood. Soon, humanlike WBEs were being created, then, finally, WBEs with the features of specific individuals, all under careful supervision to see that civil rights were respected, pain and suffering were minimized, and so on. Meanwhile, technology had been developed to do "digital readouts" of solid objects, capturing information down to the level of atoms, coupled with advanced data compression to reduce the size of the enormous resulting files without sacrificing essential information.

From a digital readout of Kirsten's brain, a WBE of Kirsten is created, in an appropriate virtual setting. The place is Nova Terra, a solar-orbiting platform somewhere far from Earth but filled with emulated or simulated reminders of that planet. Included also are WBEs of many other people, some of them cryonics survivors like Kirsten. Kirsten wakes up in a "hospital room" that looks much like the one she last remembers, long before, the time interval having subjectively passed in an instant. But rather than the misery of being near death, Kirsten now feels terrific, with her cancer gone, her virtual body youthful and lithe, her mind sharp and clear. A "doctor" named Jim comes into the room, a vigorous, middle-aged-looking man with

gray hair, and in a gentle, friendly voice starts to explain that Kirsten has undergone cryopreservation, and now, revival. It is hard to believe at first, especially about the uploading he goes on to explain, and that everything now visible, that seems so substantial and material, is "virtual." But yes, Kirsten was on record saying she didn't have a problem with the uploading scenario, "if they could pull it off." Kirsten asks about her dad, Dr. Jim says he is still "on hold," but his revival can be expected "soon."

Life on Nova Terra, it now is clear, will offer many, mind-bending options but Kirsten should "take it slow" and stick to familiar things at first, Jim wisely advises, and Kirsten has no problem with that. Quarters nearby are available, a small, neat house with a nice back yard and a shiny new-model car to drive that never runs out of gas. When Kirsten arrives, she is overjoyed to find Peach, now lithe and youthful like herself, waiting with many kisses.

After getting and giving attention, a happy Peach lies down for a nap and Kirsten and Dr. Jim take a stroll, Kirsten especially enjoying the feeling of walking so energetically on her own again. She is relieved to be away from something suggesting a hospital, even if it was nice, then surprised. "Why, I recognize this street!"

"Of course, responds Dr. Jim," smiling. "We've replicated your hometown, and basically, it's yours."

"Mine?"

"That's right. Your own, personalized Anytown, for you and just a few others, other cryonics survivors like yourself, and some others who wanted to join the group, a few dozen people altogether."

"You did all this just for just us? What about all these people I see out here?" They had stopped by a shopping mall. People in droves were getting out of cars, getting back in after putting their purchases in back, cars coming and going, and overall, it seemed like a normal day back – how long ago? "Who are all these people? Will you tell me that? I don't think they all are just cryonicists or those others like you say?"

Dr. Jim is patient. "There are many, many others besides the few dozen I referred to. People who came along after your time. Billions of them altogether. But truth be told, there are few of them in places like you see, they don't spend their time with reenactments made specially for survivors like you. Instead the ones out there," he made a sweeping gesture, "we call them 'avatars'. They aren't real people, but stand-ins that do their thing and provide a background for you and others like you. Some of them serve as store help, in case you go inside. And the question you raise, about how can all this be just there for you and a few others, is a good one, but it has a simple answer."

"Well, I'd like to know what it is."

"Remember that you and I are just two individuals here in this particular sector of our virtual reality platform, which altogether contains about ten thousand full persons. (I'm one of them too, not an avatar.) There are about a hundred sectors in turn on our platform, for about a million people in all. There are other platforms also, many in fact, all orbiting the sun and drawing their energy from it.

"The system here – and there are similar ones elsewhere – knows what sensory impressions to furnish us so we will, in fact, perceive a normal city scene with people milling about if we make a certain choice to 'go' on a certain journey, like the stroll we are taking. So it generates the necessary input and we see something that, in your case especially, looks normal to you. To us it looks like vast resources are being spent, but not really. Think about a dream – of things you are familiar with. You are in a big city, on a busy street, with hordes of people doing normal things. You may even talk to some of them, a small sample of all that are there, and they sound normal. Some people have exceptionally vivid dreams. Your brain could do all this for you on less power than an old-style light bulb. The people in the dream were, well – dream people not real people, though they did seem real. Your dream could also have presented you with a personalized version of the city you were in, where you had some special privileges. Make allowance for advances that have occurred since you were put in cold storage – and voila! Walk into a store, Kirsten, behave toward the avatars just as if they are people like you and me, and all will be well."

"Actually," Kirsten responds, "I don't need to go in stores at all, do I? Everything is just done automatically, as far as I can see."

"That's right." Dr. Jim smiled. "You could shape shift, have a body that needed neither food nor sleep. Have no body at all but be invisible. Or have a body with wings, and fly. Or have no wings and still fly, like Superman. All such things are possible, physically, or I should say, cybernetically, but not all are recommended, and some are forbidden or restricted on various grounds. We strongly recommend you not try for too much at first, just be content with being like you were – with obvious improvements. You'll still eat, sleep and breathe, still shop for food, but find you never run out funds to pay for it. Or need gas for your car, as we noted already. And your body is always healthy and fit. You do have quite a lot of benefits already."

Kirsten thought, started to say something, found herself at a loss for words. What do you say when you've just woken up to find your terminal illness cured and your aging body made youthful again? Your bank account essentially infinite? Your beloved, cryopreserved pet also restored to youthful fitness and happy to see you again? The other one you specially care about, that you haven't seen in years, reportedly "on his way." "Er, she finally managed to stammer, "I'm with you, I guess, you've done a lot

for me already, I don't need, uh, full divinity or whatever you want to call it – not yet."

"Very good!" Dr. Jim smiled. "And soon we're going to move you from your temporary quarters to something more permanent, unless you just want to stay there; we can arrange that, or more properly, put you up in a replica just like it. But how'd you like to go back to your old house in Anytown? You'd still have the same access to others, including me."

Kirsten thought it over. "A replica house, I gather, in this replica town."

"Yes, and both very well done. Some repairs on your place, I think you'll be more than happy with the renovations if you choose this alternative. Your car would go with you, or you could get back a spruced-up replica of the car you used to drive. Peach will have a nice new doghouse, where she can stretch out more for the naps she likes to take. And you'd find you have special privileges in the replica Anytown. Walk into any hotel, say what room you want, and it's probably yours for as long as you want. If someone else is already there, well, there is likely a room nearby that you can have. Your privileges aren't unlimited, mind you, but you'll have a generous helping, as a start toward whatever future you map out for yourself. In the end, you will have to decide on how to do that."

The very last sentence was delivered with a note of seriousness and duly noted by Kirsten, who responded, "well, I guess the thing to say, is let's get on with it, eh Peach?" The dog had been nearby watching the two intently, looking back and forth at whoever was speaking. She wagged her tail in response as Kirsten reached out and patted her on the head. The three of them piled into the car Kirsten had been assigned and Jim drove the few miles to Kirsten's house, Kirsten noting with reassurance how the streets were all familiar. On the way she said, yes, why not, she would like her old car again, only with repairs and such.

"Okay, fine," said Dr. Jim with his trademark smile. "Just remember, though," his voice got more serious, "every privilege carries a responsibility. We don't need to go into it much right now, but we can work on it later. Don't worry, you won't owe any trillion-dollar debt for the favors we've done you in bringing you back and everything else. But we have our hopes and expectations for the people we help, who in time will help us, and we hope, love doing it."

Kirsten decided not to worry. At one point in their journey, they passed by a church building, one that Kirsten remembered, though she had never attended church. "Do people still go to church, or something like it?"

"Oh yes, said Dr. Jim. Quite a few do. Then others don't."

"You do have separation of church and state."

"Oh yes."

Kirsten felt an odd, calming curiosity as the familiar-looking streets rolled by in the tranquil setting. And the house didn't disappoint either. All spruced up, with new carpeting, it certainly seemed like the original, only better. And Peach liked her surroundings, and her new doghouse. Soon Kirsten was in contact with other cryonics survivors, who sometime before her revival had formed a support group.

Meeting James Bedford[3]

The group held a picnic in a park, and Kirsten brought along some treats she'd made, and of course Peach also. Among the members of the group, Kirsten was not surprised to learn, was Dr. Jim himself. He is just being his usual, helpful self, she thought. Nothing wrong with that, even though the other members seemed to be bona fide cryonics survivors, like herself. When Kirsten realized the good doctor too was not "just a helpful visitor" she was surprised.

"You're one of us, too!"

"Yes Kirsten, definitely one of you people, the very first you might say."

"You started this group?"

"No, I didn't actually, but I'm the first long-term cryonaut. Dr. James Bedford."

"You're James Bedford? The one we used to celebrate every year, January 12, the anniversary of your freezing, when was it, in 1967?"

"Yes, that's right."

Kirsten felt her head spinning. (The emulation was good, she had to admit, sometimes a bit better than she liked.) "But how could that be? Your preservation was primitive. No vitrification, and all that. Uh, it's good you came back at all, great! Great! But how was it you came back before I did?"

"Well, it was a quirk of developing technology. And it just underscores the magnitude of the technology needed for cryonics revival, *any* revival that is anything like yours *or* mine. By the time technology reached the level needed for you, it was not so much more to scale it up to do me, even though in absolute terms, my revival was far harder. But the rate of progress by that point was huge. I think it took only a few days to get from being able to do the "easy" later cases like yours, to mine, and that due to an unexpected delay. So a lot of the earlier cryonics cases were actually among the first, not the last, to be revived."

"Amazing. But then, how did you end up working with this group?"

