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Member Profile: Hal Finney

page 3

Case Report: A-1990

page 12

Victor Frankenstein and the Modern Quest for the Secrets of Life

page 30

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CRYONICS

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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
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Contents

Member Profile: Hal Finney

By Nicole Weinstock

The crypto corners of the Internet saw a surge in conversation this past January when a now-historic tweet, "Running bitcoin," officially turned ten. It was posted by long-time cryptographer, cypherpunk, and computer programmer Hal Finney. In addition to being the first recipient of a Bitcoin transaction, Hal ran the first cryptographically based anonymous remailer, programmed some of the earliest console games, and helped develop the now-standard email encryption software, Pretty Good Privacy (PGP), under Phil Zimmerman.

Though widely known for his pioneering professional achievements across cyberspace and tech circles, Hal's daily life paints a much more nuanced portrait. He was a devoted husband and father and accomplished (yet eternally modest) Renaissance man. Hal was an eclectic athlete who challenged himself to distance versions of traditional exercises like running and biking, while exploring off-beat hobbies like juggling and pogo-sticking. He spiced up family gatherings with magic shows of his own design, aweing generations with his disappearing ghost and guess-your-domino acts. Hal was also an amateur astronomer who, together with his wife, Fran, named their children and dogs after celestial bodies.

In remembrance of Bitcoin's tenth anniversary, this special issue of *Cryonics* magazine honors Hal Finney with an in-depth profile, made possible by the generous support of his wife and children.

SoCal roots

Hal Finney was born in the spring of 1956 in the small town of Coalinga in Fresno County, California. The economy of Hal's birthplace was largely supported by jobs in the local state prison, agriculture, and oil, the last of which accounted for the Finney's residency. Hal's father, Harold T. Finney I, was a long-time employee of Union Oil of California or "Unocal," which supported the family's relocation to a number of different places throughout his lifetime. After just three months in Coalinga, the oil exporter moved the family to Abbeville, Louisiana for six years, and Houston, Texas for two years before supporting their return to California – Temple City, to be precise.

As was traditional for many families in the 1950s, Mrs. Finney supported her husband and children as a full-time homemaker. By 1957, they were a family of five, with Hal being the third of four children. While he and his younger brother, Mike, were almost exactly a year apart, their two older sisters, Pat and Kathy, were more than a decade older. Kathy provided some relief in the childcare department for their busy mother. The two boys were born so close together that they were often mistaken for twins, though Mike's prankster-inclined nature was a source of differentiation. Hal admired his mischief and occasionally partook, but ultimately hewed his own identity through his more earnest personality, dedication to school, and penchant for mental puzzles.

Hal (left) stands with his father (center) and brother, Mike (right) in the mid-60s. He and Mike were just a year apart in age and often mistaken for twins.

The roots of his later work as a developer and privacy advocate reached as far back as elementary school. He would create analog codes with letters and numbers for written materials found in something as innocuous as a paper booklet. Computers weren't prevalent in schools until the 1980s, but Hal's high school in Arcadia was lucky to have a few of the earliest versions during his time there. The administration used punch cards in combination with FORTRAN (an early programming language)

Though this photo was taken in the early 90s, Hal's love of skiing started when he was young. His family went on regular ski trips, both locally and out-of-state.

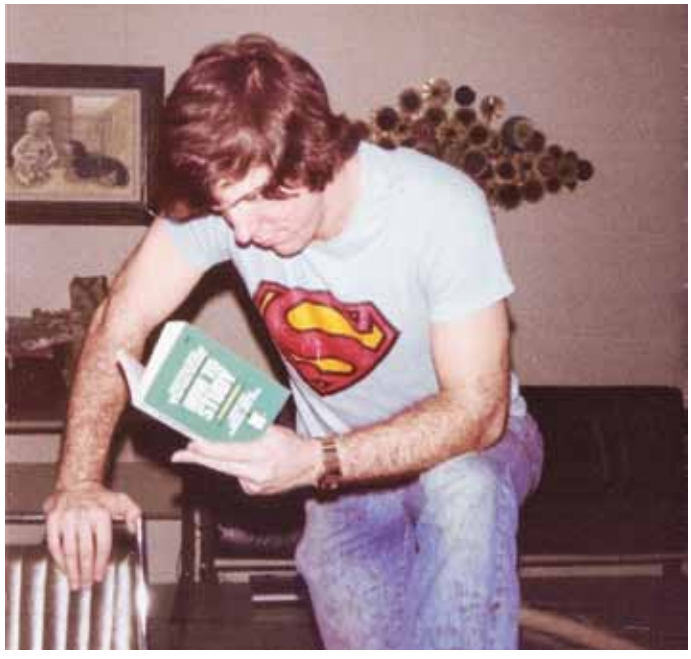
to digitally store simple data such as student attendance records. It wasn't as sophisticated as the kind of programming he'd see in later years, but for someone who had spent his childhood making analog codes, it was a definite upgrade. Somehow, Hal made his interest known to the school, and they entrusted him to help with some of their calculations. It wasn't uncommon for his fellow classmates to see him walking the halls with a stack of stiff, rectangular, perforated cards in hand.

Hal graduated from Arcadia High School in 1974 as valedictorian of his class with near perfect SAT scores and a spot at the prestigious California Institute of Technology (Caltech for short, and simply "Tech" for insiders). His intelligence was obvious enough, but maybe less apparent, given these achievements and a subdued, independent personality, was his attraction to more unstructured and spontaneous adventure. As one such activity, he came to excel in skiing during his teenage years thanks to regular family trips to wintry locales, from more distant resorts in places like Salt Lake City, to local snowpack in the nearby San Gabriel Mountains. Not only could he could tackle the exceptionally steep slopes of the double black diamond trails (typically a 40% grade or steeper), but his agile frame could land aerials in the powder as well.

Standing out at Caltech

When Hal became an official "Techer," as it were, he initially pursued his Bachelor of Science in math, eventually transitioning to engineering. At the time, there was no corresponding degree for computer programming – his true passion – so he made do by taking all the programing classes that he could. Humanities classes were required at Caltech to try to make their very technical student body a bit broader-based educationally, but Hal tended to avoid them. "He was into ideas, concepts, learning for the pleasure of it. He attended the classes he enjoyed, and just took the exams for the ones he felt were a waste of his time," says his wife, Fran. She was a biology major at Caltech with her sights on a career in medicine.

Fran and Hal met less than a month into Hal's first semester, during the so-called "rotation week" on-campus. The closest that a top tier technical school such as Caltech could come to anything resembling hazing, "rotation week" was a string of days where upperclassmen would gleefully assert dominance over the entering freshmen. Hal was in the midst of it – quite literally – when he first caught Fran's eye. A gifted mind herself, who graduated from high school a year early, Fran was already a junior at the time. "I saw him in the middle of being lifted and carried by [upperclassmen]," she recalls. There was a certain



Hal holds the book, "How to Study" in a memorably ironic photo from the late 70s; he never studied at school.

toughness and strength to him that felt curiously atypical for the average Techer. As fate would have it, they ended up living in the same dorm, and instantly struck up a friendship.

Ironically enough, though Hal's physique evidenced his enthusiasm for physical activity, it was the institution's Physical Education (PE) requirement that caused him the most frustration. Hal ran in Caltech's 24-hour relays, where teams of runners would take turns running a mile, handing off a baton between one runner and the next, for a full day. He was also an enthusiastic participant in the impromptu steeplechases that were announced at the last minute by his dormmates. Like the horse races after which they were named (less the horse component in this instance), a handful of students would group together to run a few miles of neighborhood terrain, creating an improvised obstacle course with bushes, fences, and other common features of suburbia.

Though Hal frequently participated in these more informal physical activities throughout his studies, they were not eligible for PE credit. Unlike other subjects, PE was structured in such a way that students had to attend class in order to pass the course; they couldn't ace a final exam in lieu of attendance as Hal so often did. So bothered was Hal by the PE policy, that he didn't attend class, confident that he could appeal it with the administration. In the end however, his appeal was denied, and he had to enroll for a fifth year at Caltech in order to fulfill this lingering requirement.

As much as the PE saga may have suggested a level of obstinacy about Hal, he was a humble person and confirmed Libertarian who valued a life of reason and freedom (barring harm to others). These values shaped many of his exchanges with other students, garnering the attention of many – not just his wife-to-be. "People would cluster around and get into all these philosophical discussions," says Fran of their college days together, "and the things he said were just so thought-provoking, so interesting. He always had good arguments to back up anything that he was proposing...I admired that. It was really clear that he was bright. Brighter than the typical Techer. He really was. There are some people at Tech that stand out. Hal was one of them."

On top of his thoughtful approach to debate and conversation among cohorts, Hal also distinguished himself through his patient attentiveness. "He certainly spent more time listening in general than talking," says Fran. "When he spoke, what he said was usually worth listening to." After she graduated in 1976, their friendship developed into a romance that would last more than 30 years. In 1979, after Hal's fifth and final year at Caltech, they wed in a San Diego park near Fran's family's home.

From student to cryptographer

Hal's reputation in programming preceded him and enabled a smooth transition from student to professional before he even graduated. He landed his first job in the summer of 1978 with APh (Applied Physics) Technological Consulting, a small engineering firm founded by classmates Glenn Hightower and John Denker four years prior.[1] By that time, the company was well into a notable contract with Mattel for the design of their Intellivision system (APh eventually developed their operating system and early games as well), though, according to an interview with Scott Stilphen in 2006, Hal himself worked on

Hal and Fran at APh, where Hal programmed early video games.

cash register software that first year.

During his tenure with APh, Hal worked on Intellivision's *Space Battle* and *Star Strike*, as well as the Atari Video Computer System's (VCS), *Adventures of Tron*, *Astroblast*, and *Space Attack* to name just a few. As quoted by Stilphen, he admitted, "I never really thought of myself as primarily a games programmer. I was more of a general purpose Assembly language developer," alluding to a few of his other APh projects, such as the cash registers, a Bausch and Lomb spectrometer, and special effects camera control software.[2] After APh, Hal developed operating systems with Ametek for a few years until he and his family relocated to Santa Barbara in 1991, where he worked for Greenhill Software developing compiler code generators and optimizers.

In addition to professional advances, the 80s also gave way to important personal landmarks for Hal. He and Fran decided to grow their small family, welcoming their first child, Jason, in 1983 followed by their daughter, Erin, in 1985. "Hal was a very easygoing father," says Fran. "But he was very appreciative and proud of the fact that the kids allowed him to be that way." Having instinctively well-meaning children freed Hal to make the most of his strengths to bring whimsy to their lives. For example, he designed a program that matched letters with pictures – "C" for "Cow" and so on – to help Jason learn the alphabet and sound out words. It was only when they received a disgruntled call

With the help of a plastic bag, Fran snapped an underwater photo of Hal and their two smiling children in 1986.

from their son's kindergarten teacher complaining about the disruptive nature of parents teaching their children how to read ahead of time, that they realized that Jason had independently applied the knowledge from his father's simple computer game to read the daily newspaper.

Needless to say, the Finneys were early adopters of all things online. When the World Wide Web became publicly available in 1991, they were already signed up with Prodigy (the second most popular online service provider, next to CompuServe), which they had engaged in 1990.[3] Around this time, Hal became quite active with the cypherpunks, a group of activists strongly advocating for cryptography and other technologies increasing online privacy. His personal website included a few pieces that he wrote for publication on their electronic mailing list on the subjects of digital cash, the politics of privacy, anonymous remailers, and other related areas of inquiry. In fact, Hal ran the first cryptographically-based anonymous remailer – a server that can receive and send messages to (a) particular recipient(s) through embedded instructions without betraying their source.

The Finneys at a family portrait sitting in the early 90s.

While Hal was making a name for himself in cryptography circles at home, veteran software engineer, Phil Zimmerman, approached him about a pro-bono opportunity. Hal would develop early versions of Zimmerman's encryption program, called Pretty Good Privacy (PGP). Little did he know, it was destined to become the most popular email encryption software across the globe following its 1991 release.[4] Hal's skills helped paved the way for Zimmerman to secure financial backing for a commercial version. In 1996, he founded PGP Inc, and Hal became its Senior Software Engineer. Hal stayed with the company, which became Network Associates, Inc., then PGP Corporation, and then Symantec through a series of acquisitions, until he retired in early 2011.

In the interim, Hal continued to follow his curiosity through the realm of cryptography, developing the first reusable proof-of-work system (RPoW) in 2004. He presented it at a conference in San Francisco in 2005 after practicing his delivery with Fran in the days leading up to it.

Introducing Bitcoin

In early 2009, Jason noticed his father's computer processor running 24-7 at full speed. "He mentioned that he was helping someone test a kind of prototype online cash system. That was how he thought of it. It wasn't real, it was a test for a prototype." In more specific terms, this test was Hal's recipiency of the first Bitcoin transaction. Though it was just another part of the process for him, Hal's role would forever secure him a place in the annals of cryptography across the globe.

Bitcoin was named and developed by the potentially pseudonymous creator, Satoshi Nakamoto. He or she or possibly even they (a group of cryptographers working under one pseudonym) originally introduced the concept in the now heavily-referenced whitepaper, *Bitcoin: A Peer-to-Peer Electronic Cash System*. In most general terms, it defined Bitcoin as a "purely peer-to-peer version of electronic cash" that could be sent and received without the typical intermediary of a financial institution. The dreaded fear of double-spending – when a digital currency is spent not once, but twice – would then be prevented (or at the very least, made extremely difficult) by a different kind of intermediary, an ever-growing list of all transactions that would be verified by peers in the system.[5] Though the term isn't referenced in that particular paper, the publicly available list or ledger is known as the "blockchain." As described by Keegan Macintosh in his article, *Bitcoin and Cryonics*, the blockchain "forms the backbone of the Bitcoin network," and is "so called because transactions between addresses of the network are recorded in the ledger in sequential 'blocks' of data one megabyte in size."[6]

Though there are many more cryptocurrencies available in 2019 – Ethereum, Monero, and Ripple, to name just a few – Bitcoin was the first cryptocurrency to be decentralized and utilize the game-changing blockchain technology. It is now reportedly used by about 15% of financial institutions and has seen a surge of interest in various applications, broadly speaking.[7] As Macintosh writes, Bitcoin is particularly promising in the realm of cryonics for its potential use in asset preservation. Cryopreserved cryonicists might be able to maintain their wealth in this form until their resuscitation. Similarly, it could be used by cryonics nonprofits to collect donations, or for cryonicists to securely pay their member dues.[8]

The possibilities ignited by Bitcoin are quite expansive, and yet, Hal's perspective on those first few days is one of humbling attention to process and detail. In a Bitcoin Forum post on March 19, 2013, he writes:

> *"When Satoshi announced the first release of the software, I grabbed it right away. I think I was the first person besides Satoshi to run bitcoin. I mined block 70-something, and I was the recipient of the first bitcoin transaction, when Satoshi sent ten coins to me as a test. I carried on an email conversation with Satoshi over the next few days, mostly me reporting bugs and him fixing them.*
>
> *Today, Satoshi's true identity has become a mystery. But at the time, I thought I was dealing with a young man of Japanese ancestry who was very smart and sincere. I've had the good fortune to know many brilliant people over the course of my life, so I recognize the signs.*
>
> *After a few days, bitcoin was running pretty stably, so I left it running. Those were the days when difficulty was 1, and you could find blocks with a CPU, not even a GPU. I mined several blocks over the next days. But I turned it off because it made my computer run hot, and the fan noise bothered me. In retrospect, I wish I had kept it up longer, but on the other hand I was extraordinarily lucky to be there at the beginning. It's one of those glass half full half empty things."*[9]

Given his tame description from above, it makes sense that Hal was surprised by the success of Bitcoin. Jason recalls, "[My father] was kind of shocked later when it turned out that Bitcoin actually started to have value." His mother agrees, explaining that, "I think it was kind of Hal's perspective as well. 'This is cool. This is a fun game. Look! This is actually working! Some of my ideas might be useful someday.'" Once Bitcoin took off, becoming a viable currency, Hal's excitement inspired a Bitcoin Christmas of sorts. He ventured forth into the ether of bitcoin-positive retailers to gift something to each of his family members. For Fran, he found an Alpaca wool retailer that accepted bitcoin, purchasing a pair socks that would forever be known in their house as her "bitcoin socks."