Dr. James Bedford about 1949

"Well, Kirsten, on revival I really felt lost at sea, since, you know, my whole family, wife, associates, they weren't into this freezing thing, it was so brand new at the time, and when I came back, they were all gone. Avatars of some of them helped, but avatars can go only so far, and it can hurt more than help, when you face up to their not being the people you'd really like them to be. I understand something more substantial than avatars of your loved ones is being looked into, but it isn't available yet, if it ever will be. So, there I was, like a fish in a desert, and it was tough going for a little while, and then I adjusted, lucky I could do that, and things got better. But I found I faced another problem, which was just what did I want to do with this new life, now that I had it? Where did I go from there? And the upshot was, that I became a sort of counselor to other cases, like yours. It fit my background, I was a psychologist and vocational counselor before, so that's about where I'm at now too, only in a strange new way I never imagined. I'll say too that, as you expect, there are powers that control things here, our "Sysop," we call it, a sort of consortium, and they were highly sympathetic to my wishes to be this counselor, and gave their assistance, putting some revivals on pause while I could get some training, which could be accelerated via time compression."

"Time compression?"

"Yes, it's one of the basic features of being an emulation. You can be run at different speeds. Faster running takes more power, there is a tradeoff. I'd say, don't worry about it now."

"All right, I won't. But I guess I face a problem something like you did, only I didn't have as much in the way of a family, my dad, though, and the other closest to me is here now." She thought of Peach, who was having endless fun right then, frolicking with some avatar birds and ground squirrels that gathered round to entertain her. (They did this at home, too.) "There's one more thing I've been meaning to ask you, or somebody who knows." What Kirsten wanted to know about was whether there was a way of seeing the outside world as it really was, "rather than this virtual reality, granted it has its marvels. But it still bothers me that I'm in this sheltered existence, a pure fantasy world you might call it, and have no way of seeing what the real, material surroundings look like."

"We have a number of possible answers for that," Dr. Jim responded. "One is the planetarium. There you can see what it looks like in space, from where we are here on this platform. And you can see other parts of the solar system and the cosmos beyond that from other vantages. Quite a thing to see, all told. But as a preliminary I also have some powers to show 'the real world,' the sky overhead, if you're interested. I recommend you be seated first." Dr. Jim nodded to the others present, who indicated it was okay with them, and Kirsten seated herself on the grass in a lotus position (noting with approval that she could do that again so easily). Soon the sky and everything else darkened, and bright stars could be seen overhead, blazing against the velvety blackness. Kirsten, who had studied astronomy as a child, recognized some constellations – there was the Big Dipper, and over there, Orion. Then it lightened up again and returned to "normal." (Peach was startled by all this but didn't seem upset.)

"Actually," said Dr. Jim, "You were still seeing a virtual reality, but one that happens to show just what it looks like from this platform, facing away from the sun. And you can acquire this skill too. …"

Confronting the "Last Enemy"

Kirsten drove home with Peach, then later had a long walk with her dog. It was nice that Peach could follow along without needing a leash, but then, other dogs and people she encountered were mostly avatars, under control of the Sysop, or whatever, if you didn't mind that they were, in fact, avatars. But as the two of them proceeded, Kirsten found herself thinking about her father. Nobody had said anything beyond her earlier conversation with Dr. Jim. Were they just waiting for her to take the initiative? She thought more about her parents. Her mother had died before Kirsten got involved in cryonics and there was a conventional funeral. In fact, it was the death of her mother that caused a crisis in her life, where she'd looked into ways of dealing with death, the "last enemy," as she'd heard a religious authority call it. The religious approach didn't appeal to her, though, nor did any of the others she considered, with their emphasis on "acceptance." Then she'd heard of a group who were freezing people after clinical death for possible later revival, a practice called cryonics, and she was quickly hooked and signed up with one of the service providers. Her father was still alive, but try as she might, she could not interest him in the practice, he would just say he wanted to "be with Mom" when the end came. Then finally, seeing how much she wanted this way of "saving" him too, he had relented and signed the paperwork. It was well he did, for soon afterward he had a stroke and, though he still recognized his daughter and could say her name, he was

childlike and unable to sign documents, also wheelchair bound. A few more years went by, while she took care of him, and then he expired and was cryopreserved. *Dad, if you could just see this place ...* Hopefully he soon would, but in what shape?

And Dad, of course, would want Mom to be there too (he had said so, even after his stroke), but Mom had been buried, not frozen. Kirsten was now making calls on her cellphone, an antique replica she preferred, like her car. She contacted Dr. Jim, who was reassuring about her father, saying the man would be along shortly, though there were some things to discuss about that, and recommended Dr. Lexa, "who is more versed in these matters than I am." A short, dark-haired, dark-skinned lady of about forty by appearance (to contrast with Kirsten's lighter complexion and hair and greater height), Dr. Lexa soon showed up, smiled, said "call me Julie," as they shook hands, and the conversation began.

"Uh, Julie," Kirsten was a little awkward in starting. "As I said, I want to see my father again, when can it happen?"

Julie was forthright. "Well, Kirsten, the answer is, soon indeed, almost any time in fact. Some things though, we ought to discuss first. Could you be a little patient?"

Kirsten felt a chill of apprehension, but said certainly she could, and Julie began.

"Your father was one of the tougher cases, as you probably expect."

"Yes," Julie, with his stroke and all."

"His stroke, plus he had dementia, and, well, we found a lot of areas missing, and had to fill in things. We used a lot of your own memories of him to make some of our reconstructions, and this is one reason we wanted to discuss this whole thing with you before we proceeded with the revival."

Kirsten took a deep breath (glad they had left in that feature of her emulation, she thought, even though it wasn't "necessary"), then felt reassured. "Of course, glad you used my memories, good you did that."

"Good." Julie continued, "In other areas we made reasonable guesses about what he should have remembered, about old acquaintances, and such, using surviving records when available. Sometimes though, the records were not available, and our guesswork was, you could say, 'more creative,' In all the guesswork cases, we have to keep careful records of any information we generate, to make sure it doesn't conflict with what we've done in similar cases."

"Hm." Kirsten thought about that. "I think what you're saying is like, if my dad knew someone else named Joe, say, then if Joe also was revived, and his memories had to be augmented too, then the two sets of memories would need to be mutually consistent, so you'd need to keep your records of just what you did with one, before you did the other. Is that about it?

"Exactly, Kirsten."

"Only, Julie, I don't think there would be many Joes like you say. There weren't that many cryonicists, even though all too often the preservation wasn't that good, so you might have a lot of reconstruction to do.. But my Dad didn't have any people like you're talking about. His friends weren't into cryonics."

Julie was slightly hesitant in responding. "You've touched on a touchy subject. Actually, everyone has friends like that, or most people, if you think about it. They weren't involved in cryonics at all. So their need is all the greater, we can guess their features too, just like we can with the less-than-perfect cryopreservations. An active area of research now."

Kirsten felt her stomach tighten. "My mom."

"Yes, your mom, Kirsten. We aren't ready for her, but we can do your Dad. I suggest we focus on that."

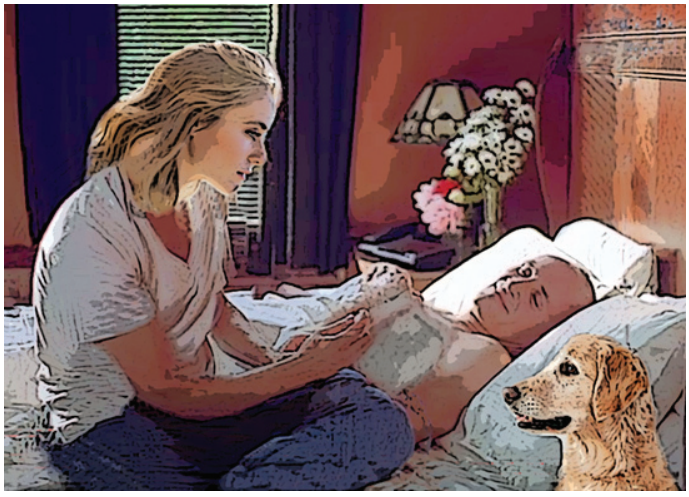
Getting Dad Back

It had started with data mining. First, his cryopreserved remains. Go as far as you can with that. A lot there, really, but a lot missing too. What next? Kirsten's memories were already recorded as preliminary to her cryonic revival. Her memories of her father could be important as Julie had said. Then: look at school records, employment records, marriage records, surviving photographs, letters, and so on. Basic things, speech patterns, gait, school learning, and so on, could be inferred to reasonable accuracy and reinstated. Guess lots of intimacies of his married life; such information wasn't likely to be recorded somewhere you didn't look. Kirsten had been an only child, like many cryonicists, and that made it simpler though more information might have survived about her dad if she'd had siblings.

So all the information was collected that was readily available. But, Julie had warned, there might be more tucked away somewhere, and it might take a while longer to be sure that you really had it all. Still, though, it seemed likely you had most of it, and the go-ahead was given to begin the revival. Ironically, it would happen in the same (virtual) hospital where Kirsten was revived – fitting though, when you thought about it – especially with Kirsten herself playing the role, more or less, that Dr. Jim had done for her.

On the appointed day, Kirsten drove out in her car, taking Peach along. Peach had been a puppy when Dad had passed, but he would remember her, be surprised to see her now grown up, be surprised at a lot of things …. Kirsten had talked about it at another gathering of her local group. "We are cryonicists and expected or at least hoped we'd see the light of day again.

But my father, I think, really thought his passing would be the end, even though he signed up for cryonics to make me happy. So we'll have to, uh, break the news that the old life wasn't the end. A pleasant duty, really, I think he will take it in stride, as he, himself used to say you had to do with a lot of things." Dad did seem to be one of those who basically enjoyed living and wouldn't regret coming back, Kirsten thought, despite the hardship that Mom wouldn't be there with him.



Dad Comes Back

And that is pretty much how it worked out. There was an emotional scene in the hospital room when Dad came back. The prone, familiar figure on the bed opened his eyes, Kirsten said, gently, "Dad," he focused his eyes, replied "Kirsten," and their new relationship began.