Fran and Hal brought their tandem bike to celebrate their 28th anniversary with a 28-mile ride in San Luis Obispo in 2007.

A difficult diagnosis

Before they even had kids, Fran and Hal began running 5K road races together for fun. Fran stuck with the shorter races. Around 2008, to ward off the effects of aging, Hal began to push towards half-marathons, and eventually, marathons. He had his eye on the epic 2010 Boston Marathon but needed to run a qualifying marathon in order to enter, so in late 2008 he signed up for the spring 2009 LA Marathon. An urban path from Dodger Stadium to the beaches of Santa Monica, it promised to tour him through many of the major landmarks of the city: the Disney Concert Hall, Grauman's Chinese Theater, Rodeo Drive, and quite a few more. In the end however, Hal only got to see half of them. Around mile 13 at the Hollywood Sunset Strip, he cramped up badly and had to quit. It wasn't totally unheard of in the world of distance running, though it was strange given Hal's training and preparation.

A similar episode occurred in cycling not too long after. Hal was a strong cyclist, who even had some triathlon experience. At one point, he and Fran decided to celebrate their anniversary by bicycling the equivalent of their married years in miles. When their kids were old enough to stay home alone, they even expanded their nuptial tradition by launching their ride from the famous Madonna Inn in San Luis Obispo, where they'd overnight in Hal's favorite – the Caveman Room.

In July 2009, 30 years after they tied the knot back in San Diego, he fatigued before they hit the mark on their ride. "We should've been able to do the 30 miles," says Fran. "It should've been really easy, but he couldn't do it...One week later he got his official diagnosis."

In August 2009, Hal ran a half marathon one month after being diagnosed with ALS. It was his last race.

Amyotrophic lateral sclerosis (ALS), popularly referred to as Lou Gehrig's disease after the famous Major League Baseball player who had it in the 1930s, is a progressive degenerative disease that causes the neurons controlling voluntary muscles – muscles that are usually attached to the skeleton – to die. The principal symptom of ALS is muscle weakness or stiffness, which in retrospect, shed light on Hal's marathon and cycling incidents. As the disease advances, actions like speaking, eating, moving, and eventually breathing, become increasingly impaired.

An ALS diagnosis is far from desirable news that can understandably cause unrest, depression, or indifferences. Hal became paralyzed, dependent on tubes for feeding and breathing assistance, and using a speech synthesizer and commercial eyetracker system to communicate. Yet, when he shared his diagnosis as part of the aforementioned post in a Bitcoin Forum, he still showed immense resilience, gratitude, and inventiveness. "Even with the ALS, my life is very satisfying," he wrote, after noting the interface that he created to help control his wheelchair position with his eyes, and the project he was tackling to harden Bitcoin wallets. Despite his admittedly slower pace, he added, "...I still love programming and it gives me goals."[10]

Cryonics in the long-term

In addition to family and friends, another comfort in Hal's ALS diagnosis was his Alcor membership. A long-time atheist, Hal had already read Robert Ettinger's seminal book, *The Prospect of Immortality*, and started following cryonics by his freshman year of college. "He was not afraid of death," Fran recalls from their early conversations about it.

The Finney family goes for a neighborhood stroll in July 2011, about two years after Hal's ALS diagnosis, and one month after his tracheostomy.

They were a perfect complement in this regard, as death topped her own personal fear list. "At the point where I met Hal, I didn't even want to think about death. I was terrified of death." Though Fran came from a Jewish family, she was never religious, following instead her passion for science. Although she did not pursue medicine ultimately, she did stay in the healthcare field, opting for a career in physical therapy. Fran knew about cryonics before meeting Hal, but with all of her medical training, felt that the science of it just hadn't progressed enough to ensure a successful cryopreservation and resuscitation. In that regard, it bore some similarities to religion for her. "I thought of [cryonics] as another dream, not all that different from the dream of going to heaven, that you could freeze someone and then have them undamaged enough that you could somehow bring them back to life again."

Years into their marriage, it was Hal who convinced her to consider cryonics more in terms of its longer-term potentiality, to consider the advances that might come in the years prior to their own cryopreservations. From there, the couple made their decision official. On October 15th, 1992, in their thirteenth

year of marriage, they drove out from their new home in Santa Barbara to the organization's then-location in Riverside to sign the final membership paperwork in the presence of Alcor mainstays Michael Perry, Joseph Hovey, Carlos Mondragon, and Ralph Whelan.

Twenty years later, their decision that October day became more meaningful than they had anticipated. Hal's ALS had rapidly progressed, affecting not just his body, but his mind as well. "It's not a normal kind of dementia," says Fran, "but the brain is involved. Hal felt that it was affecting his ability to do his fast thinking, to do his mental math. He felt like he was losing that, and he would lose more."

The couple decided that when he could no longer communicate with friends and family, even with his many technological aids, that this would be his moment of transition. They would fly to Scottsdale, support of vital functions would end, and his body would be allowed cease function independently before a swift cryopreservation. That time arrived on August 26, 2014. Flanked by family, Hal was admitted to the ICU of a Scottsdale hospital, not far from Alcor's patient storage facility. Two days later, he became Alcor's 128th patient. After the incredible stress of that period, Fran was grateful to be present:

"I watched Hal's preservation, and I was so impressed with all the care that was taken, all the strategy, all the techniques. It was really good. It was very reassuring for me to be there. And be able to watch that. But even seeing all that was done, I know that Hal's body in storage is damaged." She and Hal long agreed that a more sparing preservation plays a vital role in the success of cryonics; however, particularly given the circumstances of Hal's passing and others cryopreserved with or on account of fatal disease, Fran emphasizes the importance of cellular repair as a key element to resuscitation – one that will require increasing research and funding as Alcor and cryonics mature into the future.

An optimistic futurist

As many of Hal's friends and family can attest, he was a very optimistic futurist, who wholeheartedly supported change – yet another reason why cryonics held such appeal. He was excited by many technological potentialities of the future, like nanotechnology, the Singularity, Artificial Intelligence, and mind uploading. In Fran's own words:

"I know Hal wanted to be around. He wanted to experience the future. He was very excited about change. When things change, the typical response of a lot of people is, 'Oh, remember the good old days.' Hal was never like that. It seemed like he was happier with each and every change. Each change was great! He embraced it, and he was always looking forward to more. I think that was a lot of his motivation for getting involved in cryonics in the first place. He just wanted to be able to see what the world turned into, because it was going to be such an amazing, wondrous place."

As Fran puts it so succinctly, "He did not believe in God. He believed in the future."

Hal is survived by his wife, Fran, and two children, Erin and Jason. Erin is a passionate vegan working as a programmer, and Jason is an up-and-coming science fiction writer and math educator. Fran works as a Care Manager for the ALS Association Golden West Chapter. She applies her personal experience with ALS and background in physical therapy to educate and connect families affected by the disease in Santa Barbara County and adjacent areas of Southern California with the resources they need to provide better quality of life to their loved ones. Every year, the Finneys raise money for the ALS Association through their team, "Hal's Pals Fight ALS." To learn more about ALS or to support their team, please email Fran at fran.finney@gmail.com. ■

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Hal Finney Cryonics Research Fund

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

You can read more about Hal's life and tremendous contributions to humanity below.

The fund is currently focused on research to:

- Advance the cryopreservation of brain tissue or whole brains, or
- Advance the clinical practice of cryonics, including patient stabilization, transport, and cryopreservation practices.

Project proposals of all sizes will be considered. For examples of the kinds of projects that will be considered for funding, you can read about past and ongoing Alcor-funded projects at https://alcor.org/AboutAlcor/researchcenter.html.. These should be taken as indicative of topics relevant to Alcor's mission, but should not be considered exhaustive.

To be considered for funding, please submit a short (1/2 to 1 page) letter of interest to info@alcor.org that includes:

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

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

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**
- **A dollar-for-dollar credit toward full membership sign-up fees for any dues paid for Associate Membership**

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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 cryopreserved 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.

Alcor A-1990 Case Report

Prepared by Linda Chamberlain, Co-Founder and Director of Special Projects, Alcor Life Extension Foundation
Sources: Sayer Johanson, NREMT, and Ryan Levesque of Suspended Animation; and Chris Divver, NRP, MPA, CPM; Hugh Hixon and Steve Graber, Alcor Life Extension Foundation
Editing by R. Michael Perry, Ph.D. and Marji Klima, Alcor Life Extension Foundation

Personnel

Standby, Stabilization and Transport:

Christopher Divver, NRP, MPA, CPM, Alcor Medical Response Director

Ryan Levesque, Donor Recovery Manager, Suspended Animation, Inc.

Sayer Johanson, NREMT, Operations Manager, Suspended Animation, Inc.

Cryoprotective Surgery and Perfusion Team:

Tom Wolvos, M.D., General Surgeon

Christopher Divver, NRP, MPA, CPM, Alcor Medical Response Director, Assistant Surgeon

Hugh Hixon, Jr., Alcor Research Fellow, Lead Cryoprotection Perfusionist, cooldown, data reduction

Steve Graber, Alcor Technical Coordinator, Assistant Cryoprotection Perfusionist; setup, cooldown, data reduction

Sandra Russell, readiness, supplies, cleanup

Linda Chamberlain, scribe

Deployment Committee:

Max More, Ph.D., Alcor Chief Executive Officer

Steve Harris, M.D., Alcor Chief Medical Advisor

Summary

Information is derived from multiple sources and is all converted to Mountain Standard Time (MST).

Norman Hardy, a non-confidential, neurocryopreservation Alcor member was pronounced legally dead on October 30, 2018, in Mountain View, CA. This case was the first time the newly enacted California End of Life Option Act (EOLOA) was used to reduce the potential ischemic damage that can result from a prolonged dying process.

Alcor's Medical Response Director (MRD), Alcor's Chief Medical Advisor (CMA), and other Alcor staff worked for over a week after being notified of the member's end of life choice to make sure that all legal requirements were in place. The hospice facility and the family members were all cooperating with Alcor to make this case as flawless as possible, legally, logistically, and technically.

The cryoprotective perfusion was relatively successful. Perfusion flow rates were high throughout the procedure. However, the post-cryopreservation CT scan showed poor cryoprotection and extensive CT-visible ice formation in the cerebellum, and incomplete cryoprotection with a small amount of CT-visible ice formation in the frontal lobes.

Patient Assessment and Pre-Deployment

The member was an 85-year old Caucasian male, 6'4" in height and weighing approximately 160 lbs. He had been diagnosed with Stage IV prostate cancer that had metastasized to his bones and lungs. While living with his daughter and ex-wife, he had been admitted into an in-home hospice program. The member had been on Alcor's Watch List for several months but failed to notify Alcor that he planned to end his life by using the newly enacted EOLOA (End of Life Option Act; https://www.cdph.ca.gov/Programs/CHSI/Pages/End-of-Life-Option-Act-.aspx).

Monday, October 22, 2018

Alcor received a call from a northern California Alcor member who stated that his friend planned to use the EOLOA to legally end his life. He further stated that the member had received his aid-in-dying (AID) medications from the State of California and was planning to take those medications on Wednesday, October 24, 2018, just two days hence.

This created a logistical problem for Alcor. It would be the first time an Alcor member used EOLOA in conjunction with their arrangements for cryopreservation. It was imperative that Alcor make sure the laws were followed exactly and two days was not enough time to do that proficiently. The member agreed to postpone taking his AID medications but only for a few days. Additional time would have given Alcor more confidence that no legal requirements had been overlooked.

Preparation and Deployment

Tuesday, October 23, 2018

There was extensive discussion on Slack (Alcor's internal communication system for the team members) about making sure that all legalities were handled properly and sufficiently. That included having Suspended Animation (SA) do the Standby, Stabilization and Transport (SST) since this case took place in California and having Alcor's new Medical Response Director (MRD) involved for additional training and experience. It was also decided that the MRD would deploy the next day to evaluate the situation and the member's condition and to collect Health Insurance Portability and Accountability Act (HIPAA), Advance Directive and end of life paperwork.

There was also discussion about how to best time the arrival of SA with the member taking his prescribed AID medications, the fact that SA and Alcor personnel could not be in the room with the member when he took the AID medications, and how long after ingestion before the medications would take effect. Several northern California Alcor members volunteered to assist with this case.

Alcor's MRD spoke with the family in an attempt to get a signed HIPAA form to enable Alcor to obtain the member's medical records and to ensure that the member was fully compliant with the legal requirements pertaining to the EOLOA legislation.

Wednesday, October 24, 2018

Alcor's Chief Medical Advisor (CMA) sent two citations to the team, one of which was the legislation itself and the other contained two required forms. There was a discussion about the need to acquire: 1) a signed form from the two physicians who confirmed that they interviewed the member and approved him to use the EOLOA, 2) documentation that the member had made two requests 15 days apart, and 3) documentation from the physician who prescribed the AID medications.

The member had earlier planned to take the AID medications on Thursday, November 01, 2018, but had gone for blood work that morning and had a near-syncopal episode. That caused him to become agitated and he voiced his desire to take his AID medications earlier than planned. His family gave him some prescribed Dilaudid for his pain which subsequently calmed him and allowed him to sleep.

Alcor's CMA requested information about the member's then current pain medication and dose, requested a phone number for hospice and asked if a signed HIPAA form was in place so that he could speak with them. The MRD was still en route to California but replied that as soon as he got off the plane, he would try to get more information; the hospice staff was supposed to have gotten the HIPAA form signed the previous day.

SA requested contact information for the member's physicians as this would be needed in order to expedite the death certificate and the transit permit. They also requested a copy of any form to be signed by the designated power of attorney (DPOA).

The MRD arrived at the member's home that afternoon and met with the member and his ex-wife. They spoke briefly as the hospice nurse (RN) and the home health aide (HHA) were changing the member's dressings on two kidney shunts. One of the shunts was constantly draining and caused him discomfort.

There was a discussion between the RN, the HHA and the family about the member's Dilaudid, how much he could receive over each four-hour period and the importance of maintaining the narcotic log, which had not been filled out prior to that conversation. All entries into that log prior to October 24, 2018, at 15:00 hrs were an estimate of time and dosage. All entries after that were accurate for dosage and administration time. The hospice RN gave the MRD a copy of the Authorization for Use and/or Disclosure of Member/Patient Health Information form.

During this meeting with the family, several outstanding concerns were addressed regarding the AID medications. The main concern was that the member had no access to any of his medications. He also needed to, per the laws of the State of California, provide a 48-hour notice prior to ingesting the AID medications and he needed to sign a letter of attestation stating that he was of sound mind and body. The law stipulated that no food and only a little liquid was to be ingested within 12 hours of taking the AID medications. The member had chosen the following AID protocol: diazepam 1 gram (to relieve anxiety), digoxin 50 mg (to decrease HR), morphine 15 grams (to relieve pain) and propanolol 2 grams (to decrease HR).

That same afternoon SA had spoken with the San Jose coroner's office and because the member was in home hospice the case would not go to the coroner as long as all the proper documentation was on hand, the member's physician had signed the death certificate, and the designated Power of Attorney (DPOA) had signed off to release the remains to Alcor.

The member's daughter was identified as being the DPOA, which was helpful with making various aspects of this case come together well.

Alcor's CMA worked with the hospice staff to better control the member's pain. Concurrently, Alcor staff urged the SST team to inform Alcor and all team members as soon as a time and date were chosen by the member and his family for ingestion of the AID medications.

There were planning discussions about which air ambulance company to use and the type of aircraft to use. There was also a discussion about whether or not to do the neuroseparation in California or wait until the patient arrived in Arizona. It was decided that except for unforeseen circumstances there would be no need to do the procedure in California.

Thursday, October 25, 2018

The MRD spent many hours working to obtain the needed HIPAA and EOLOA paperwork. In spite of being given inappropriate paperwork and being sent to incorrect locations, requiring additional trips, he finally accomplished the task. Upon returning to the member's home he found that the member had gone to the emergency department (ED) to have a draining shunt repaired. The member was comfortable and had no pain that morning. The hospice RN supervisor told the MRD that the AID medications should take effect within an hour after ingestion and hospice could be called to pronounce as soon as the member ingested the medications.

That afternoon there had been no change in the member's plan to ingest the medications on Monday, which was four days away. Once all the paperwork was in hand and verified, Alcor could then officially call a deployment that would give SA ample time to deploy.

Friday, October 26, 2018

That afternoon the MRD received documents from the hospice and there was extensive discussion on Slack about being sure that all the required paperwork had been gathered, who could act as witnesses, whether family members with an interest in the member's will could witness, and if not, that disinterested local Alcor members could fill that role.

Saturday, October 27, 2018

SA confirmed that their contract surgeon and perfusionist were flying to California on Sunday afternoon, and SA team members would drive from southern California to northern California in their mobile operating vehicle (MOV) on Sunday.

Alcor reminded the team that a video recording was needed that showed that no one from Alcor or SA was in the room with the member when he took the AID medications and not before he was pronounced legally dead. There was also a discussion about making sure all details were covered for obtaining the death certificate and moving the member from California to Arizona.

The member's ex-wife had asked the member to delay his ingestion of the AID medications since he was having less pain; the member was considering the request. That evening the member's daughter told the team that the date of ingestion had been officially changed from Monday to Tuesday. SA moved the arrival of the surgeon and perfusionist from Sunday to Monday.

Sunday, October 28, 2018

The member had slept well the previous night with little discomfort and was in good spirits. The member was still planning to take the EOL medications on Tuesday.

Monday, October 29, 2018

SA confirmed in the morning that they were leaving their southern California facility and on their way to the member's location. Stabilization operations were still scheduled for Tuesday. The MRD had spoken with the hospice supervisor; she informed him that due to a mandatory meeting from 9:00 hrs to 11:30 hrs on Tuesday no one from hospice would be able to respond and pronounce during that time frame. The MRD got the name of the hospice physician that would be on duty and forwarded that to SA as well as to the member's family. The member's daughter informed the MRD that she had informed her father about the time constraints and he planned to take his medications at 11:00 hrs on Tuesday.

Hospice personnel had made assurances that they were going to cooperate in every way possible. The CMA advised the team that the law specified that in cases using the EOLOA, for statistical purposes the death certificate should *not* state that the cause of death was either homicide or suicide. He asked that the physicians be advised of this since this legislation in California was new and the member's physicians may not already be aware of this.

Standby

SA reported that they had just arrived in Mountain View and were with Alcor's MRD. Alcor's Arizona mortician had been updated on the status of this case and his staff was ready.

Tuesday, October 30, 2018

The MRD reported at 08:12 hrs that they were on schedule for medication ingestion at 11:00 hrs. The air ambulance had been scheduled to depart from Moffett Field. SA began setting up their equipment and drawing up the medications in preparation for the stabilization procedure.

The Alcor MRD and the SA team arrived at the member's house at 09:48 hrs. They set up the stabilization equipment in a part of the home separate from where the member was located. There was a locked door between the team and the patient. The rectal occluder and the nasopharyngeal wax were not in the vehicle and therefore not available to use on this patient.

Alcor's CMA instructed the team at 10:01 hrs that propofol, a standard part of the stabilization medications, would not be needed in this case since the AID drugs would accomplish the reduction in cerebral metabolism and suggested that the stabilization protocol begin with the infusion of sodium citrate or heparin. SA agreed to make the change to the protocol. At 10:30 hrs the member's friend informed the team that the member had taken a dose of Zofran which was to prevent the possibility of vomiting once the AID medications were ingested.

At approximately 11:20 hrs the MRD, SA and the hospice RN reviewed Alcor's post-mortem procedures and verified that all

necessary paperwork was in place. Once the hospice staff was satisfied that the documentation was all in order, they said they would send a nurse out to the patient's bedside to pronounce. This information was relayed to the family. At 11:30 hrs the AID medications were administered by the family.

At 11:50 hrs the member's friend informed the team that the member had taken his AID medications. An hour later no hospice nurse had yet arrived; they were one hour into the wait and there was no update yet from the family. Shortly thereafter the hospice nurse arrived at the house. The member was still breathing but unresponsive. The hospice nurse reported that there was no blood pressure, respirations were shallow, and the heart rate was low.

Stabilization

The member was pronounced at 13:14 hrs. After the family left the patient's room, using his bed sheet, the team lifted the patient and carried him into the garage; the doors between the team and the family were closed behind the team. The patient was placed into the portable ice bath (PIB).

Ice was placed around the patient's head and over his body. At 13:20 hrs, the AutoPulse mechanical chest compression device was turned on to circulate the medications through the vasculature. The mask of the surface conduction cooling device (SCCD) was placed over the patient's face at 13:21 hrs to increase cooling efficiency.

Concurrently, #9 nasopharyngeal temperature (NPT) probes were placed in the patient's left and right nares along with therapy putty in lieu of the missing nasal wax, and an intraosseous (IO) needle was placed in the left tibial tuberosity for infusion of the stabilization medications. At 13:23 hrs the endotracheal tube was placed and ventilation was initiated. At 13:27 hrs the patient was covered with additional crushed ice and the portable ice bath was moved to the mobile operating vehicle (MOV).

All the stabilization medications were infused between 13:30 hrs and 13:44 hrs (see the below Table of Medications Administered for the specific medications and the times of infusion).

Upon administering the first medication into the IO line, it was noticed that there was substantial resistance. A second IO line was placed in the same area. This line too was not adequately infusing the medications. A third IO was placed into the left humeral head and flushed to ensure patency. At 13:44 hrs all the high-volume medications had been infused.

While transferring the patient to the MOV, and due to the steep incline on which the vehicle was parked in the driveway, the patient shifted in the ice bath during transport causing the AutoPulse to shut off briefly. Manual cardiopulmonary support was initiated until the Autopulse could be restarted two minutes later. During transport in the MOV to a location away from the patient's home, topical cooling, ventilation and cardiopulmonary support were continued.

Field Surgery and Washout

The contract surgeon and perfusionist were in the MOV and ready to begin the cardiopulmonary bypass procedure when the patient arrived. The procedure was performed with the patient in the portable ice bath with the SCCD pump and face mask running, but cardiopulmonary support was discontinued at 13:50 hrs. The NPT was 25.8°C in the right nare and 27.3°C in the left nare.

Per the reports from the contract surgeon and the perfusionist, the chest was prepped and sterile drapes were placed. A standard median sternotomy incision was made at 13:55 hrs and deepened to the level of the sternum, which was divided with an oscillating saw. The pericardium was opened and the cardiac structures were noted to appear grossly normal. Purse-string sutures of 2-0 Prolene were placed in the distal ascending aorta and the right atrial appendage, and appropriate small cannulae were inserted and connected to the cardiopulmonary bypass circuit at 14:12 hrs.

Flow was initiated immediately, and streptokinase was infused during the open circuit washout three minutes later. Cooling continued until the patient reached an eventual NPT of 4°C to 5°C. A good washout resulted, although there remained a faint tinge of blood in the effluent.

At this point, SA received an email from the southern California funeral home with an attached death certificate and transit permit. With these two documents, the member would have no obstacles to transport.

The closed-circuit perfusion was initiated at 14:26 hrs. The remainder of the Vital-Oxy was added to the closed circuit. The closed-circuit procedure was terminated at 14:59 hrs and took 33 minutes. The highest flow rate was 2.3 L/min.

The cannulae were removed and the cannulation sites were oversewn. The sternum was closed with two #5 stainless steel wires. The subcutaneous tissues were closed with running 2-0 Vicryl, followed by staples for the skin.

Transport

At 15:43 hrs the team departed for Moffett Field where the private air ambulance was waiting. The patient and team arrived within 15 minutes. During transit, double-bagged water ice had been placed around the patient's head for cooling during air transport. Upon arrival at the airfield, the SCCD pump was turned off and the mask removed.

The patient was moved from the PIB to a body bag and double-bagged water ice was placed around the patient's head. While

transporting the member to the body bag it was noted that there was a heavy-duty body bag missing that would normally be used to prevent leakage from the ice bags. Since ice bags were only placed around the member's head, instead of around the whole body, there was no leakage during transport.

The patient was officially handed off to Alcor's MRD and the patient was loaded into the aircraft to be transported to Alcor in Scottsdale, AZ. Arrival time was estimated to be approximately two hours later. The SA team returned to their California facility.

Alcor staff met the plane upon arrival in Scottsdale. The patient was offloaded from the aircraft onto a gurney and then loaded into Alcor's rescue vehicle and secured. The team was approximately one minute from Alcor.

Cryoprotective Surgery

In preparation for the arrival of the patient, the OR staff connected and checked out the perfusion circuit and the data being sent to the large wall screen in the operating room (OR). Upon checking out the cephalic enclosure, the red rubber Robinson catheters had not been clamped off when placed into the box. Approximately 30 mL of B1 perfusate was lost into the packaging when the pump was again switched on.

The pump and circuit were working properly and the B1 bladder was switched to recirculation to await the arrival of the patient. The back pressure on the pump was 7 psi; the flow rate was high at nearly 300 mL/min. Alcor's surgeon arrived in the OR and started to prepare the surgical table.

The patient was brought into the OR at 18:28 hrs. No stress loops had been used for the temperature probes when stapled in place. The OR cameras were turned on. The patient's head and shoulders were raised with a 12" polyethylene support. The NPT probe was attached to the data acquisition system at 18:31 hrs and the initial NPT was 4.4°C.

The patient's face was marked designating the left and right sides to prevent errors once the cephalon was placed into the cephalic enclosure. The easily accessible portion of the patient's head was shaved and incisions were made in the scalp for the burr holes. At 18:38 hrs the first incision was made to identify and raise the carotid arteries. The left carotid artery was isolated first, cut and tied off, then the right carotid artery was isolated, cut and tied off.

Concurrently with the surgery to raise the carotid arteries, the burr holes were made using a Codman perforator that was cooled with normal saline. While drilling the left burr hole the perforator clutch stopped before the burr hole was sufficiently deep. Several minutes was spent trying to correct the problem before others in the OR were available to help. Additional skin was cleared from around the burr holes in order to make them deeper and success was obtained when a slower speed setting and more pressure was used.

Using an osteotome and mallet, the vertebra was incised and the cephalic separation was completed at 18:51 hrs. The cephalon weighed 5.56 kg (12.26 lbs.). The cephalon was placed in the cephalic halo and it was observed that the vertebral arteries were large and visible. The NPT probes were again connected to the data acquisition system.

The surgeon trimmed the catheter and placed a purse-string in the right carotid artery using 3.0 silk. The main pump was started at 83 rpm in order to fill the catheters with B1 perfusate. The right carotid artery was cannulated with an 18 Fr red Robinson catheter and tied off. An additional purse-string was placed to better secure the catheter. Open circuit perfusion was initiated at 19:01 hrs, the NPT was 5.0°C.

The left carotid artery was cannulated with an 18 Fr red Robinson catheter and a 3.0 silk purse-string was placed to secure the cannula. The catheter was filled with B1 perfusate and the cannulation of the left carotid artery was tied off.

Perfusion was clamped off and was held at 80 mmHg and 59 rpm (210 mL/min). The right sampling line was secured and cryoprotective surgery was complete at 19:19 hrs.

Cryoprotectant Perfusion

At 19:19 hrs the cryoprotective ramp was initiated using nM22 perfusate; the NPT was 2.5°C.

The starting ramp pump speed was set to 15 (~20 mL/min). The mixing reservoir volume was 1.01 L. The left sampling line was secured and the cephalon was rotated in the cephalic enclosure to provide better flow. Both vertebral arteries were clamped off. The brain retraction detection device (BRDD) was placed in the right burr hole.

The main pump rate was over 300 mL/min, the mixing reservoir volume was 1.1 L, and the refractive readings were noted to be increasing (see the Cryoprotection graph at the end of this report).

The cephalic enclosure was closed, cleaning of the OR was begun, and the noncephalic remains were prepared for pickup by the funeral home.

At 19:42 hrs the mixing reservoir volume was 1.25 L and two minutes later the arterial pressure was dropped to 70 mmHg, the main pump was still running at 94 rpm (335mL/min) and the main pump pressure 9.5 psi. A few minutes later it was noted that the sampling system was not drawing air bubbles, contrary to normal occurrence.

Ten minutes later, the mixing reservoir volume was 1.44 L, the main pump speed was 100 rpm (356 mL/min). The perfusate

concentration in the right venous sampling line was 14.5 Brix and in the left venous sampling line, it was 15.3 Brix. Three minutes later the right venous concentration was 15.3 Brix and the left venous was 15.9 Brix.

At about the same time the ramp pump rate was approximately 16, the arterial concentration was 19.3 Brix. The patient's face had started to darken uniformly, the patient's vasculature was large and open resulting in rapid perfusion, but the corneas and eyeballs had not yet been affected.

Perfusate was flowing forcefully from the neck stump at 20:06 hrs. The arterial perfusion was turned down to a pressure of 50 mmHg. The cephalic enclosure was opened, and the affected vessels were clamped with a hemostat. The enclosure lid was put back in place.

The left burr hole edges were cleaned away at 20:20 hrs with a rongeur to insert the borescope camera to photograph the brain surface. The borescope camera was placed in the burr hole and the bottom of the brain casing could be seen.

The brain had continued to shrink (see Brain Shrink Distance and Perfusate Concentration graph at the end of this report) and it was noted that the skin was uniformly tanned, but the eyeballs had not yet shrunken. All systems were functioning properly.

Per the cryoprotection protocol, the ramp is to be paused at 30 Brix (50% of the desired end concentration) to allow the patient to come to osmotic equilibrium. The neuroperfusion box and the chiller are switched from +3°C to -3°C operation. At the end of the 30-minute pause the ramp is resumed at the maximum addition rate (maximum without losing total volume in the circuit) to go to 105% of the desired end concentration (52.5 Brix) and held between 102% and 105% concentration until, hopefully, the goal is obtained.