There had been complications. Initially, Dad had deficiencies of memory because a fill-in of these areas by guesswork, though possible, was considered too hazardous for various reasons and would have to be postponed. As Julie had explained, the recovery of someone in the difficult cases could not just happen in isolation, like Kirsten's own revival. There you had all the information you needed right from the start. You didn't need to do any guesswork. But with the tougher cases that wasn't so, and you had to keep track of information created by guesswork for one revivee, to make sure it was consistent with that for any others facing the same predicament.

Kirsten remembered that in the old life there was the blockchain used for a cryptocurrency, a record of all transactions ever performed, to ward off certain unwanted possibilities such as double spending. Here you had something like that, a revival blockchain, to make sure everything you filled in by guesswork jibed with everything else, for all those you brought back this way. In all, an exciting challenge indeed, but one with great rewards too. With her dad it had gone very well, despite the minor problems with amnesia ("damnesia," the irritated man had called it on occasion, when he couldn't think of a name from the past; mercifully such occasions weren't common).

Later both Dad and Kirsten would think increasingly about Mom who had not been cryopreserved and was not revived. They found the group that Dr. Jim had said was looking into cases like that, to see what could be done, and joined them. …

A Larger Picture[4]

Returning to the more prosaic world of nonfiction, what sort of "responsibilities" might a revived cryonicist be expected to have, particularly in a virtual reality setting like that suggested above? It would not, I submit, be the usual sort of "job" people have today, something they would not pursue if independently wealthy. The people in the scenario above will be, in effect, wealthy beyond any sort of privilege today. They will be like oil sheiks, with the sun overhead or "out there" as the "oilwell." It will not be necessary to do "labor" as we understand it, if things are properly set up, as should be possible. But still there will be preferred activities and responsibilities, by reasonable extrapolation. This topic we shall return to.

For now, it is worthwhile to consider some basic numerical features of the proposed virtual-reality setup, granted that there are many unknowns. But for some basic data: the power output of the sun (total solar flux) is about 3.8×10^{26} watts, whereas a human brain runs on roughly 20 watts. At one billion kilometers from the sun's center, or 10^{12} meters, the solar flux is about 30 watts per square meter. A brain, then, as a WBE, could be "run" on a platform-segment of one square meter area, assuming as an upper bound that we could be at least as efficient, in the end, as nature has been with us. If we imagine a population upper limit of 10^{12} (over 100 times the present Earth population) a square platform 1,000 km (10^6 meters) on a side would be adequate. If the thickness of a brain-running platform segment averages 1 centimeter (a pure guess), the total volume of the apparatus to sustain the 10^{12} people would be 10^{10} cubic meters, which, compacted into a cube, would stand about 2.15 kilometers tall, the size of a modest space rock. If a whole meter of thickness was needed per person, the compacted cube would be 10 kilometers tall, still quite modest on the scale of available materials in the solar system.

Most of the ongoing needs of a platform would be energy needs which would be met by the incoming solar flux, much as a computer today can operate for long stretches with no supporting resource but electricity (and temperature ultimately derived from sunlight). Other needs, for repairs and occasional materials from surrounding space, could be met by crews of robots under supervision of those in control of the platform (the "Sysop" – see below). This labor, I think, should not be extreme or demanding, in view of the prospects for automation.

A platform able to run 1 million people (as suggested in the story), in effect, an "em city" in space would be equivalent in area to a square 1,000 meters or 1 km on a side. Such a platform orbiting at 10^{12} meters from the sun would be between the orbits

of Jupiter and Saturn, beyond the asteroid belt that lies between the orbits of Mars and Jupiter, and thus should be in a relatively safe region for long-term residence. It might have the physical form of just a flat circular disk, like a flattened telescope mirror, always facing toward the sun as it completed its revolution around that warming body, in this case requiring about 17 years to do so. In general, the more distant the orbit, the larger the platform must be to collect the same energy flux per unit time (and the longer the revolution time). It appears that many options might be workable. If one platform holds 10^6 people, then 10^6 platforms would provide for the 10^{12} population limit. They could be distributed in orbits ranging evenly from 1.0 to 1.01 x 10^{12} meters from the sun, so 10^{10} meters would be available for 10^6 platforms, which then would be at a minimum distance of 10^4 meters or 10 km apart at opposition. (If the platforms were in independent orbits, approaches this close would be very rare events that could be avoided altogether if desired by minor occasional nudging using onboard rockets powered by compressed gas or maybe lasers.) The total surface area of 10^{12} square meters for all the platforms would be only about 10^{-13} of the total available area at the 10^{12}-meter distance, a negligible fraction.

Granted we are indulging in liberal speculation here, and many details could end up quite different. Still the clear suggestion is that a scenario like that envisioned, which could support many times Earth's present population in grand fashion, would not greatly strain the resources of the solar system. It is also worth noting that the solar system itself is just a tiny part of the visible universe, which so far has not revealed to us any advanced civilizations or even signs of life at all, except in our little corner of it. It seems likely that other solar systems could furnish additional vast space and materials to continue our civilization, and the individuals that make it up, according to our needs, but our own system might suffice for many millions of years.

One key to our imagined scenario of abundance is that it is to be "done in software." So, a person who desires a mansion, say, will not have to actually have a physical building built, but only a virtual one. At anything like the brain's present level of development, allowing for significant excursions beyond it, that should not be so difficult or resource-consuming. Nature makes us dream with no great expenditure of resources beyond our usual metabolic needs, so future advanced tech, in constructing our virtual realities, should also be able to get by on a quite limited budget of energy and materials.

I think that, for the most part, it could lead to states of happiness and fulfilment that would make such an existence seem well worthwhile. In short, once the necessary technical mechanisms are in place, a simple life, with only modest demands on the deep space environment, could be a very good life that many will enjoy for vast stretches of time. (It should be clear that such a life would not have to seem simple at all, given the vast anticipated powers of future computing devices to bring it about. Again, such devices in turn should not greatly strain the available resource base.) For this reason, I have not emphasized in this essay how such issues as "economics" will be dealt with. "In cyberspace there will indeed be many mansions" – or should be.

Such a world of abundance, coupled with radical life extension and the high intelligence of participants (who can be expected to be smart since intelligence improvement will be an option), should greatly simplify issues of resource allocation and governance. This will follow, though, only if attitudes of the right sort are cultivated. So, we are faced with such issues as what sort of thinking and conduct would be preferred and ought to be encouraged in a future world, and how should desirable conduct be encouraged.

Finding the Right Path[5]

A world of abundance could confront us with many pitfalls. Indulging in simple pleasures would not necessarily produce states of enlightenment. A state of pleasurable paralysis or "hedonic stasis" could result, which to an outsider would appear as an infinite loop, forever "locking away" an individual so entrapped. (The infinite loop would not necessarily be sustaining states of pleasure either.) If this happened to one of our comrades, we should be deeply concerned, not indifferent or thinking "they did what they wanted, I won't be bothered about it." On the other hand, we will not be alone in this concern. Our "coming back" would be closely watched and monitored by "whoever or whatever is in control," we have called it the Sysop, to see that bad outcomes are avoided or corrected as far as possible.

Here I distinguish between the Sysop and its charges – those beings it looks after in the em city it governs. These might include recent cryonics revivals or others, anyone who lives in the city who is considered a moral agent with civil rights So avatars as "dream figments" would presumably be excepted, or have only limited rights, and care would be needed to determine which rights they should have, if they too should be considered as moral agents, et cetera. Another class of being that would deserve special consideration is pets and any others which were not avatars but operated at less than a human level.

That the Sysop should be well-motivated, and the charges as well, would be essential. "Love is essential" – as the Truths of Terasem (a futurist organization started by Martine Rothblatt) proclaim, and this must carry over. The Sysop must be like a loving parent to its charges. By analogy, the Sysop would try to help its charges to a happy, meaningful, progressing, kind-hearted, unlimited existence, and would extend its kind intentions and good deeds elsewhere too, respecting reasonable tradeoffs. Like children of parents today, the charges would be encouraged by the Sysop to develop their own capabilities and sensitivities. The charges then would have responsibilities of their own, to behave wisely and benevolently toward others,

and to work toward their own advancement and betterment, with some attention to activities that have larger implications to improve the whole of society. (As one possibility, we imagined two recent revivals joining an effort directed toward reviving people who passed and were not cryopreserved. This could be a great, but ultimately rewarding challenge.) Sysops in turn would need supervision (at least in principle), which suggest there would be a Master Sysop in charge of every other level, as well as itself. In time the charges might progress and join their Sysop or, eventually the Master Sysop. In our fictional setting Dr. Jim has clearly started down that path. (Another prospect is that even pets and other sentient creatures among the charges would be helped to gradually advance and would eventually approach and exceed present human levels.)