At 21:18 hrs the ramp pump was stopped for the standard 30-minute pause because the nM22 concentration was over 30 Brix in both the left and the right venous sampling lines. The arterial refractive index reading was 32.7 Brix, the right jugular was 30.1 Brix and the left jugular was 30.5 Brix. The ramp was turned off and the cephalic enclosure and the main chiller were both set to -3°C. The mixing reservoir volume was lowered from 1.76 L to 1.2 L because the reservoir was too full to start the ramp at the end of the 30-minute pause.

The borescope camera was used to look into the burr hole. Substantial brain retraction was observed. The main pump pressure was 29 psi, the main pump output pressure was 5.5 psi and the arterial pressure was 50 mmHg. A second filter was brought into the system.

The 30-minute pause was ended at 21:48 hrs. The ramp pump was turned on full at speed 92 (330 mL/min). A normal amount of foam was observed in the mixing reservoir.

At 21:51 hrs the right cornea had collapsed from dehydration of the eye. (This is a normal response to cryoprotective perfusion.) It was noted that both times when the cephalic enclosure was opened to observe the brain through the borescope camera, the BRDD reading fluctuated with a spike.

The flow slowed due to the pump speed declining. The arterial pressure was increased to 60 mmHg. The chiller temperature was changed to -2°C to increase cooling.

The arterial refractive index reading was 51 Brix. The ramp pump was stopped and started several times to compensate for latency. Cleanup of the surgical instruments was begun and the setup of the cooldown system was started. The ramp pump was turned off at 52 Brix arterial. The right venous concentration was 47.45 Brix and the left venous was 48.23 Brix.

At 22:48 hrs the left cornea had not collapsed, it was even somewhat convex. Measurements were made to ensure the cephalon would fit into the neuro can.

The 30-minute countdown to termination of perfusion was started at 23:09 hrs, holding between the limits of 52 and 55 Brix and compensating for latency. Cryoprotective perfusion was terminated at 23:41 hrs. The arterial refractive index reading was 51.96 Brix, the right venous was 51.00 Brix and the left venous was 50.73 Brix.

Per the cryoprotection protocol, the normal endpoint criterion for whole body patients is over 100% for over 30 minutes from the venous return and for neuro patients, it is over 100% for over 30 minutes from both jugular veins.

At 23:43 hrs, in preparation for moving the cephalon into the patient care bay for cooldown, the catheters were cut and it was noted that the left eyeball had become more convex. It was also noted that the right sampling line was about 2" into the right jugular vein and the left sampling line was about 1.25" into the left jugular vein. A hole was drilled and an eyebolt was put into the vertebra stump for handling the cephalon and the rest of the monitoring lines were removed.

The borescope camera was inserted one last time for photos of the brain. The overhead surgical camera was found not to be functioning but after viewing the video, all critical operations had been captured. A card failure had caused the camera to malfunction.

At 23:52 hrs the cephalon was removed from the halo. The weight of the cephalon was 4.425 kg and the weight loss was (5.56 – 4.425) = 1.135 kg.

The cooldown dewar was precooled with liquid nitrogen (LN2). The thermocouple extension was connected and the cephalon was lowered into the precooled dewar. The thermocouple probes were taped to the side of the cooldown dewar and the lid was put in place. The lines were connected to the cooldown computer and the lid was secured with duct tape. The cooldown dewar was connected to the LN_2 source and the LN_2 was turned on.

Cooling to Liquid Nitrogen Temperature

The computer program "Cryoprotected Neuro" was initiated and cooldown was initiated at 23:59 hrs on October 30, 2018, plunging to -110°C and descending thereafter at -1°C/hour to LN2 temperature. On November 4, 2018, an uneventful cooldown was terminated. On November 15, 2018, the patient was transferred to long-term maintenance at LN2 temperature.

Timeline and Time Summaries

October 30, 2018

13:14 Pronouncement of legal death

13:20 Start of mechanical cardiopulmonary support

13:21 Start of ice bath cooling

13:21 Placement of the intraosseous device

13:23 Placement of an endotracheal tube

13:27 The patient was moved to SA's mobile operating vehicle

13:30 Administration of the first medication (20 g sodium citrate)

13:50 Termination of cardiopulmonary support: right NPT = 25.8°C, left NPT = 27.3°C

13:55 Start or field surgery

14:12 End of surgery and start of open circuit washout

14:26 Start of closed-circuit perfusion

14:27 Administration of the final medication (27 mL Vital-Oxy IV)

14:59 End of closed-circuit perfusion

15:43 Departure of transport vehicle to airport

18:28 Arrival of patient at Alcor; no NPTs with patient

18:31 NPT probes attached to data acquisition system; initial temp 4.4°C

18:38 Start of surgery (burr holes, cannulation, vertebrals, sampling lines, cephalic isolation)

18:51 The cephalon weighed 5.56 kg when isolated

19:01 Open circuit started with B1; NPT 5.0°C

19:19 Completion of surgery

19:19 Start of cryoprotection; NPT 2.5°C

21:18 50% of concentration necessary for vitrification (CNV) achieved

23:09 Start of sub-zero terminal concentration ramp

23:41 Termination of cryoprotection; final Brix readings: arterial 51.96, right venous 51.00, left venous 50.73

23:52 The weight of the cephalon was 5.56 kg and the weight loss was (5.56 – 4.425) = 1.135 kg.

23:59 Start of patient cryogenic cooldown

The patient reached LN_2 temperature and the cooldown ended November 4, 2018. The patient was transferred to long-term maintenance at LN_2 temperature on November 15, 2018.

Time Summaries

Stabilization

hrs: mins

00:06 From pronouncement to start of cardiopulmonary support: 13:14 to 13:20

00:16 From pronouncement to start of meds administration: 13:14 hrs to 13:30 hrs

00:57 From start to end of medication administration: 13:30 hrs to 14:27 hrs

05:14 From pronouncement to patient arrival at Alcor: 13:14 hrs to 18:28 hrs

Field Surgery and Washout

hrs: mins

00:41 From pronouncement to start of surgery: 13:14 hrs to 13:55 hrs

00:16 From start of surgery to end of surgery: 13:55 hrs to 14:11 hrs

00:58 From pronouncement to start of washout: 13:14 hrs to 14:12 hrs

00:47 From start of washout to end of closed-circuit cooldown: 14:12 hrs to 14:59 hrs

01:45 From pronouncement to end of closed-circuit cooldown: 13:14 hrs to 14:59 hrs

Cryoprotective Surgery

hrs:mins

00:10 From arrival at Alcor to the start of surgery: 18:28 hrs to 18:38 hrs

00:13 From start of surgery to end of the cephalic isolation: 18:38 hrs to 18:51 hrs

00:41 From the start of surgery to the start of the cryoprotective ramp: 18:38 hrs to 19:19 hrs

05:03 From the start of surgery to the end of the cryoprotective ramp: 18:38 hrs to 23:41hrs

Cryoprotectant Perfusion

hrs:mins

04:22 From start to end of cryoprotective ramp: 19:19 hrs to 23:41 hrs

00:18 From the end of cryoprotective ramp to start of cooldown: 23:41 hrs to 23:59 hrs

05:31 From arrival at Alcor to the start of cooldown: 18:28 hrs to 23:59 hrs

10:45 From pronouncement to start of cooldown: 13:14 hrs to 23:59 hrs

Notes:

1. Per the recommendation of Alcor's Chief Medical Advisor, propofol was not administered.

2. Based on this patient's weight, 54 mL of Vital-Oxy were drawn up into a 250 mL IV saline bag. The first infusion was approximately 1/2 the total bag volume, so 27 mL of

Tables of Medications Administered and Temperatures

TIME	MEDICATION	DOSE	PURPOSE
13:30 hrs	Sodium citrate	65 mL (1st dose)	Anticoagulant; prevents blood clot formation.
13:32 hrs	Sodium citrate	65 mL (2nd dose)	Anticoagulant; prevents blood clot formation.
13:33 hrs	Sodium citrate	65 mL (3rd dose)	Anticoagulant; prevents blood clot formation.
13:35 hrs	Heparin	50,000 IU	Anticoagulant; prevents blood clot formation.
13:36 hrs	Vasopressin (first dose)	40 IU	Vasopressor; increases blood pressure during CPS.
13:37 hrs	SMT (S-methyl-isothiourea)	400 mg	Neuroprotectant (iNOS inhibitor); protects the brain from ischemic injury; raises blood pressure.
13:37 hrs	Minocycline	200 mg	Antibiotic; reduces microbial overgrowth during long transport times.
13:37 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (1st dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:38 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (2nd dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:39 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (3rd dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:40 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (4th dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:41 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (5th dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:41 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	60 mL (6th dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.

13:42 hrs	Decaglycerol/THAM [tris(hydroxymethyl) aminomethane]	40 mL (7th dose)	Decaglycerol inhibits cerebral edema. THAM is a buffer to mitigate acidosis.
13:43 hrs	Vasopressin (second dose)	40 IU	Vasopressor; increases blood pressure during CPS.
13:44 hrs	Vital Oxy	27 mL (1st dose)	Antioxidants: melatonin, vitamin E (D-alpha tocopherol), PBN (alpha Phenyl t-Butyl Nitrone) and anti-inflammatory carprofen.
14:15 hrs	Streptokinase	250,000 IU	A thrombolytic used to break up existing blood clots. *This was added to the open circuit washout.*
14:27 hrs	Vital Oxy	27 mL (2nd dose)	Antioxidants: melatonin, vitamin E (D-alpha tocopherol), PBN (alpha Phenyl t-Butyl Nitrone) and anti-inflammatory carprofen

Vital-Oxy with 125 mL saline or 152 mL diluted Vital-Oxy/saline solution. The second was the same, 27 mL of Vital-Oxy with 125 mL saline or 152 mL diluted Vital-Oxy/saline solution into the closed-circuit perfusion. Each mL of Vital-Oxy contains 194 mg Sigma Cremophor EL (or Sigma Kolliphor EL), 155 mg ethanol, 19.4 mg PBN, 3.24 mg carprofen, 1.55 mg melatonin, and 198 IU vitamin E.

3. Hetastarch was not given as the patient was well hydrated.

4. The standard formulation for citrate is 50 mL vials of 20% w/v = 10 grams sodium citrate, with a maximum of two vials being administered depending on patient weight. This patient received 20 grams of sodium citrate as per protocol because his weight was over 40 kg. The 20 grams was administered in three divided doses of 65 mL each with the extra solution volume provided by saline removed from a 250cc bag of sodium chloride to make room for the Vital-Oxy in the bag.

5. Decaglycerol/THAM is administered as a custom formulation of 20% w/v decaglycerol and 4.5% w/v THAM (tromethamine) in water.

Discussion

Transport

1. Two items of new equipment worked very well. First, the brain retraction detection device (BRDD) is now functional and providing useful information. The previously noticed brain re-expansion is no longer theoretical.

   Second, the new gurney loading system engineered for use with the black Sprinter rescue vehicle also worked well. This is important when loading a portable ice bath with a patient and ice water into the back of the vehicle.

2. An important aspect of cryonics stabilization is that cardiopulmonary support (CPS) goes on for a long time, sometimes 60 minutes or more, before it is possible for logistical or temperature reasons to stop CPS before the surgery required for cooling by washout. This is especially true for Scottsdale cases. That differs from cardiopulmonary resuscitation (CPR) in which hopefully the patient can be defibrillated in only a few minutes. Prolonged CPS makes a cryonics patient analogous to an unconscious, living patient with a heartbeat (the heartbeat being the thumper that the patient is going to depend on for the next hour or more). It is just as important for a cryonics patient receiving CPS after a standby to have a patent airway as it is for a living patient.

Table of Nasopharyngeal Temperatures during Field Surgery and Washout

Time	Temp
13:37	25.7°C R
13:37	28.2°C L
13:48	25.8°C R
13:48	27.8°C L
14:06	25.0°C R
14:06	25.0°C L

Time	Temp
14:11	23.0°C R
14:11	24.0°C L
14:19	21.5°C R
14:19	21.7°C L
14:33	15.8°C R
14:33	14.6°C L

Time	Temp
14:36	13.4°C R
14:36	13.9°C L
14:40	11.8°C R
14:40	11.8°C L
14:45	10.0°C R
14:45	7.9°C L

Time	Temp
14:51	5.2°C R
14:51	7.5°C L
14:53	5.2°C R
14:53	7.5°C L
14:54	4.4°C R
14:54	5.3°C L

Perfusion

1. Three (instead of the usual one) filters were used both in this case and the one before it. In view of the filter loading and the fact that three filters were used, more blood should have been washed out. Also, the filter loading was not linear; the filters loaded up with more material in the jump to 100% concentration. The perfusate in the mixing reservoir remained cherry-red throughout the first half of the perfusion, clearing up only in the second half, probably due to massive dilution with the concentrate, so the loading and the color came from hemolyzed red blood cells that were still being released from the vasculature.

   A better understanding of cellular release from the vascular system is needed. The protocol for field washout is for SA to use 30 L of MHP-2. Research should be done to determine whether more B1 solution is needed in the field, if additional B1 should be used for washout in the OR, or for both procedures.

2. At 19:42 hrs, during the cryoprotective perfusion, the mixing reservoir volume was 1.25 L and two minutes later the arterial pressure was dropped to 70 mmHg. It was speculated that the patient's vasculature was so unobstructed that the pump could not keep up. This situation had never been seen before. A few minutes later it was noted that the sampling system was not drawing air bubbles, contrary to normal occurrence; this also could have been due to the fast flow rate.

3. The left burr hole edges were cleaned away at 20:20 hrs with a rongeur to insert the borescope camera to photograph the brain surface; this was the first time this equipment was experimentally used. The borescope camera was placed in the burr hole and the bottom of the brain casing could be seen.

4. At 21:51 hrs the right cornea had collapsed. It was noted that both times when the box was opened to observe the brain through the borescope camera, the BRDD reading fluctuated with a spike. This could have been the result of vibrations from handling the enclosure and the cephalon, but the reason is not definitively understood.

5. At approximately 21:51 hrs the box temperature controller appeared to be running at -7°C rather than the -3°C called for in the protocol. This was corrected before the next case. It was of no practical consequence because the freezing point of the cryoprotectant being perfused at that time was a far lower temperature.

Issues & Actions

A debrief meeting was held on November 7, 2018, and attended by all persons involved in this case. The following issues and actions were identified.

Standby, Stabilization, and Transport

Mobile operating vehicle (MOV) not in a secure location

The MOV was parked in a pharmacy parking lot while the blood substitution was done. This could have potentially become a negative and dangerous situation. In future cases, the Alcor Medical Response Director (MRD) or person in charge will arrange with prior permission to have the MOV parked either 1) in a medical facility parking lot, 2) a local mortician's parking lot, 3) some other private parking situation such as at the home or business of another Alcor member [in this instance, there were a lot of northern California members who would have been willing to assist and would have had appropriate parking locations], or 4) some other legal way or location for the mobile operating vehicle to be parked during surgery and washout procedures.

Field kit not complete

Three items were not in the field kit or in the mobile operating vehicle (MOV): the rectal occluder (necessitating field improvisation), wax for the nasopharyngeal probes, and a second heavy duty body bag. Always take time to ensure that the vehicle and/or all supplies are properly stocked and ready to go immediately after a case is concluded. The time to discover an item is missing is *not* when it is needed. A miscommunication between the team members about the location or existence of additional waste containers resulted in improper disposal of bio-hazardous waste. This resulted in part due to a new team member who lacked familiarity but who has since been further trained.

Bone intraosseous (IO) gun not placed correctly

The bone intraosseous (IO) gun was not placed correctly and had to be reset twice. The IO cannot be reset in the same extremity. Team members need frequent re-training of all skills. SA will make this a priority on their next annual recertification training.

Successful establishment of an IO line by a new team member was verified by injection of 5 mL of ice bath water due to perceived lack of availability of saline.

External team members unfamiliar with team procedures and supplies will be counseled to refrain from performing parenteral administration of agents unless at the specific direction of the team leader. Unless at the direction of Alcor's Chief Medical Advisor, team members will be counseled to never parenterally administer material that they would not administer to a legally living patient, including any non-sterile liquid.

Miscommunication between Alcor and SA

The hospice facility was not given the cryonics documents from Alcor until just before stabilization was to begin. This could have

resulted in a delay in procedures. Due to miscommunication between Alcor and SA about who was in charge of this case and therefore who was responsible for providing the appropriate cryonics-related documents to the hospice personnel, the hospice legal department became involved at the last minute. In the future, the cryonics documentation must be delivered as early as possible and it will be the responsibility of the team leader of the team assigned the case to see that this is done.

Water entered the patient's nose

Some cooling water may have entered the nose before the endotracheal tube was placed. In future cases, start cardiopulmonary support (CPS), secure the airway and nasal temperature probe(s) before starting the surface conduction cooling device (SCCD).

Field Washout

Surgeon Availability

The timing of this case could have conflicted with the availability of our preferred surgeon. Alcor does have several back-up surgeons but they have not been used recently. Observation and training sessions will be set up so that in the event the preferred surgeon is not available, other surgeons can be called who have current training.

New nasopharyngeal plugs

The nasopharyngeal plugs made of "therapy putty" worked well on this case. Alcor would like to use this putty instead of the "swimmer's wax" currently being used. SA will send Alcor information to purchase this product.

Cryoprotective surgery and Perfusion

OR setup error

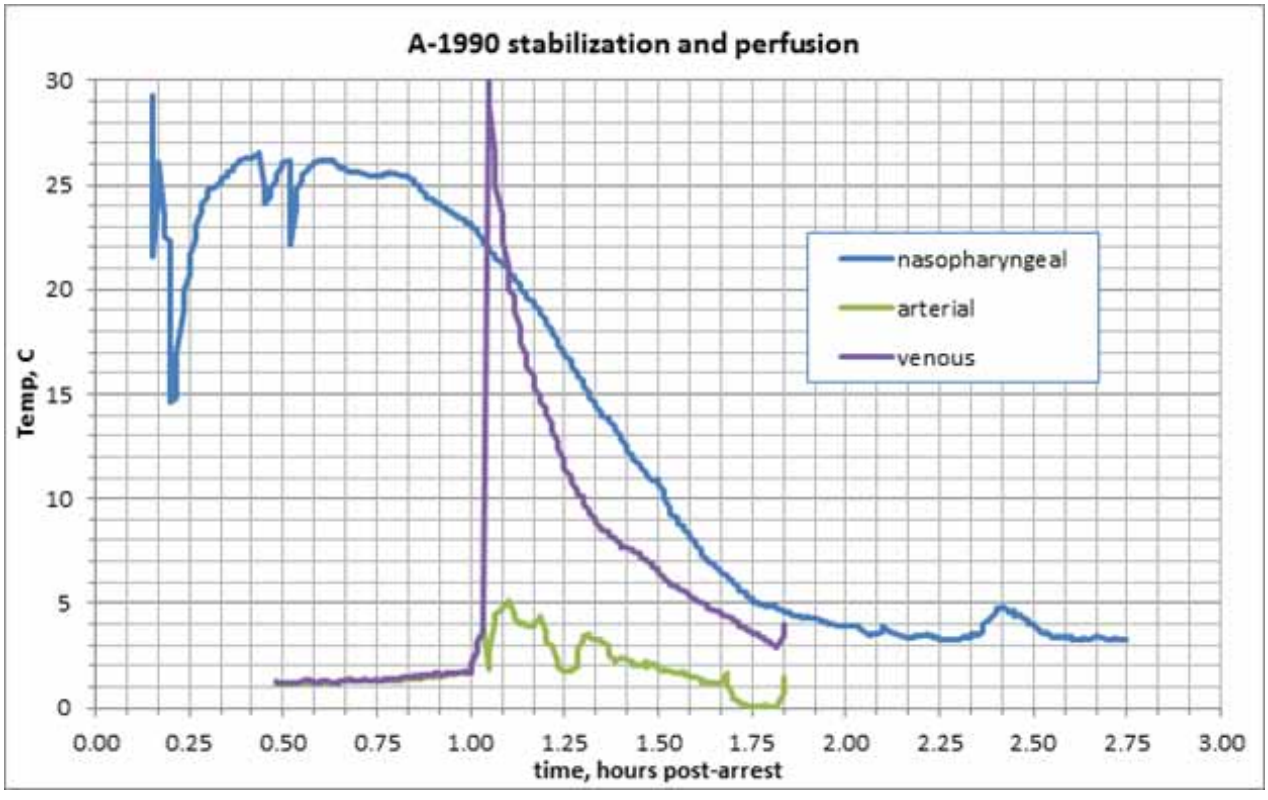
When the red rubber Robinson catheters were placed in the cephalic halo during the OR setup, they were not clamped shut. When the pump was turned on during the testing of equipment prior to the arrival of the patient, approximately 30 mL of B1 was lost. This has been added to the OR Setup standard operating procedure to make sure these clamps are closed.

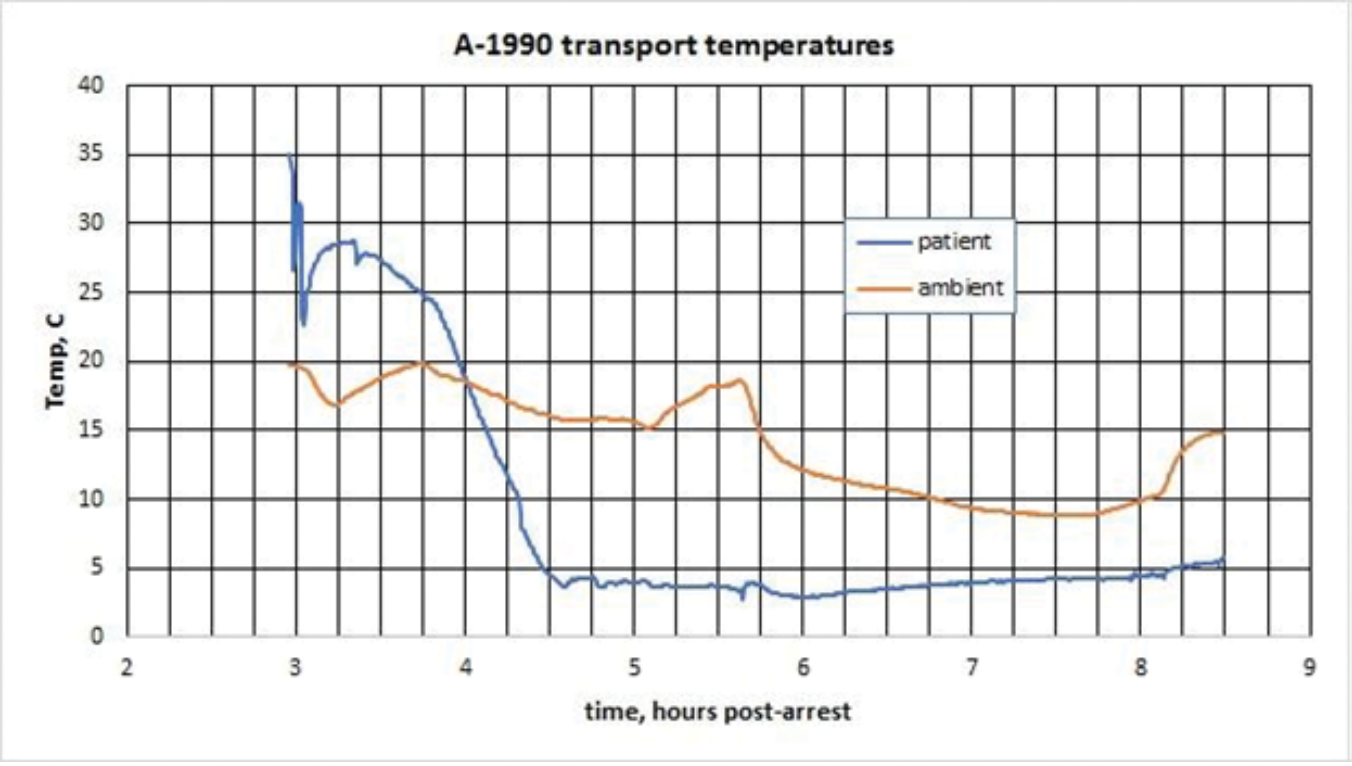
Perforator declutched

The clutch shut off the perforator before the burr hole was deep enough. Some finesse is required with this equipment. For best results, the user should push harder against the drill, use a lower speed and use a rocking motion.

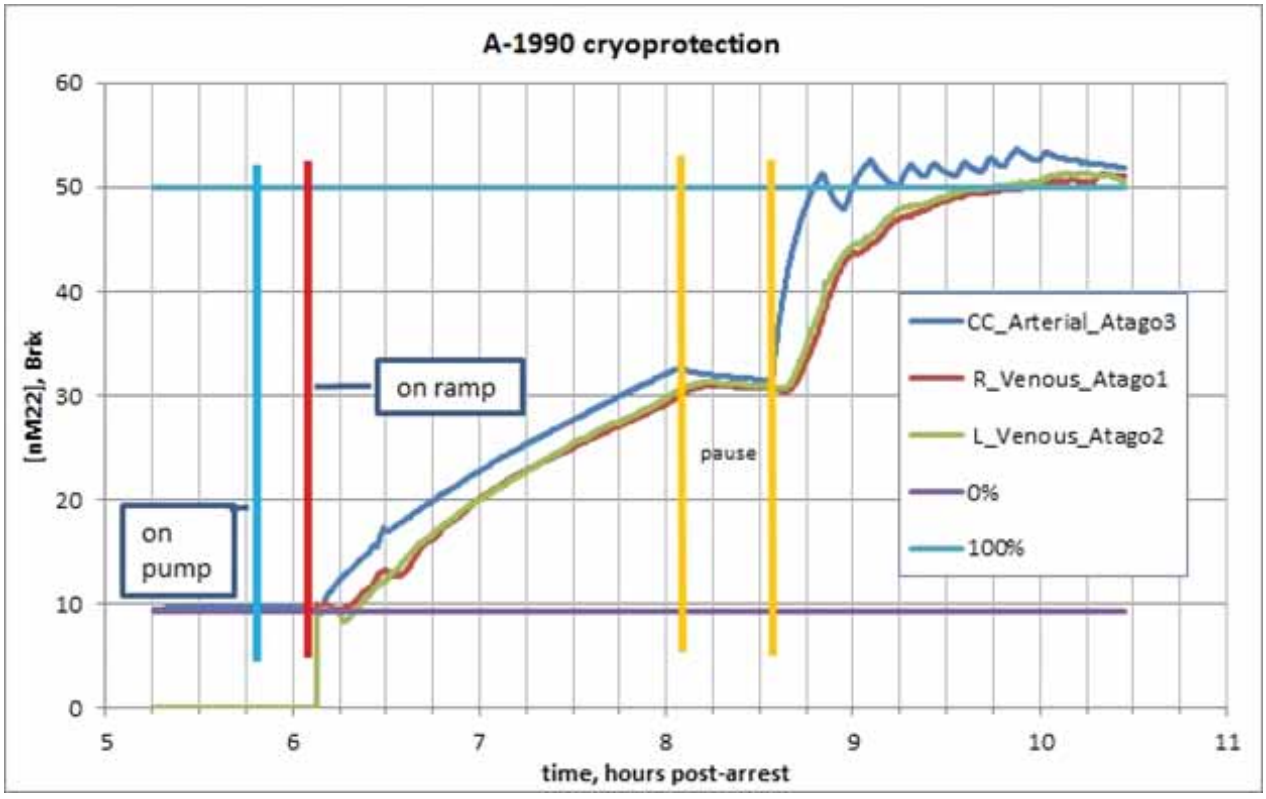
Temperature controller malfunction

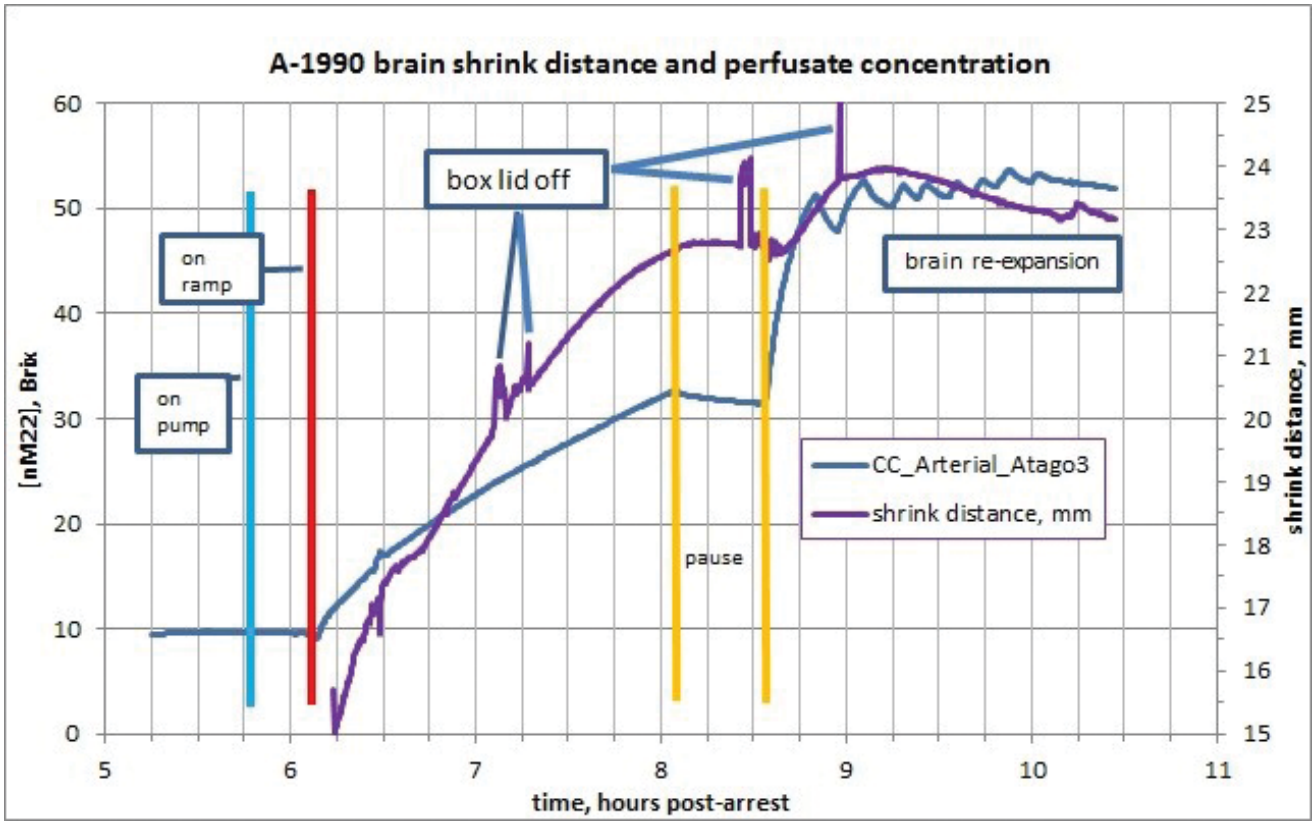
The cephalic box temperature controller appeared to be running at -7°C rather than the protocol mandated -3°C. The set point on the chiller will be corrected before the next case.