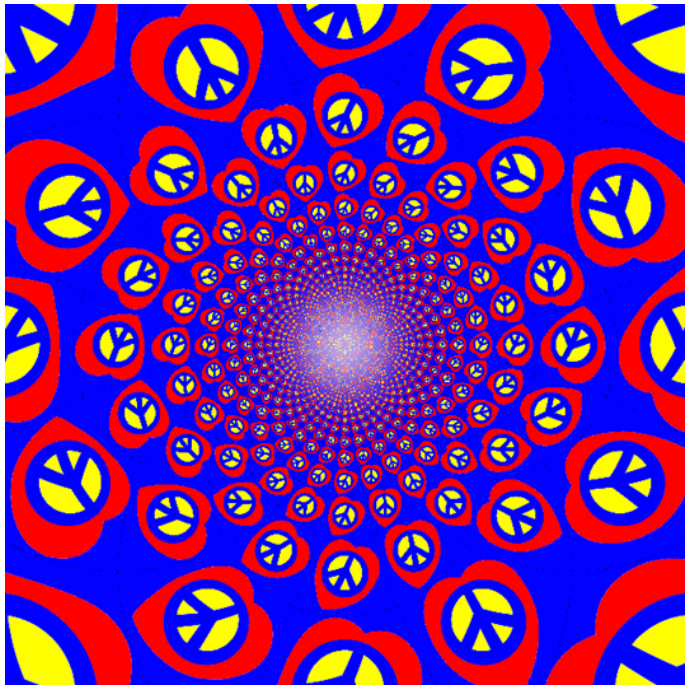
Martine Rothblatt

Though the solar system might be adequate for the needs of the anticipated em civilization for a very long while, its resources are finite. But surrounding it is the whole visible universe, which so far has seemed empty of anything that looks like other, intelligent civilizations or individuals. This may, of course, not be true, but by appearances there are many suns out there that could serve as nuclei for other em civilizations started by maverick groups from our own, if it seemed necessary. (And interesting contact with space aliens may result, which, if they are reasonably advanced and reasonably enlightened, would welcome our contact and hasten to establish friendly relations, perhaps assisting us to find new territories as needed, or we might assist them.)

It occurs that the "Fermi paradox" (named after physicist Enrico Fermi) of why we haven't already seen some signs of intelligent life in the universe at large may be explained as follows. The aliens are out there, but by and large are happy to be living in their own em cities which supply most of their needs, both physical and psychological. So, the incentive to "explore and colonize" outside of their own original solar system, while nonzero, is muted. Intelligent life in turn is probably difficult enough to evolve that it is relatively rare, on a per-solar-system basis, leaving ample room for civilization expansion, again if the need should arise.

The whole visible universe is also finite, which might seem to pose a threat that one day must be terminal, if life continues long enough. It is not clear how long that might be, but "quite long" – billions of years at least, and a simple workaround may be found long before, if indeed the threat really exists. The apparent discovery of an accelerating universe in the last few decades upended then-current ideas of the long term behavior of the universe, and further surprises could well be in store. On the other hand, who can say what discoveries might be made by highly advanced beings that might be working hard in their em cities over geologic time scales?

In any case, it seems likely that there will never be a shortage of interesting problems to work on, as we see in the field of mathematics alone, so no reason life rightly lived must ultimately lose its meaning.



"Peace and Love without End"

Respecting a Religious Perspective[6]

In effect then, the em world envisioned here can be seen to resemble religious concepts of the afterlife, and this is no accident, since these concepts reflect deep human wishes of how a future ought to turn out. Our em world would, of course, be a technological artifact and put in place by beings like ourselves, or who at least started as beings like ourselves or were an outgrowth of technology started by ourselves. But I submit that the mechanism whereby the future world will be realized is less important than that the sort of world we would like is, in fact, realized in some feasible way.

Here it seems appropriate to mention the 19th-Century Russian scientific-religious philosopher Nikolai Fedorov (1829-1903). Though a committed Christian, Fedorov believed that

humankind should use its God-given powers to construct a world freed of diseases and death, rather than trusting matters to divine intervention. Indeed, he thought there would be a form of divine retribution if we did not carry out this task ourselves, something he considered the "common task" of humanity. Fedorov believed that even the dead of past generations could eventually be restored to life through technology we could develop, and doing this was part, indeed the central part, of our moral obligation.

One possible scenario for restoring the dead to life through technology, when the information to accomplish this is "irretrievably lost," was explored in a previous article.[7] It depended, not upon some future discovery of how to retrieve this information that seemingly was lost but actually was not, but on properties that would obtain in a multiple-worlds setting. (In cryonics, of course, it is assumed that without sufficient preservation of information revival cannot occur. The multiple-worlds scenario would challenge that, though arguably still not render cryonics superfluous.)

Whatever one thinks of the resurrection prospect, there is another sense in which I think a religious perspective could prove useful. It is that religious thinkers over the centuries have put a great deal of serious thought into what to expect in an afterlife. If nothing else, it could serve as a starting point for *more* thought along the same lines. We will need this, as well as considering many other issues, to construct the sort of world that would be appropriate to our revival and our interests after that.

Some Final Thoughts

In considering the possible revival of cryonics patients we have put heavy emphasis on the uploading scenario, in which information is extracted from the preserved remains and used in a computational device of the future to "run" a whole-brain emulation – WBE – of the patient. The emulation is assumed to be equivalent to the original, even if "run" on a very different, generally nonbiological, substrate. There is no special reason that revivals must assume this form, and some object to this idea of "coming back."

While not denying that a WBE will not satisfy everyone's idea of what would be an acceptable revival, we found reasons to continue with this scenario. Mainly, the revival problem is seen as very difficult, at least in terms of technology anything like today's. So to do the best job of it, even for the cases that would use the original, biological material, it would be desirable to first extract brain information sufficient for a WBE, and to then analyze this and carry out necessary repairs electronically, before proceeding further with whatever revival approach is used.

Another thought is that the biological brain-and-body will be far more energy-intensive to maintain and protect from possible harm than the best that future science can accomplish with WBEs. The WBEs, then, seem likely to be the "wave of the future" just on grounds of resource management. We may conjecture that most if not all of those opposed will, in time (lots of that!), rethink their position.

An issue that we have not really explored here, despite some hints, is just what would people in general be doing in em cities, given that their needs are met through solar energy and other avenues requiring only minimal labor on their part. What interesting, compelling, worthwhile, hard work would they do? The thought occurs, to invoke a kind of "recursion" – that *finding* really worthwhile things to do would itself be a problem deserving of hard effort on many fronts and could occupy many sharp minds, perhaps indefinitely. (And we noted that mathematics alone appears inexhaustible in interesting ways, to furnish a possible starting point, plus we have noted the cosmological problem of how to really attain a non-terminating existence.) Addressing this topic further is beyond the scope of this essay, but I am inclined to think that, for us here and now at least, useful insights could be offered by something like a religious perspective. According to Paul Tillich, religion "is the state of being grasped by an ultimate concern, a concern which qualifies all other concerns as preliminary and which itself contains the answer to the question of the meaning of our life."[8] Might we draw inspiration and insight from such an approach as we confront the problems we must face in a future that will take us beyond our biological origins? ■

References

1. RH; WB.

2. CR.

3. JB.

4. BP; OP; SO.

5. T1; T2; FP.

6. NF1; NF2.

7. MP.

8. PT.

Image Credits

Golden retriever: Public Domain Pictures

James Bedford: *La Reata* (Glendale Junior College, CA yearbook) 1949, 39.

Martine Rothblatt: UCLA

Dad Comes Back, "Peace and Love": author; usage of web images believed consistent with "fair use" criteria.

Sources

BP (brain, power requirement). https://hypertextbook.com/facts/2001/JacquelineLing.shtml#:~:text=The%20average%20power%20consumption%20of%20a%20typical%20adult%20is%20100,of%20the%20brain%2020%20W.&text=Glucose%20is%20the%20main%20energy%20source%20for%20the%20brain, accessed 3 Oct. 2020.

CR. (For example) Cryonics 41(3) (3Q 2020) 58.

FP (Fermi Paradox). https://en.wikipedia.org/wiki/Fermi_paradox, accessed 3 Oct. 2020.

JB. https://en.wikipedia.org/wiki/James_Bedford, accessed 3 Oct. 2020.

MP. R. Michael Perry, "Contrastive Underdetermination Resolution, with Application to Cryonics Revival and Other Possibilities for Life after Clinical Death," *Cryonics* 40(1) (1Q 2019) 27-36.

NF1. https://iep.utm.edu/fedorov/, accessed 3 Oct. 2020.

NF2. Nikolai Fedorov, "Supramoralism," q. XI, "Concerning minority and he coming of age," in *What Was Man Created For?*, Elizabeth Koutiassov and Marilyn Minto, eds., London: Honeyglen Publishing, 1990, 129, http://www.regels.org/N-Fedorov-1/N-Fedorov-Supramoralism.htm, accessed 4 Oct. 2020.

OP (orbital periods). https://sciencing.com/calculate-period-orbit-5840979.html, accessed 3 Oct 2020.

RH. Robin Hanson, *The Age of Em: Work, Love and Life When Robots Rule the Earth*, Oxford, Oxford University Press, 2016.

PT. Paul Tillich, *Christianity and the Encounter of the World Religions*, New York, Columbia University Press, 1964, 4.

SO (solar output). https://ag.tennessee.edu/solar/Pages/What%20Is%20Solar%20Energy/Sun's%20Energy.aspx#:~:text=The%20Sun%20releases%20an%20estimated,radius%20of%20approximately%2093%2C000%2C000%20miles, accessed 3 Oct. 2020.

T1. https://en.wikipedia.org/wiki/Terasem_Movement, accessed 3 Oct. 2020.

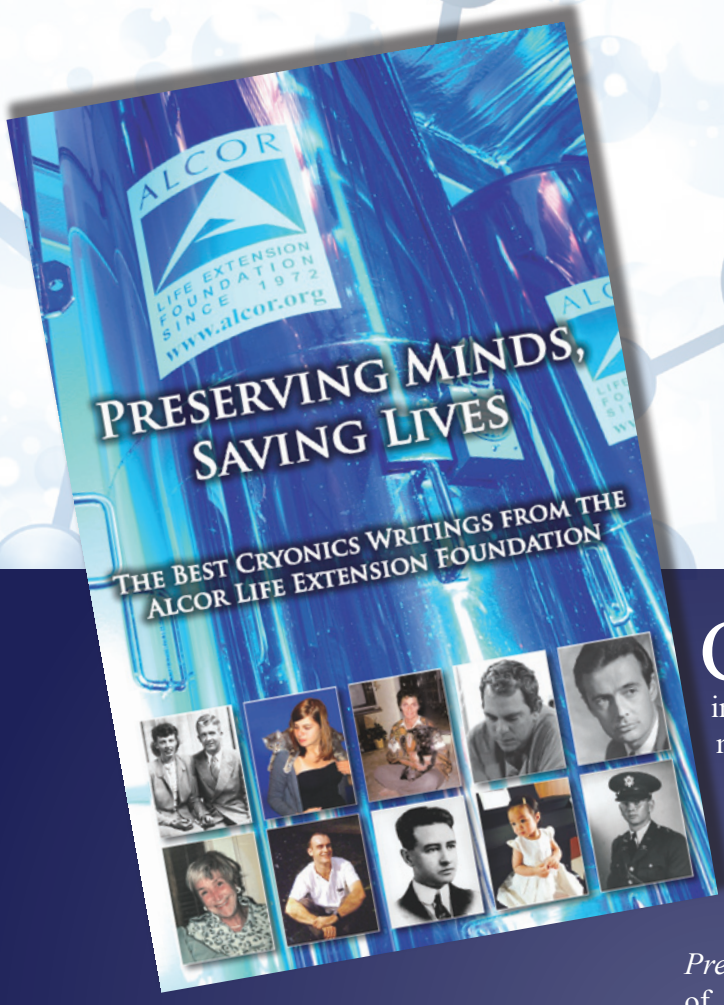
T2. https://terasemfaith.net/beliefs/, accessed 3 Oct. 2020.

WB. Sandberg, A. & Bostrom, N. (2008): Whole Brain Emulation: A Roadmap, Technical Report #2008-3, Future of Humanity Institute, Oxford University, https://www.fhi.ox.ac.uk/brain-emulation-roadmap-report.pdf, accessed 3 Oct. 2020.

ORDER NOW!

Preserving Minds, Saving Lives

The Best Cryonics Writings of The Alcor Life Extension Foundation



"Cryonics magazine introduced me to Alcor and cryonics at its best back in 1983. The visions and technological breakthroughs that you will read about in this book continue to shape Alcor's mission to preserve life through science."

– Max More, Ph.D.
President and CEO of Alcor

Cryonics is an experimental medical procedure that uses ultra-low temperatures to put critically ill people into a state of metabolic arrest to give them access to medical advances of the future. Since its inception in the early 1960s, the practice of cryonics has moved from a theoretical concept to an evidence-based practice that uses emergency medical procedures and modern vitrification technologies to eliminate ice formation.

Preserving Minds, Saving Lives offers an ambitious collection of articles about cryonics and the Alcor Life Extension Foundation. From its humble beginnings in 1972, and its first human cryonics patient in 1976, Alcor has grown to a professional organization with more than 1,000 members, more than 150 human patients, and more than 60 pets, all awaiting a chance to be restored to good health and continue their lives.

This book presents some of the best cryonics writings from *Cryonics* magazine from 1981 to 2012. There are clear expositions of the rationale behind cryonics, its scientific validation, and the evolution of Alcor procedures. Also covered are repair and resuscitation scenarios, philosophical issues associated with cryonics, and debates within the cryonics community itself.

Soft Cover Edition: $20 – Hard Cover Edition: $35
To order your copy, go to: www.alcor.org/book
or call 1-877-GO ALCOR (462-5267)

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.

In Search of Very Rare Genetic Variants with Large Effects on Longevity

May, 2020

Genetic studies of the past twenty years have quite effectively ruled out the idea that genetic variation has a meaningful impact on life span in the overwhelming majority of people. To a first approximation, there are no longevity genes. Rather there is a mosaic of tens of thousands of tiny, situational, interacting effects, that in aggregate produce an outcome on health that is far smaller than the results of personal choice in health and lifestyle. Near the entirety of the effects that your parents have on your health and life span stems from their influence on the important choices – whether you smoke, whether you get fat, whether you exercise.

But this is not to say that there are no longevity genes. It only constrains our expectations on their rarity, just as human demographics constrains our expectations on how large an effect size is plausible. Big databases and modern data mining can still miss rare variants and mutations. There is the example of the single family of PAI-1 loss of function mutants who might live seven years longer than their peers – possibly as a result of the influence of PAI-1 on the burden of cellular senescence. One might also suspect that the exceptional familial longevity of some Ashkenazi Jews is simply too much for good lifestyle choice to explain, though there no single variant really stands out after many years of assessment.

The commentary here notes recent research into rare variants and life span that, once again, fails to find a sizable contribution to longevity or its inheritance. At some point, we must accept that genetics is most likely not a direct and easy path to enhanced human longevity. It is an important tool in the toolkit, enabling therapies for a range of uses, but the goal of a modest adjustment to a few genes that produces an altered metabolism that yields significant gains in longevity (with minimal side-effects) may be a mirage. Time will tell.

Aging: Searching for the genetic key to a long and healthy life

For centuries scientists have been attempting to understand why some people live longer than others. Individuals who live to an exceptional old age – defined as belonging to the top 10% survivors of their birth cohort – are likely to pass on their longevity to future generations as an inherited genetic trait. However, recent studies suggest that genetics only accounts for a small fraction (~10%) of our lifespan. One way to unravel the genetic component of longevity is to carry out genome-wide association studies (GWAS) which explore the genome for genetic variants that appear more or less frequently in individuals who live to an exceptional old age compared to individuals who live to an average age. However, the relatively small sample sizes of these studies has made it difficult to identify variants that are associated with longevity.

The emergence of the UK Biobank – a cohort that contains a wide range of health and medical information (including genetic information) on about 500,000 individuals – has made it easier to investigate the relationship between genetics and longevity. Although it is not yet possible to study longevity directly with the data in the UK Biobank, several GWAS have used these data to study alternative lifespan-related traits, such as the parental lifespan and healthspan of individuals (defined as the number of years lived in the absence of major chronic diseases). These studies have been reasonably successful in identifying new genetic variants that influence human lifespan, but these variants can only explain ~5% of the heritability of the lifespan-related traits.

The GWAS have only focused on relatively common genetic variants (which have minor allele frequencies (MAFs) of ≥1%), and it is possible that rare variants might be able to explain what is sometimes called the 'missing heritability'. Now researchers report how they analyzed data from the UK Biobank and the UK Brain Bank Network (which stores and provides brain tissue

for researchers) to investigate how rare genetic variants affect lifespan and healthspan.

One type of rare genetic variant, called a protein-truncating variant, can dramatically impact gene expression by disrupting the open reading frame and shortening the genetic sequence coding for a protein. The team calculated how many of these rare protein-truncating variants, also known as PTVs, were present in the genome of each individual, and found ultra-rare PTVs (which have MAFs of less than 0.01%) to be negatively associated with lifespan and healthspan. This suggests that individuals with a small number of ultra-rare PTVs are more likely to have longer, healthier lives. This work is the first to show that rare genetic variants play a role in lifespan-related traits, which is in line with previous studies showing rare PTVs to be linked to a variety of diseases. However, these variants only have a relatively small effect on human lifespan and cannot fully explain how longevity is genetically passed down to future generations.

Link: https://doi.org/10.7554/eLife.57242

Ten Weeks of Resistance Training in 60-Year-Olds Doubles NAD+ Levels in Muscle Tissue

May, 2020

When looking at any of the work presently taking place on improving metabolism in older individuals, whether by stress response upregulation, or by improving mitochondrial function, it is always worth checking the human data, where it exists, to compare the effect size with that of exercise. This open paper is a useful resource when comparing exercise to the class of approaches that fairly directly increase levels of NAD+/NADH. These molecules are involved in mitochondrial function, and for various reasons – decline in recycling, decline in synthesis – become less available with age.

A number of supplements and treatments are on the market or under development to increase NAD+ levels in older people, and an initial human trial has been published for nicotinamide riboside. In that trial, nicotinamide riboside supplementation boosted NAD+ by 60% or so in immune cells from a blood sample. In the paper here, NAD+ was more than doubled in muscle cells following ten weeks of resistance training, restoring levels in older people to that of college-aged individuals. This is not an apples to apples comparison, but worth considering while thinking about the present enthusiasm for NAD+ upregulation. The long term effects of exercise and resistance training are quite well catalogued, and while beneficial, do not greatly extend life.

Nicotinamide adenine dinucleotide (NAD+) is a metabolite involved in numerous biochemical reactions. In particular, NAD+ is involved with electron transport where the reduced form (NADH) transfers electrons to other substrates and intermediates of metabolism. There is enthusiasm surrounding the role that tissue NAD+ concentrations play in the aging process, and researchers have determined skeletal muscle NAD+ concentrations are lower in older rodents and humans. These findings have led some to suggest that the age-associated loss in skeletal muscle NAD+ levels contributes to mitochondrial dysfunction. NAD+ biosynthesis can be catalyzed through the salvage/recycling pathway, and nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in this pathway. Beyond its involvement with redox reactions, NAD+ binds to and activates a class of enzymes that possess deacetylase activity called sirtuins (SIRTs).

Endurance training appears to be capable of increasing skeletal muscle markers related to NAD+ and SIRT signaling. For instance, endurance training in rodents and humans has been shown to modulate SIRT1 and SIRT3 protein levels and increase the activity of these enzymes in skeletal muscle. Additionally, skeletal muscle NAMPT protein levels have been reported to be higher in endurance-trained athletes versus untrained individuals. However, there is a paucity of research examining these biomarkers in response to resistance training. It remains plausible that resistance training can increase skeletal muscle markers related to NAD+ biosynthesis and SIRT signaling, and this may be an involved mechanism in facilitating training adaptations.