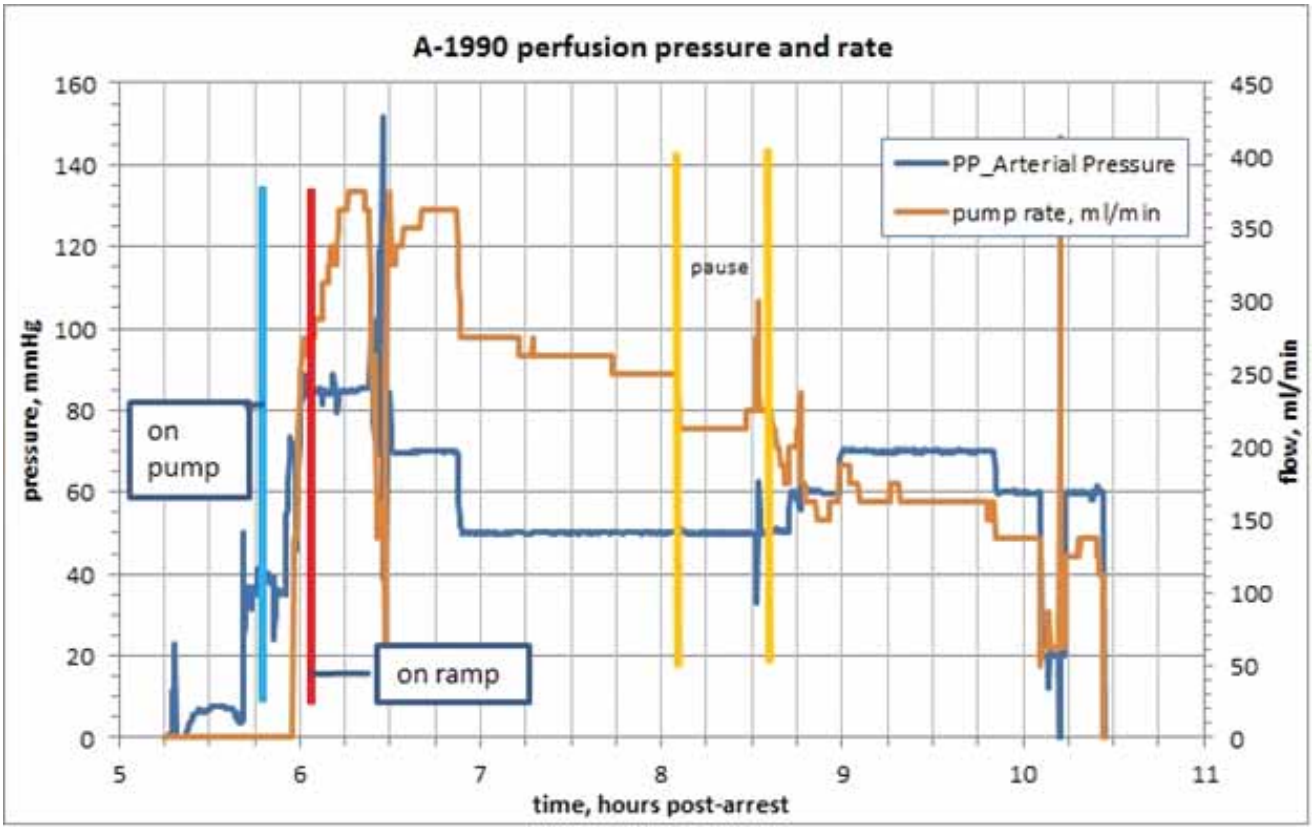


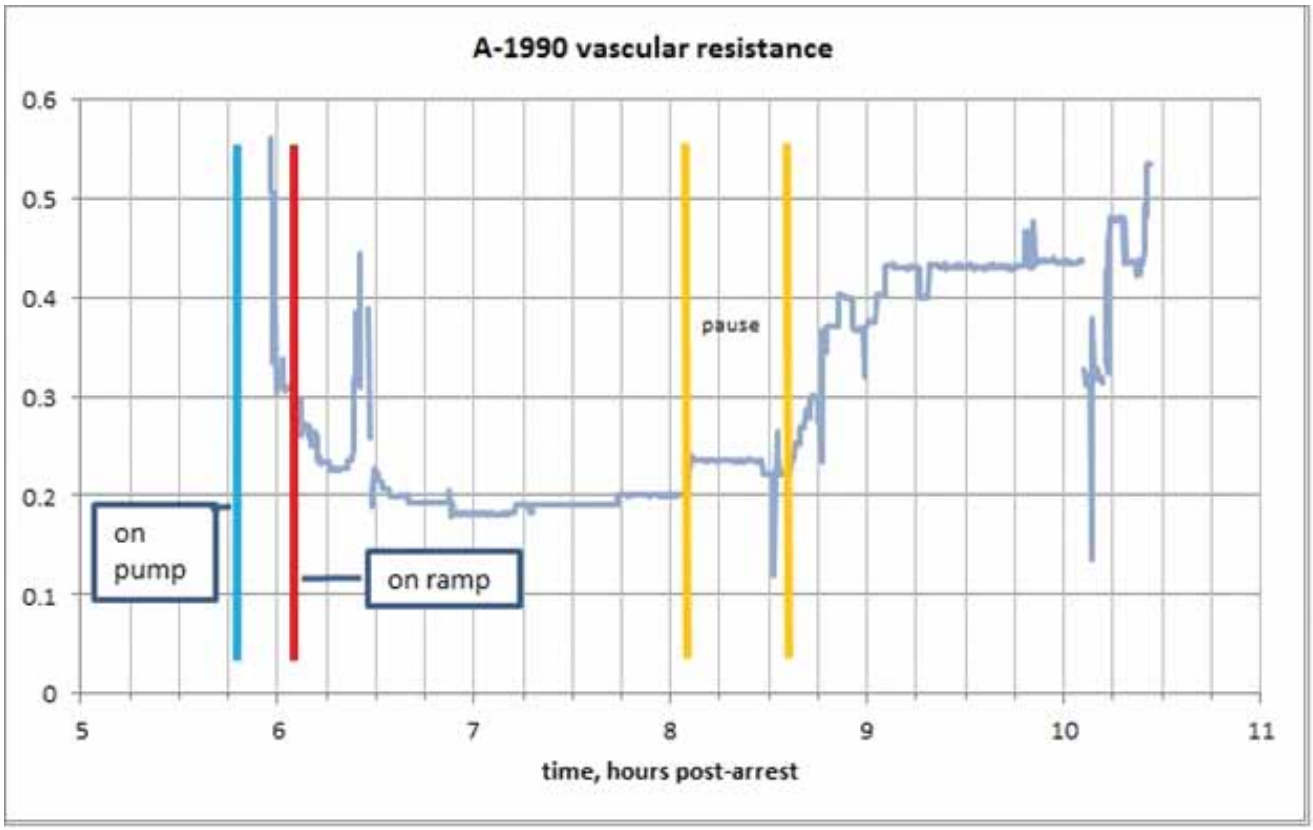
Note: The anomalously low nasopharyngeal temperature readings until 0.6 hrs post-arrest are believed to be due to ice water entering the nasal passages due to the absence of wax sealant normally used around the nasopharyngeal probe wire. The airway was protected by an endotracheal tube during this time. The venous and arterial temperature loggers are not activated until 30 minutes into the case to conserve battery life; data before priming the patient circuit for perfusion would be inconsequential.



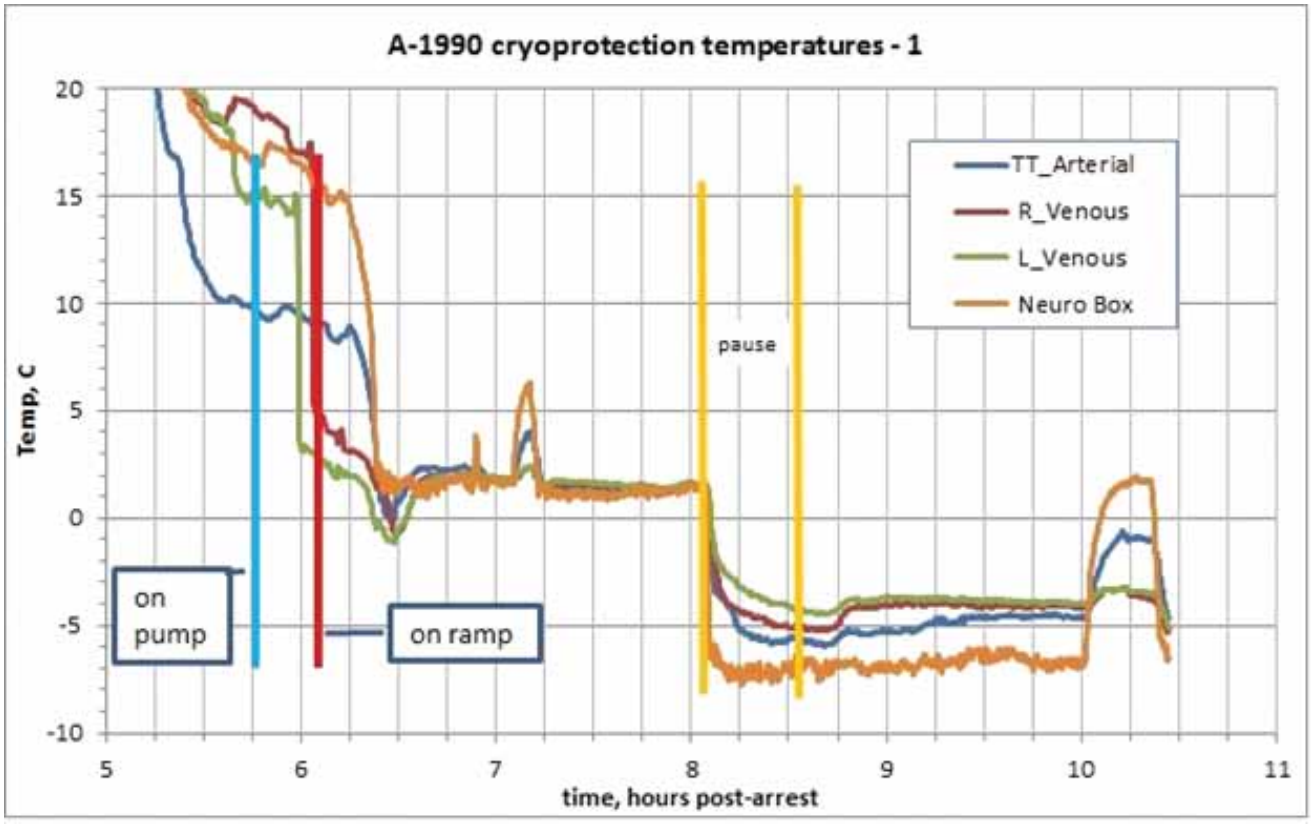


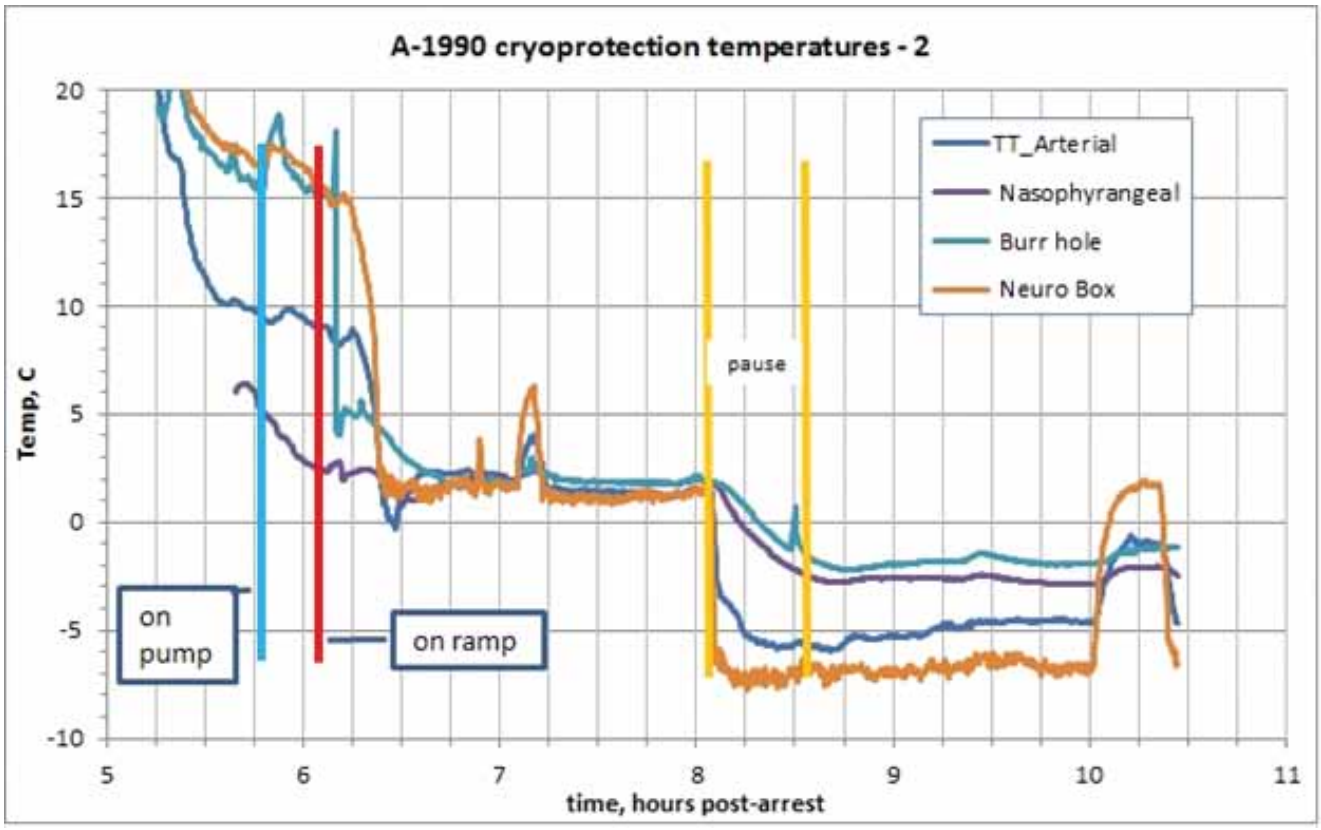
Note: Using a laser, the Brain Retraction Detection Device (BRDD) measures the contraction and expansion of the brain surface directly below a burr hole during cryoprotection. The output from the device is calibrated to derive a standardized reading in millimeters.