Given the paucity of data in this area, we sought to examine the effects of resistance training on skeletal muscle NAD+ concentrations as well as NAMPT protein levels, SIRT1/3 protein levels, and markers of SIRT activity in middle-aged, overweight, untrained individuals. In the middle-aged participants, the 10-week training intervention: i) promoted training adaptations (i.e., increased strength and localized hypertrophy), ii) robustly increased muscle NAD+ and NADH concentrations, iii) modestly (but significantly) increased NAMPT protein levels and global SIRT activity, and iv) robustly increased citrate synthase activity levels in muscle suggesting mitochondrial biogenesis occurred. This is the first evidence to suggest resistance training in middle-aged individuals restores muscle NAD+ and NADH concentrations to levels observed in recreationally-trained college-aged individuals.

Link: https://doi.org/10.18632/aging.103218

A Biomarker of Aging Based on Protein Glycosylation Patterns

May, 2020

I note the development of a commercial aging clock based on glycosylation patterns of immunoglobulin G, a marker for the

inflammatory status of the immune system, by startup biotech company GlycanAge. There are at present any number of approaches to measuring biological age, the burden of cell and tissue damage that leads to dysfunction. Stage of development varies widely, with the most work to date being on clocks based on changes in DNA methylation. There are also clocks that use protein levels in blood, weighted combinations of simple measures such as grip strength, and other approaches besides these. The important goal in these efforts is to produce a measure that can quickly be applied before and after a potential intervention to quantify the degree to which it reverses aging. A generally accepted, fast, cheap measure of age would greatly accelerate development of rejuvenation therapies, and might finally focus more research attention on repair-based interventions that have a greater chance of producing large-sized effects.

That still lies a way in the future, however. The challenge with nearly all these clocks is that they are constructed by comparing data that is far downstream of the causes of aging against outcomes such as mortality risk. Thus there is no good understanding of what exactly it is that these biomarkers of aging are actually measuring, under the hood. The glycosylation clock is clearer than most, in that it is very directly an assessment of the chronic inflammation of aging, but even then it is a challenge to say which underlying causes of aging are more or less important in that outcome. The situation is much murkier for other clocks.

This lack of knowledge means that a clock must be calibrated against each potential intervention, in the slow, hard way, by waiting to assess lifespan, in order to ensure that it is a valid test. This somewhat defeats the point of the exercise, to make development faster for new interventions. Further, it means that most of the commercially available tests are not actionable: the test will produce a number, but that number says nothing about what might be done to change it. The glycosylation clock is at least ahead of the game on that front, pointing directly to whatever approaches are known to reduce chronic inflammation, but this may or may not still be somewhat disconnected from other processes of aging.

Start-up claims first commercial glycan-based age test

GlycanAge is a British-Croatian start-up focused on analysing glycosylation patterns to deliver what it claims is the "most accurate" measure of biological age. Glycans are complex sugars that contribute significantly to the structure and function of the majority of proteins. Changes in glycans have been reported in many inflammatory diseases, where they reflect disease activity, or in some cases even precede the development of disease.

The company, leveraging patents from leading glycomics research lab Genos, has developed a direct-to-consumer glycan test kit that measures biological age and chronic low grade systemic inflammation. When the company first started in 2016, it worked using plasma samples, which was expensive and hard to scale commercially, but it has since developed a dry blood spot based test that delivers the same results.

"Telomeres are DNA timers that limit the lifespan of a single cell. On the individual cell level, telomeres are the best marker of aging. However, we are composed of trillions of cells and each of them has different age and expected lifespan. GlycanAge is different because it measures your immunoglobulin G glycosylation, which directly correlates with the level of inflammation in your body. It will give you information about the immune balance of your organism that changes with age, health and life circumstances."

https://www.longevity.technology/start-up-claims-first-commercial-glycan-based-age-test/

GlycanAge

GlycanAge is a science-based test that will accurately determine your biological age. This is a first commercial glycan-based test that will put a single number to your health. Glycans are complex sugar molecules (carbohydrates), and one of the four main building blocks of life. They are involved in almost every process in our body.

More than half of all our proteins are glycosylated, with their glycan parts often playing an essential functional role. Glycans are crucial for the functioning of our immune system. Glycans attached to the antibodies modulate their activity and determine if they will have a pro-inflammatory or anti-inflammatory function. Thus, it is not surprising that glycan profiles can serve as a measure of an individual's health. The GlycanAge test looks at the glycosylation pattern of the immunoglobulin G (IgG) molecule. IgG is the most prevalent antibody type in our blood and especially important in controlling inflammation and pathogens.

Immunoglobulin G (IgG), the most prevalent antibody type in our blood, is always glycosylated – meaning it has glycans attached to it. The type of the glycan group attached to the IgG determines if IgG will enhance or reduce inflammation. Since inflammation can exhaust our resources to keep the body in good health, low level of inflammation was shown to be a predictor of successful ageing. Therefore, IgG glycosylation is also a good measure of biological age.

https://glycanage.com/

Analysis of Dasatinib and Quercetin as a Senolytic Therapy

May, 2020

The Forever Healthy Foundation publishes a series of conservative risk-benefit analyses of presently available interventions that

might prove beneficial in addressing aspects of aging. These range widely in proven effectiveness, quality of animal evidence, and theoretical utility. Some do not in any way attack the known root causes of aging. Some are still pending any sort of rigorous human trial data. Some have plenty of human data that strongly indicates small, unreliable effects at best. It is nonetheless a useful exercise to make clear which are which. In a world in which the "anti-aging" industry propagates all sorts of nonsense to sell their snake-oil products, there is a comparative lack of good, unbiased analysis of approaches that might actually work to some degree, coupled with a responsible attitude towards uncertainty and risk.

The latest publication in the Forever Healthy series covers what is probably the best of the few presently available rejuvenation therapies, the use of dasatinib and quercetin in combination as a senolytic treatment. Senolytics selectively destroy senescent cells. These cells accumulate with age, and their presence actively maintains an inflammatory, dysfunctional state of metabolism, contributing meaningfully to the progression of degenerative aging and age-related disease. In animal models, senolytic therapies produce impressive results in turning back the manifestations of a wide range of age-related diseases. It is not hyperbole to say that this data is far, far better, more reliable, and more robust than the equivalent data for any other intervention targeting aging in old animals. Several small human trials have either been conducted or are underway for dasatinib and quercetin, and the published results to date are promising but not yet conclusive.

Risk-Benefit Analysis of Dasatinib + Quercetin as a Senolytic Therapy

When a cell reaches the end of its life or becomes damaged beyond repair it normally either kills itself or signals the immune system to remove it. Unfortunately, every so often this mechanism fails. The cell stays around indefinitely and starts poisoning its environment. Over time, more and more of these harmful, death resistant, senescent cells accumulate. Senescent cells are thought to be one of the main drivers of aging and age-related diseases.

Senolytics are drugs that selectively remove senescent cells by disabling the mechanisms that allow them to survive. Dasatinib (D), a well-established medication used in the treatment of cancer and quercetin (Q), a flavonoid common in plants were among the first senolytics to be discovered. As they have been shown to affect different types of senescent cells, they are often employed in combination.

Studies in rodents have shown that clearing senescent cells can prevent, delay, or alleviate multiple age-related diseases and extend the healthy lifespan by up to 35%. Based on the promising results in animal testing, it is supposed that intermittent dosing of D+Q also leads to the elimination of senescent cells in humans with the accompanying health and rejuvenation benefits. As the first clinical trials in humans have been completed and interest in the practical application of D+Q is increasing, Forever Healthy seeks to assess the risks, benefits, and therapeutic protocols of using D+Q as a senolytic therapy.

Currently, there are only results from 3 trials in humans in which D+Q was evaluated as a senolytic therapy. The majority of human studies used D or Q in cancer therapy and provided information on side effects and safety. The benefits shown in animals were significant and were observed in many organ systems. However, several of the benefits only occurred in diseased animals (i.e. diabetic mice), while the healthy control group did not benefit from the treatment.

The benefits reported in human studies are mainly focussed on senescent cell markers. So far, these markers are only hypothesized to translate to clinically meaningful effects. Few benefits had direct clinical relevance, and those were not really convincing. Additionally, 2 out of the 3 clinical studies were in patients with pre-existing disease so there is very limited information on the effect in healthy individuals. The potential risks of D are extensive and well-known through its use in the treatment of cancer. While the clinical trials that used D+Q as a senolytic therapy reported only mild to moderate adverse events, it is of note that the low number of participants in these studies might not deliver a representative result.

Furthermore, the human studies all used different treatment protocols and there is no consensus on the measurement of efficacy in clinical practice. Therefore, until there are more studies showing benefits in humans, a clearer picture of the senolytic-use specific risk profile, and a consensus on a treatment protocol, it seems prudent to avoid the use of D+Q as a senolytic therapy.

Link: https://www.forever-healthy.org/news/risk-benefit-analysis-of-dasatinib-quercetin-as-a-senolytic-therapy

---

Send email to Reason at Fight Aging!: **reason@fightaging.org**

Alcor Associate Membership

Supporters of Alcor who are not yet ready to make cryopreservation arrangements can become an Associate Member for $5/month (or $15/quarter or $60 annually). Associate Members are members of the Alcor Life Extension Foundation who have not made cryonics arrangements but financially support the organization.

Associate Members will receive:

- ***Cryonics* magazine by mail**
- **Discounts on Alcor conferences**
- **Access to post in the Alcor Member Forums**
- **Access to local Alcor meetings and training events**

ALCOR
LIFE EXTENSION FOUNDATION
The World's Leader in Cryonics
www.alcor.org

To become an Associate Member send a check or money order ($5/month or $15/quarter or $60 annually) to Alcor Life Extension Foundation, 7895 E. Acoma Dr., Suite 110, Scottsdale, Arizona 85260, or call Marji Klima at (480) 905-1906 ext. 101 with your credit card information.

Or you can pay online via PayPal using the following link: http://www.alcor.org/BecomeMember/associate.html *(quarterly option is not available this way)*.

Associate Members can improve their chances of being cryo-preserved in an emergency if they complete and provide us with a Declaration of Intent to be Cryopreserved (http://www.alcor.org/Library/html/declarationofintent.html). Financial provisions would still have to be made by you or someone acting for you, but the combination of Associate Membership and Declaration of Intent meets the informed consent requirement and makes it much more likely that we could move ahead in a critical situation.

Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Breaking the Next Cryo-EM Resolution Barrier – Atomic Resolution Determination of Proteins!

Ka Man Yip, Niels Fischer, Elham Paknia, Ashwin Chari, Holger Stark

bioRxiv, 21 May 2020, https://www.biorxiv.org/content/10.1101/2020.05.21.106740v1, accessed 25 Aug. 2020.

(This article is a preprint and has not been certified by peer review.)

Summary

Single particle cryo-EM is a powerful method to solve the three-dimensional structures of biological macromolecules. The technological development of electron microscopes, detectors, automated procedures in combination with user friendly image processing software and ever-increasing computational power have made cryo-EM a successful and largely expanding technology over the last decade. At resolutions better than 4 Å, atomic model building starts becoming possible but the direct visualization of true atomic positions in protein structure determination requires significantly higher (< 1.5 Å) resolution, which so far could not be attained by cryo-EM. The direct visualization of atom positions is essential for understanding protein-catalyzed chemical reaction mechanisms and to study drug-binding and -interference with protein function. Here we report a 1.25 Å resolution structure of apoferritin obtained by cryo-EM with a newly developed electron microscope providing unprecedented structural details. Our apoferritin structure has almost twice the 3D information content of the current world record reconstruction (at 1.54 Å resolution). For the first time in cryo-EM we can visualize individual atoms in a protein, see density for hydrogen atoms and single atom chemical modifications. Beyond the nominal improvement in resolution we can also show a significant improvement in quality of the cryo-EM density map which is highly relevant for using cryo-EM in structure-based drug design.

Single-Particle Cryo-EM at Atomic Resolution

Takanori Nakane, Abhay Kotecha, Andrija Sente, Greg McMullan, Simonas Masiulis, Patricia M.G.E. Brown, IoanaT. Grigoras, Lina Malinauskaite, Tomas Malinauskas, Jonas Miehling, Lingbo Yu, Dimple Karia, Evgeniya V. Pechnikova, Erwin de Jong, Jeroen Keizer, Maarten Bischoff, Jamie McCormack, Peter Tiemeijer, Steven W. Hardwick, Dimitri Y. Chirgadze, Garib Murshudov, A. Radu Aricescu, Sjors H.W. Scheres

bioRxiv, 22 May 2020, https://www.biorxiv.org/content/10.1101/2020.05.22.110189v1 , accessed 25 Aug. 2020.

(This article is a preprint and has not been certified by peer review.)

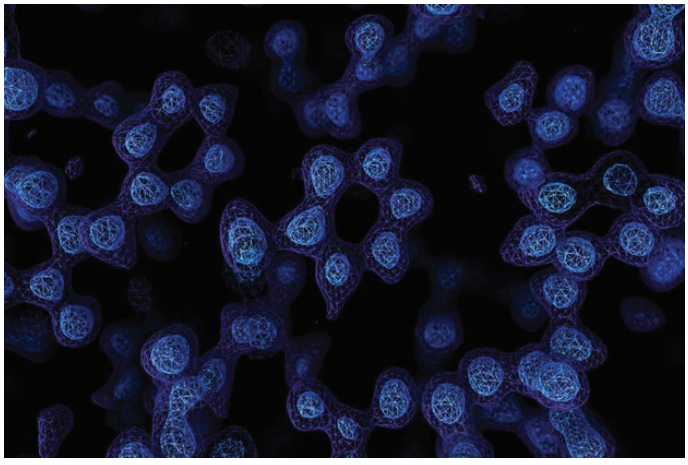
Abstract

The three-dimensional positions of atoms in protein molecules define their structure and provide mechanistic insights into the roles they perform in complex biological processes. The more precisely atomic coordinates are determined, the more chemical information can be derived and the more knowledge about protein function may be inferred. With breakthroughs in electron detection and image processing technology, electron cryo-microscopy (cryo-EM) single-particle analysis has yielded protein structures with increasing levels of detail in recent years. However, obtaining cryo-EM reconstructions with sufficient resolution to visualise individual atoms in proteins has thus far been elusive. Here, we show that using a new electron source, energy filter and camera, we obtained a 1.7 Å resolution cryo-EM reconstruction for a prototypical human membrane protein, the β3 GABAA receptor homopentamer3. Such maps allow a detailed understanding of small molecule coordination, visualisation of solvent molecules and alternative conformations for multiple amino acids, as well as unambiguous building of ordered acidic side chains and glycans. Applied to mouse apoferritin, our strategy led to a 1.2 Å resolution reconstruction that, for the first time, offers a genuine atomic resolution view of a protein molecule using single particle cryo-EM. Moreover, the scattering potential from many hydrogen atoms can be visualised in difference maps, allowing a direct analysis of hydrogen bonding networks. Combination of the technological

advances described here with further approaches to accelerate data acquisition and improve sample quality provide a route towards routine application of cryo-EM in high-throughput screening of small molecule modulators and structure-based drug discovery.

From: 'It Opens Up a Whole New Universe': Revolutionary Microscopy Technique Sees Individual Atoms for First Time

Ewen Callaway, *Nature News*, 03 Jun. 2020, https://www.nature.com/articles/d41586-020-01658-1?WT.ec_id=NATURE-20200611&utm_source=nature_etoc&utm_medium=email&utm_campaign=20200611&sap-outbound-id=F68F5789BB7A31B1A184C14D40BE57C68D5D7664, accessed 25 Aug. 2020.



A Cryo-EM map of the protein apoferritin.
Credit: Paul Emsley/MRC Laboratory of Molecular Biology

A game-changing technique for imaging molecules known as cryo-electron microscopy has produced its sharpest pictures yet – and, for the first time, discerned individual atoms in a protein.

By achieving atomic resolution using cryogenic-electron microscopy (cryo-EM), researchers will be able to understand, in unprecedented detail, the workings of proteins that cannot easily be examined by other imaging techniques, such as X-ray crystallography.

The breakthrough, reported by two laboratories late last month, cements cryo-EM's position as the dominant tool for mapping the 3D shapes of proteins, say scientists. Ultimately, these structures will help researchers to understand how proteins work in health and disease, and lead to better drugs with fewer side effects.

"It's really a milestone, that's for sure. There's really nothing to break anymore. This was the last resolution barrier," says Holger Stark, a biochemist and electron microscopist at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, who led one of the studies. The other was led by Sjors Scheres and Radu Aricescu, structural biologists at the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) in Cambridge, UK. Both were posted on the bioRxiv preprint server on 22 May.

"True 'atomic resolution' is a real milestone," adds John Rubinstein, a structural biologist at the University of Toronto in Canada. Getting atomic-resolution structures of many proteins will still be a daunting task because of other challenges, such as a protein's flexibility. "These preprints show where one can get to if those other limitations can be addressed," he adds.

Cryo-EM is a decades-old technique that determines the shape of flash-frozen samples by firing electrons at them and recording the resulting images. Advances in technology for detecting the ricocheting electrons and in image-analysis software catalysed a 'resolution revolution' that started around 2013. This led to protein structures that were sharper than ever before – and nearly as good as those obtained from X-ray crystallography, an older technique that infers structures from diffraction patterns made by protein crystals when they are bombarded with X-rays.

Subsequent hardware and software advances led to more improvements in the resolution of cryo-EM structures. But scientists have had to largely rely on X-ray crystallography for obtaining atomic-resolution structures. However, researchers can spend months to years getting a protein to crystallize, and many medically important proteins won't form usable crystals; cryo-EM, by contrast, requires only that the protein be in a purified solution.

Atomic-resolution maps are precise enough to unambiguously discern the position of individual atoms in a protein, at a resolution of around 1.2 ångströms (1.2×10^{-10} m). These structures are especially useful for understanding how enzymes work and using those insights to identify drugs that can block their activity.

To push cryo-EM to atomic resolution, the two teams worked on an iron-storing protein called apoferritin. Because of its rock-like stability, the protein has become a test bed for cryo-EM: a structure of the protein with a resolution of 1.54 ångströms was the previous record.

The teams then used technological improvements to take sharper pictures of apoferritin. Stark's team got a 1.25-ångström structure of the protein, with help from an instrument that ensures that the electrons travel at similar speeds before hitting a sample, enhancing the resolution of the resulting images. Scheres, Aricescu and their group used a different technology to fire electrons travelling at similar speeds; they also benefited from a technology that reduces the noise generated after some electrons careen off the protein

sample, as well as a more sensitive electron-detecting camera. Their 1.2-ångström structure was so complete, says Scheres, that they could pick out individual hydrogen atoms, both in the protein and in surrounding water molecules.

A Programmable Fate Decision Landscape Underlies Single-Cell Aging in Yeast

Yang Li, Yanfei Jiang, Julie Paxman, Richard O'Laughlin, Stephen Klepin, Yuelian Zhu, Lorraine Pillus, Lev S. Tsimring, Jeff Hasty, Nan Hao

Science 369(6501) (17 Jul 2020) 325-329, DOI: 10.1126/science.aax9552, https://science.sciencemag.org/content/369/6501/325, accessed 23 Aug. 2020.

Abstract

Chromatin instability and mitochondrial decline are conserved processes that contribute to cellular aging. Although both processes have been explored individually in the context of their distinct signaling pathways, the mechanism that determines which process dominates during aging of individual cells is unknown. We show that interactions between the chromatin silencing and mitochondrial pathways lead to an epigenetic landscape of yeast replicative aging with multiple equilibrium states that represent different types of terminal states of aging. The structure of the landscape drives single-cell differentiation toward one of these states during aging, whereby the fate is determined quite early and is insensitive to intracellular noise. Guided by a quantitative model of the aging landscape, we genetically engineered a long-lived equilibrium state characterized by an extended life span.