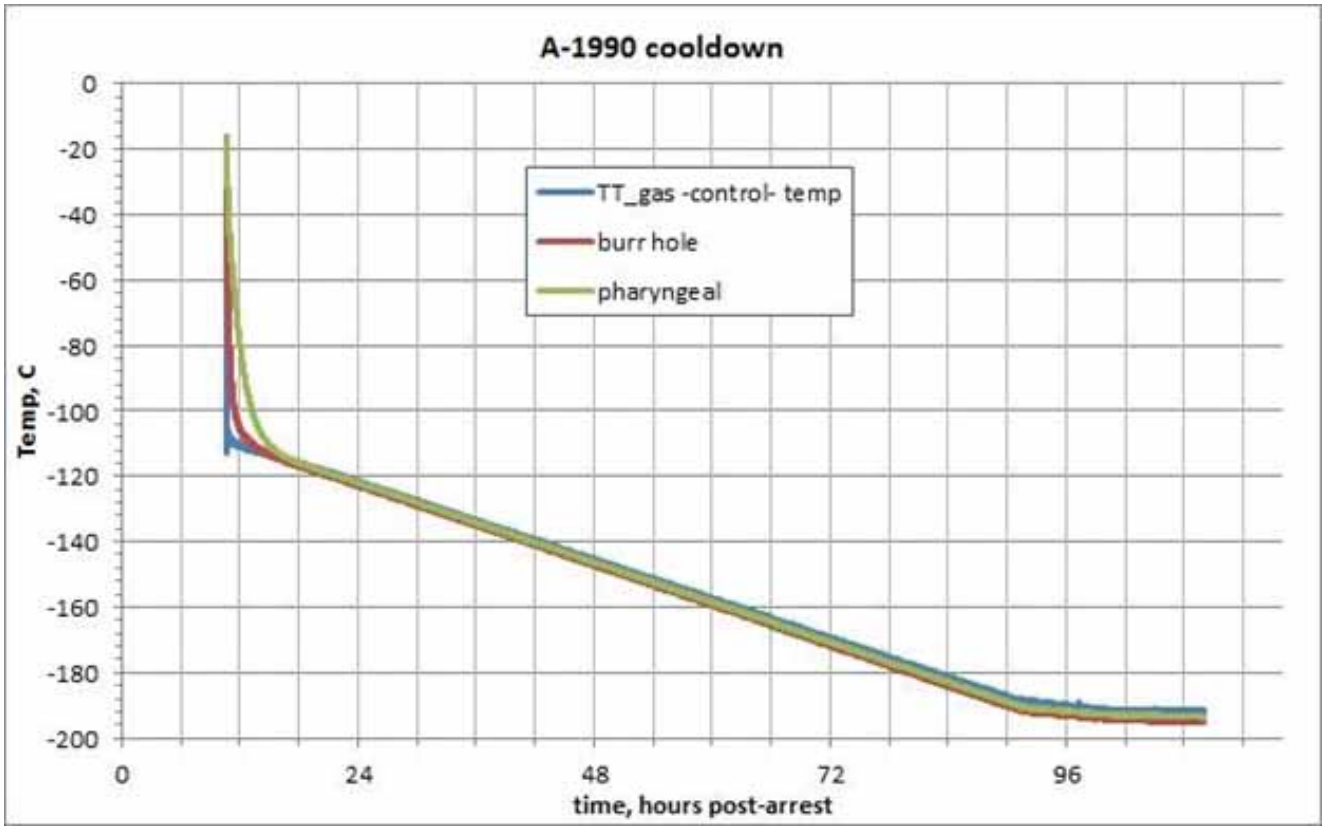




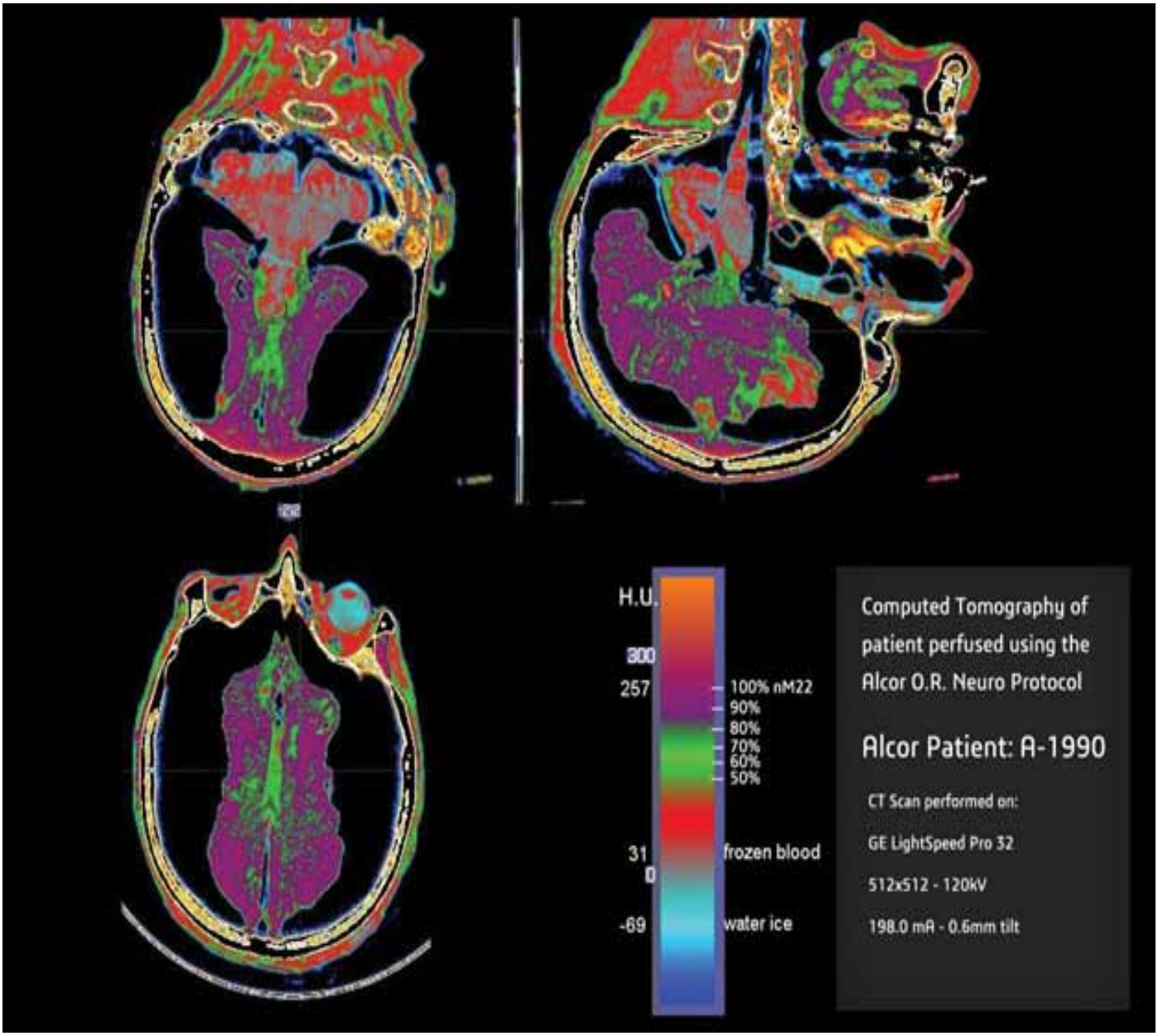
Note: pressure mmHg / flow mL/min




A-1990 cryoprotection temperatures - 2
Temp, C
time, hours post-arrest
TT_Arterial
Nasophyrangeal
Burr hole
Neuro Box
pause
on pump
on ramp

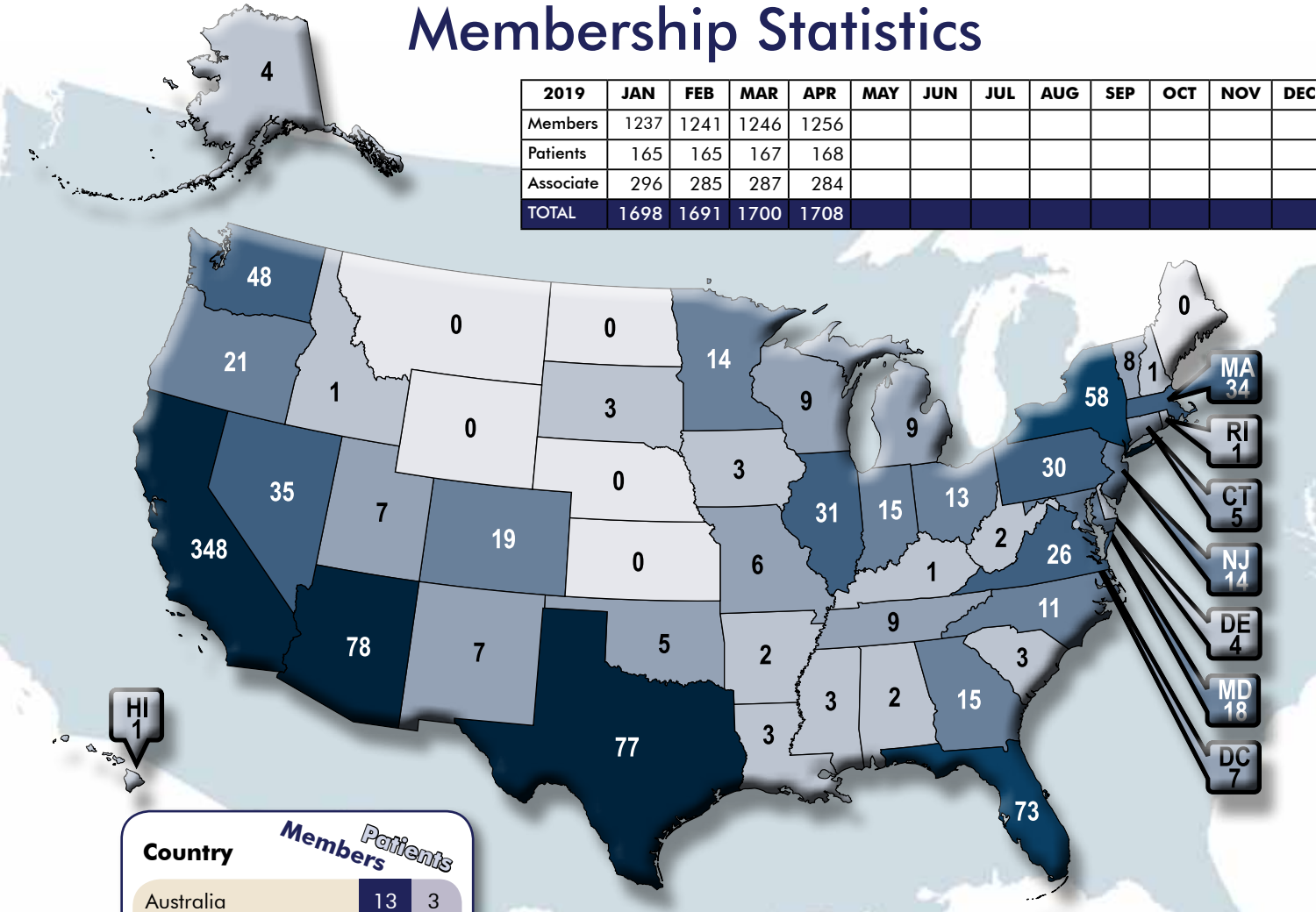

A-1990 cooldown
Temp, C
time, hours post-arrest
TT_gas -control- temp
burr hole
pharyngeal

Cryoprotectant Distribution (CT scan)



Membership Statistics

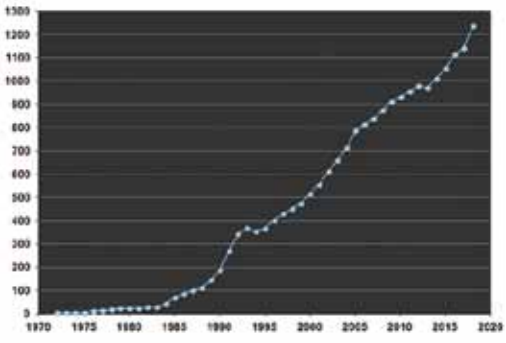
2019	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1237	1241	1246	1256								
Patients	165	165	167	168								
Associate	296	285	287	284								
TOTAL	1698	1691	1700	1708								



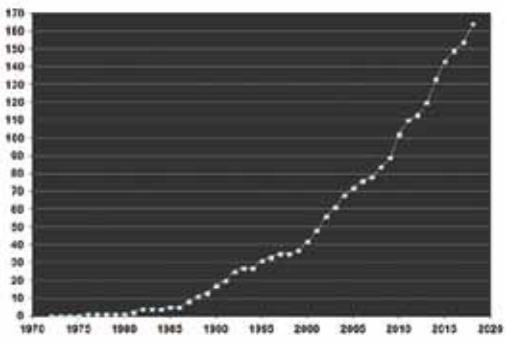
International Members & Patients

Country	Members	Patients
Australia	13	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Canada	61	3
China	0	1
Finland	1	0
France	0	1
Germany	18	0
Hong Kong	2	0
Israel	1	1
Italy	3	0
Japan	5	0
Luxembourg	1	0
Mexico	4	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	2	0
Portugal	4	1
Puerto Rico	1	0
Singapore	1	0
South Korea	1	0
Spain	5	1
Taiwan	1	0
Thailand	5	1
United Kingdom	37	3
TOTAL	172	15

- 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

Leading Cryonics Scientist Yurii Pichugin Cryopreserved

Kharkov, Ukraine

On November 28, 2018, at the age of 67, Yurii Pichugin, a leading scientist in the field of cryonics, was cryopreserved. During his 35-year scientific career, he had a chance to work in the USSR, Ukraine, the United States, and Russia. He was a man of the world and science. His main research results: successful cryopreservation of brain tissue, development of technology used by both American cryonics firms – Alcor and the Cryonics Institute, a systematic overview of the search for cryoprotectants over the 40-year history of cryobiology.

The son of Yurii Pichugin, Konstantin, a Canadian scientist, a specialist in the use of lasers in chemistry, recalls: "My father devoted most of his life to cryonics." Since 2011, Yurii worked in the Russian cryonics company, KrioRus, engaging in experimental work and consulting. In accordance with the cryonics contract signed in 2012, with the help of representatives of KrioRus in Ukraine, the Angels company (https://angels.dp.ua , Dnipro), Yuri's brain was perfused and cryopreserved.

Cryonics today promises much greater chances for recovery than in the years of its foundation. In China, preparations are underway for a head transplant to a new body; technologies of cloning, organ engineering, brain modeling are advancing. In recent years, cryonics has acquired an international character. With the support of KrioRus, cryonics projects were launched in China, South Korea, Italy, and, of course, Ukraine.

Ksenia Sidorenko, director of the funeral services company Angel, a representative of KrioRus in Ukraine, says: "Cryonics is important and promising; we were glad to be involved in this activity."

Despite the scientific challenges and organizational problems, cryonics continues to move forward, gradually becoming a common practice. "The main task now is to ensure the creation of cryonics infrastructure in all regions so [it] is no less accessible than hospices and palliative centers," said KrioRus director Valeriya Udalova.

Yurii Pichugin made a huge contribution to the development of cryonics in the USA and Russia. Thanks to the cryopreservation of his brain, there is a chance that later in this century he will be brought back to life.