From: Researchers Discover Two Paths of Aging and New Insights on Promoting Healthspan

Mario Aguilera, UC San Diego News Center, 16 Jul. 2020, https://ucsdnews.ucsd.edu/pressrelease/researchers-discover-two-paths-of-aging-and-new-insights-on-promoting-healthspan, accessed 24 Aug. 2020.

Molecular biologists and bioengineers at the University of California San Diego have unraveled key mechanisms behind the mysteries of aging. They isolated two distinct paths that cells travel during aging and engineered a new way to genetically program these processes to extend lifespan.

The research is described July 17 in the journal Science.

Our lifespans as humans are determined by the aging of our individual cells. To understand whether different cells age at the same rate and by the same cause, the researchers studied aging in the budding yeast Saccharomyces cerevisiae, a tractable model for investigating mechanisms of aging, including the aging paths of skin and stem cells.

The scientists discovered that cells of the same genetic material and within the same environment can age in strikingly distinct ways, their fates unfolding through different molecular and cellular trajectories. Using microfluidics, computer modeling and other techniques, they found that about half of the cells age through a gradual decline in the stability of the nucleolus, a region of nuclear DNA where key components of protein-producing "factories" are synthesized. In contrast, the other half age due to dysfunction of their mitochondria, the energy production units of cells.

The cells embark upon either the nucleolar or mitochondrial path early in life, and follow this "aging route" throughout their entire lifespan through decline and death. At the heart of the controls the researchers found a master circuit that guides these aging processes.

"To understand how cells make these decisions, we identified the molecular processes underlying each aging route and the connections among them, revealing a molecular circuit that controls cell aging, analogous to electric circuits that control home appliances," said Nan Hao, senior author of the study and an associate professor in the Section of Molecular Biology, Division of Biological Sciences.

Having developed a new model of the aging landscape, Hao and his coauthors found they could manipulate and ultimately optimize the aging process. Computer simulations helped the researchers reprogram the master molecular circuit by modifying its DNA, allowing them to genetically create a novel aging route that features a dramatically extended lifespan.

"Our study raises the possibility of rationally designing gene or chemical-based therapies to reprogram how human cells age, with a goal of effectively delaying human aging and extending human healthspan," said Hao.

The researchers will now test their new model in more complex cells and organisms and eventually in human cells to seek similar aging routes. They also plan to test chemical techniques and evaluate how combinations of therapeutics and drug "cocktails" might guide pathways to longevity.

Wireless Programmable Recording and Stimulation of Deep Brain Activity in Freely Moving Humans

Uros Topalovic, Zahra M. Aghajan, Diane Villaroman, Dawn Eliashiv, Itzhak Fried, Nanthia Suthana

***Neuron*, 17 Sep. 2020, DOI:https://doi.org/10.1016/j.neuron.2020.08.021,https://www.cell.com/neuron/fulltext/S0896-6273(20)30652-8, accessed 13 Oct. 2020.**

Summary

Uncovering the neural mechanisms underlying human natural ambulatory behavior is a major challenge for neuroscience. Current commercially available implantable devices that allow for recording and stimulation of deep brain activity in humans can provide invaluable intrinsic brain signals but are not inherently designed for research and thus lack flexible control and integration with wearable sensors. We developed a mobile deep brain recording and stimulation (Mo-DBRS) platform that enables wireless and programmable intracranial electroencephalographic recording and electrical stimulation integrated and synchronized with virtual reality/augmented reality (VR/AR) and wearables capable of external measurements (e.g., motion capture, heart rate, skin conductance, respiration, eye tracking, and scalp EEG). When used in freely moving humans with implanted neural devices, this platform is adaptable to ecologically valid environments conducive to elucidating the neural mechanisms underlying naturalistic behaviors and to the development of viable therapies for neurologic and psychiatric disorders.

From: Want to Decode the Human Brain? There's a New System for That, and It's Pretty Wild

Shelley Fan, SingularityHub, 22 Sep. 2020, https://singularityhub.com/2020/09/22/want-to-decode-the-human-brain-theres-a-new-system-for-that-and-its-pretty-wild/, accessed 15 Oct. 2020.

Even for high-tech California, the man strolling around UCLA was a curious sight.

His motion capture suit, sensor-embedded gloves, and virtual reality eyewear were already enough to turn heads. But what stopped people in their tracks and made them stare was a bizarre headgear, tightly strapped to his head through a swimming cap-like device embedded with circular electrode connectors. Several springy wires sprouted from the headgear – picture a portable hard drive hooked up to a police siren enclosure – and disappeared into a backpack. The half-cyborg look teetered between sci-fi futurism and hardware Mad Libs.

Meet Mo-DBRS, a setup that could fundamentally change how we decode the human brain.

The entire platform is a technological chimera that synchronizes brain recordings, biomarkers, motion capture, eye tracking, and AR/VR visuals. Most of the processing components are stuffed into a backpack, so that the wearer isn't tethered to a "landline" computer. Instead, they can freely move around and explore – either in the real world or in VR – something not usually possible with brain scanning technology like MRI.

Movement may seem like a trivial addition to brain scanning, but it's a game changer. Many of our treasured neural capabilities – memory, decision-making – are honed as we explore the world around us. Mo-DBRS provides a window into those brain processes in a natural setting, one where the person isn't told to hold still while a giant magnet clicks and clangs around their head. Despite its non-conventional look, Mo-DBRS opens the door to analyzing brain signals in humans in environments close to the real world, while also having the ability to alter those brain signals wirelessly with a few taps on a tablet.

All custom software powering Mo-DBRS is open-sourced, so neuroscientists can immediately play with and contribute to the platform. However, because the setup relies on volunteers with electrodes implanted in the brain, it's currently only tested in a small number of people with epilepsy who already have neural implants to help diagnose and prevent their seizures.

Silk Fibroin Nanofibers: A Promising Ink Additive for Extrusion Three-Dimensional Bioprinting

S.Sakai, A.Yoshii, S.Sakurai, K.Horii, O.Nagasuna

***Materials Today Bio* 8 (Sep.2020), 100078, online 19 Sep. 2020, https://www.sciencedirect.com/science/article/pii/S2590006420300387?via%3Dihub, accessed 16 Oct. 2016.**

Abstract

Here, we investigated the usefulness of silk fibroin nanofibers obtained via mechanical grinding of degummed silkworm silk fibers as an additive in bioinks for extrusion three-dimensional (3D) bioprinting of cell-laden constructs. The nanofibers could be sterilized by autoclaving, and addition of the nanofibers improved the shear thinning of polymeric aqueous solutions, independent of electric charge and the content of cross-linkable moieties in the polymers. The addition of nanofibers to bioinks resulted in the fabrication of hydrogel constructs with higher fidelity to blueprints. Mammalian cells in the constructs showed >85% viability independent of the presence of nanofibers. The nanofibers did not affect the morphologies of enclosed cells. These results demonstrate the great potential of silk fibroin nanofibers obtained via mechanical grinding of degummed silkworm silk fibers as an additive in bioinks for extrusion 3D bioprinting.

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:

- *Cryonics* magazine by mail
- Discounts on Alcor conferences
- Access to post in the Alcor Member Forums
- A dollar-for-dollar credit toward full membership sign-up fees for any dues paid for Associate Membership

To become an Associate Member send a check or money order ($5/month or $15/quarter or $60 annually) to Alcor Life Extension Foundation, 7895 E. Acoma Dr., Suite 110, Scottsdale, Arizona 85260, or call Marji Klima at (480) 905-1906 ext. 101 with your credit card information. You can also pay using PayPal (and get the Declaration of Intent to Be Cryopreserved) here: http://www.alcor.org/BecomeMember/associate.html

ALCOR
LIFE EXTENSION FOUNDATION
The World's Leader in Cryonics
www.alcor.org

Call toll-free TODAY to start your application:

877-462-5267 ext. 132 • info@alcor.org • www.alcor.org

ALCOR

LIFE EXTENSION FOUNDATION

The World's Leader in Cryonics

www.alcor.org

7895 East Acoma Drive
Suite 110
Scottsdale, AZ 85260

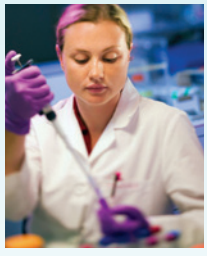
Your Body Deserves The Best!

Our focus is on quality, purity, potency.

Life Extension has been helping people stay healthy and live better for more than 40 years.

Today, we make over 350 vitamins and nutritional supplements that set the gold standard for supporting healthy longevity.

Life Extension is much more than just a nutritional supplement company. We're your partners for an extended lifetime of good health.



Blood Tests

Blood testing provides you with vital information about your general health and nutritional status, enabling you to make informed decisions and head off potential problems. We offer our unique mail-order blood test service, with comprehensive panels that can help you do everything from assess your cardiac risk factors, to determine what unseen factors may be contributing to unwanted weight gain.

Life Extension Magazine®

Bursting at the seams with the latest medical findings, research results, novel therapies, and innovative treatment protocols, *Life Extension* Magazine® is the ultimate resource for staying healthy and living better. Every month, it features the kind of hard-to-find, cutting-edge information that will empower you to make smart health choices … and become your own health advocate!

Wellness Specialists

We offer **FREE** access to an expert team of naturopaths, nutritionists, and nurses who can answer your health-related questions, every day of the year. And they'll gladly create a regimen of nutritional supplements, diet, and exercise that's customized for your needs.

$10 OFF your order of $100 or more
One time use – expires 1/31/2021
Must Use Code **INA208A**

LIFE EXTENSION®
The Science of a Healthier Life®

Please call toll-free 1-855-876-1220 to order

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.