REFERENCE

KrioRus is the largest research organization in Eurasia that provides cryonics services, starting in 2005. These include: initial preparation of patients for cryopreservation, perfusion, and storage of cryopatients at ultralow temperatures. In the future, KrioRus plans to reanimate and cure its patients. The company has already saved 66 people and 32 animals.

http://kriorus.ru/en/about-us

Contacts for the media: +7 962 947 50 79, +7 905 768 04 57, kriorus@gmail.com

Biography of Yurii Pichugin on the website of KrIoRus

Representatives of KrioRus in Ukraine – the Angels company (Dnipro)

From Bad to Good: Victor Frankenstein and the Modern Quest for the Secrets of Life

By R. Michael Perry

Introduction

In April 1815 Mount Tambora, on the island of Sumbawa in present-day Indonesia, underwent a series of eruptions over several days. It was one of the most violent volcanic episodes in recorded history, with about 10 cubic miles of rock and dust lofted into the atmosphere. For many months a dusty "dry fog" persisted worldwide, and its attenuation of sunlight caused unusually cold and wintry conditions, so much so that 1816 was remembered as the "year without a summer."[1]

During the spring, and on into this summer-that-wasn't, a small group of young literary talents gathered in a villa by a lake in Geneva, Switzerland. There was Lord Byron; his friend and physician, also a writer, John Polidori; the poet Percy Bysshe Shelley; and Shelley's soon-to-be wife, Mary Godwin. As the stormy weather and rainy days and nights persisted, Lord Byron suggested that, to pass the time, they might each try to write a ghost story. All pitched in, with varying success, but Ms. Godwin's effort, which developed into the novel *Frankenstein: or, the Modern Prometheus*, was by far the best remembered. It first appeared in print in 1818, when the now Mrs. Shelley was but 20 years old, with a moderate, final revision in 1831 (title shortened to *Frankenstein*. The help of poet-husband Percy in the early drafting should also be credited, but the work was primarily by his wife.) It remains in print today as one of the landmarks of the horror genre as well as an early, major effort in a new genre that came to be known as science fiction.[2]

In the book a young scientific genius, Victor Frankenstein, discovers the secret of making dead tissue come to life. He sets out to create a living man out of material salvaged from dissecting rooms, charnel houses, graves, and such, and succeeds. Owing to the great difficulty of operating on a fine scale, his humanoid (male) creature is scaled up in height to "about eight feet." Though the giant is intended to be beautifully proportioned, something goes amiss with the design dynamics and the result, when the creature is up and about, while fully functional and highly intelligent, is anything but eye-appealing. His maker is horrified at the Monster's appearance and, fearing harm from so huge and hideous a hulk, spurns him. The disowned creature wanders about the countryside searching for anyone to be his friend, but all who see him are likewise horrified and hostile. His anger and frustration mount, and eventually he is led to acts of mayhem and murder …[3]

Mary Shelley by Richard Rothwell, 1840.

The Frankenstein story is often seen as a cautionary tale, warning us against the dangers of going too far in our efforts to do amazing things through advances in science and technology, however well-intended. Yet today we live in a world shaped by many such advances, which have taken us far from the world of two centuries ago. Motorized transport, anesthetics, antiseptics, modern medicine more generally, mechanized farming, computers, electric lights, cellphones – the list goes on and on – have revolutionized lifestyles, extended life- and healthspan, and changed civilization and culture in innumerable ways. On the negative side, certainly there has been a fair share of frightening developments, weapons of mass destruction, world wars, technology-assisted terrorism, and the like. Some have expressed wistful desires to "go back to a simpler time" but clearly "the genie is out of the bottle" and there is no turning

back the clock, nor do most people seriously want it. While many are cautious and reserved about what they hope for in the future, some eagerly anticipate further changes and are hopeful that life will thereby be incremented and enhanced far beyond any present or past levels.

Among those who are positive about the future are cryonicists, who have a personal stake in trying to defeat clinical death through cryopreservation, hoping indeed that it will provide a pathway to future medicine, leading to cures for now-terminal conditions, not excepting old age. Radical life extension in a state of vibrant health, with unprecedented options for personal and societal advancement, is the overall prospect.

This brings us to *Death and Anti-Death, Volume 16: Two Hundred Years after Frankenstein* (DAAD), edited by Charles Tandy. This is part of an ongoing series of annually issued volumes, in which selected authors each contribute a chapter exploring some aspect of the main topic of "death and [/or] anti-death." The contributions are grouped under a unifying theme which varies from year to year; for 2018, it's the bicentennial of *Frankenstein*'s first publication. (Most of the DAAD chapters are original material but some are reprints from other sources that might have been hard to obtain otherwise, or are joint publications.)

The chapters in turn cover topics ranging, in this case, from medicine to cryonics to philosophical issues. Contributors were encouraged but not required to refer explicitly to the Frankenstein story and in some way confront that early view of possible scientific or technological progress with what has actually happened in the two centuries since. (Most but not all did.) While there is an overall optimistic tone, there is enough variation in attitudes to provide an interesting mix.

The present article is not intended as a book review or more usual appraisal of the merits or demerits of the source material as a whole. Instead the focus will be on what the Tandy book is about and specifically, how our technological progress compares with the initially pessimistic, fictional assessment found in the novel. First we consider "origins" – mainly, the then-unusual idea that Mary Godwin Shelley had of a horror fantasy based around a scientific premise rather than a supernatural or paranormal worldview. Next it seemed worthwhile to delve into attitudes expressed in DAAD about the presumption that we can make major progress relating to life and its meaning through a scientific approach. A third section is concerned with actual progress, mainly with a chapter on medical strategies for increasing life- and healthspan – and an assessment of where our progress might lead. A fourth section considers projections of future outcomes, including attempts to develop scientific counterparts to religious traditions and practices. Included in this section is a consideration of philosophical issues, such as paradoxes that could arise if multiple copies of a person could be produced. Brief, concluding remarks follow. Overall, there is a striking irony. The original Frankenstein story has deliberate emphasis on things going wrong and humankind being advised not to transgress "its proper place" in the scheme of things. In apposition, there is a wondrous promise for betterment offered by the real scientific Prometheuses who are wresting divine fire from the nether-worlds of thought and experiment and delivering benefits to a waiting humanity.

Origins

"Gothic fiction," says a Wikipedia article, "… is a genre or mode of literature and film that combines fiction and horror, death, and at times romance."[4] This well applies to the novel *Frankenstein*, where in addition the story unfolds without supernatural trappings, instead offering a scientific rationale for its events, as we have noted. The novel has entertained generations of readers, yet doesn't offer much encouragement for the idea of transcending life's limitations through science and technology, to thereby greatly benefit the human species and maybe make it into something better. Instead, its frankly dystopian outlook offers obstacles for those who, like the authors of DAAD, might use it as a starting point for their own generally optimistic projections of accomplishments yet to come.

Such an outlook – basically, that bad would come from a feat that on the face of it might seem to be good – is to be expected considering the times and circumstances. Two centuries ago science had reached unprecedented heights and the Industrial Revolution was well underway, yet at the personal level life was much the same as it had been since ancient times. You were born, you grew to adulthood, you perhaps produced offspring, you reached old age, you died. All in roughly threescore-and-ten (70) years. Or maybe you died at an earlier age from one cause or another. (Life today at this basic level is still similar also, even though people are living longer in better health and many changes at other levels have occurred.) Lifestyles in this candle-lit, horse-and-buggy era were still much as they had been in the distant past, with some beginning changes (steamships starting to navigate rivers, for instance). The invention of printing some centuries earlier, however, had made books widely available and fostered literacy, which led to, among other things, various genres of fiction. Readers of fiction would have their own preferences, which authors might be expected to keep in mind as they wrote for these audiences.

A reader, in particular, might find off-putting a piece of fantasy fiction that offered a utopian world without any significant downsides, one problem being that such a world was desirable but out of reach. Suppose, on the other hand, that it *did* have some definite and interesting downsides, such that the reader did not feel shortchanged, given that the world as depicted would disappear into the woodwork (literally) as soon as the book had been finished and put back on the shelf. This should make for a more acceptable story, which would tend to benefit the author in various ways, including financial. Such, anyway, is one line of

argument for why dystopian fiction might have appeal, and there are others, horror stories simply exerting a fascination that many find compelling, knowing in particular that they can experience the creepy moments in perfect safety.

Boris Karloff as monster in 1931 film adaptation of Frankenstein.

At any rate, Ms. Shelley settled on the horror genre, and then went to lengths to *ensure* that things turn out badly in her story. Literary merit it has, but it does also create a challenge, as noted, for those of us who, while respecting Ms. Shelley's efforts on one hand, are also positive, overall, about the real progress being made.

Mark Walker in his DAAD chapter notes that young Frankenstein's creation of a living, intelligent creature could have been celebrated "as one of the most profound and inspiring human achievements." Instead the novel, as we have noted, is "often understood as warning about the dangers of scientific hubris." That such an understanding was the author's intention seems evident from the original title, *Frankenstein; or, the Modern Prometheus*. As Wikipedia notes, "In Greek mythology Prometheus" (the name means "forethought") "is a Titan, culture hero, and trickster figure who is credited with the creation of man from clay, and who defies the gods by stealing fire and giving it to humanity, an act that enabled progress and civilization. Prometheus is known for his intelligence and as a champion of mankind." For his defiance of the gods, however, Prometheus is cruelly punished by being chained to a rock. Each day an eagle eats out his liver (often thought by ancient Greeks to be the seat of human emotions), which grows back overnight to be ready for the next day's round of predation, until finally freed by the hero Heracles.[5]

Prometheus depicted in a sculpture by Nicolas-Sébastien Adam, 1762 (Louvre).

As "proof" of the errors of Frankenstein's scientific hubris, the Monster leaves a trail of violence and dead bodies, culminating in a pact with his creator to make him a wife, in return for a promise of better conduct. These plans come to naught, however, and at the end the Monster mourns rather than celebrates the death of his problematic creator, before heading into the frozen arctic to seek his own demise. Walker, however, notes that Frankenstein's faults are not really a matter of "vainglorious technological aspirations" as the author would have you believe but are well explained by more ordinary lapses:

> "Victor Frankenstein is a moral failure. He is a neglectful, cruel parent. Recall that Frankenstein

> immediately rejects his creation simply because he is ugly. This is an astounding failure of parental responsibility. If Victor had been only a minimally morally decent parent, much of the tragedy of the novel could have been avoided. After all, we are told in the novel that the Monster has a sensitive soul, needs love and companionship – just like the rest of us. It is hardly surprising that the Monster turned to evil given the denial of his very basic needs. With even a modicum of parental love, the type we should expect of any minimally decent parent, much of the tragedy of the novel almost certainly would have been avoided. But then again, Shelley's work would probably have fallen into obscurity: nothing sells like murder."[6]

There is an incident in the book where the Monster manages to frame an innocent person, the much-respected housekeeper Justine, as the perpetrator of one of his murders, and she is tried and executed. Victor has knowledge that would exonerate her. But he does not go to the authorities for fear, he says, of "being dismissed as a madman" for trying to claim that *he* committed the crime, as he says he was prepared to do to save Justine, when evidence showed he wasn't there. Victor completely ignores at least telling part of the truth, which the evidence would support, that a large ugly man who had already committed murder was the culprit here too. As Walker surmises, "at least two crimes, child abandonment and an accessory to murder after the fact, should appear on the docket next to Victor Frankenstein's name."[7]

Ms. Shelley's gloomy portrayal of the potential for human advancement through scientific means is, on the face of it, unconvincing. This is not to deny that, in the real world, bad could follow through the use of reason and science, as it has abundantly, for example, from the wilful use of weapons of hunting and war. Fears of future calamities should not be dismissed out of hand either, for example, the worry that advanced AIs could use their superior intelligence to overpower and do away with the human species. (They might, for example, regard humans as many humans today think of cockroaches.) On the other hand, technology properly developed and applied could lead to a world reminiscent of ancient religious concepts of heaven, with now-terminal disorders banished and opportunities for advancement and meaning in life that we of today can scarcely imagine. As noted, the writings of DAAD mainly reflect the latter sort of optimistic prognostication, though with variations. We turn now to writers who focus on certain basic philosophical issues, before considering the other parts of our subject.

Attitudes about *Frankenstein* and Progress

We have just explored one set of attitudes about the Frankenstein story and agreed, sympathetically, that the story is contrived to say something worse about the technological future than warranted, granted its author, by appearances, believed it. (But see the discussion of Cerullo's chapter, below.) Other DAAD writers besides Walker have addressed this subject, many with more negative judgments, which we now briefly survey.

For Brian N. Duchaney, Shelley, it appears, was right: "Victor is a casualty in the war of progress, a pawn presented by Shelley to illustrate the danger of sacrificing the essential aspects of humanity in the scientifically advancing world."[8] Later he comments:

> "By attempting to alter nature, Victor's flaw is the pursuit of forbidden knowledge. Unlike a Faustian deal with the Devil, Victor's ills can be redeemed before it's too late. However, not without considerable hardship. At the cost of his wife, family, and friend, Victor eventually redeems himself by allowing the monster's future companion [the wife he had promised to make] to remain dead, to shut away the knowledge he's obtained and implore [his friend] Walton to follow his advice: 'Seek happiness in tranquillity, and avoid ambition, even if it be only the apparently innocent one of distinguishing yourself in science and discoveries. Yet why do I say this? I have myself been blasted in these hopes, yet another may succeed.'[9] Victor's attempts to apologize for his error while simultaneously extoling the virtues of being able to do so in the first place may be a sign of pride, but they are evidence that Victor will not be so foolish as to commit his crimes a second time. This not only proves that Victor is no madman but that his belief in the natural world, of leaving the dead lie where they may, enables a greater respect for the wisdom of others and the natural order of the world. This is likely why the monster's near immortality underscores Shelley's problem of reconciling her own questions of life and death posed by the novel."[10]

Another cautionary voice is Shane Denson, who is concerned with technological progress opening pathways that many are uneasy about. Particularly, our growing understanding of biology and how to manipulate it at the gene level gives the issue of eugenics an unprecedented urgency. In the future we might be able to create "designer children" with desirable traits, much as Frankenstein was trying, with what skill he possessed, to make his man-creature handsome as well as smart and strong. What should be our guidelines? In any case, for good or ill, "… as historically situated and technologically conditioned beings, there can be no question of our either going back to technologically simpler times or of retaining a stable identity through the course of future technological changes."[11] Denson further concludes:

> "[T]he Frankenstein myth has come to dominate thinking about biotechnology. In many ways, this is due to superficial connections drawn between the new technologies and the narrative events of Mary Shelley's novel. Equally, the story has come to articulate deep-

seated cultural fears in relation to technology. But *Frankenstein* also documents serious, historically specific, material disruptions of human subjectivity effected by modern technologies. In evaluating the polemical uses to which the tale is put today, we shall have to historicize our technological hopes and fears in terms of the technological irreversibilities witnessed by Shelley's text. And if we find ourselves in the midst of another technological revolution today, we would do well to return to this record in an attempt to understand ourselves and our technological lifeworlds better. …It is too late to ward off danger with a cautionary tale of the consequences of playing God. But it is equally wrong to think that dismissing such admonitions as irrational can help us (re)establish a situation in which we are unambiguously the masters of our technologies… The lesson of technological irreversibility is not, however, that we must resign ourselves to technological determinism. Instead, we must look for new ways of embodied being to cope with the material monstrosities of technology, and in this quest *Frankenstein* will continue to play an unpredictable, contradictory, and – in the best sense – *monstrous* role."[12]

Langon Winner offers another warning against the reckless pursuit of scientific innovation:

"One can, of course, identify more precisely the motivations that typically lead people to forge ahead with reckless abandon: the intrinsic pleasures of scientific inquiry and technical invention; the promise of recognition from one's peers or, perhaps, lasting historical fame; the possible advantage that the outcome will prove useful to one's society in competition or conflict with others; the potential for substantial monetary gain; etc. Whatever the expected return, however, the impulse to power typically comes first, while the recognition of one's moral obligations happens later, if at all. Within that unfortunate gap – between aspirations to power through scientific and belated recognitions of responsibility – often arise generations of monstrosity. Mary Shelley's insights on such matters were prescient, well ahead of their time, foreshadowing some of the most ominous hazards and most ghastly calamities found along the path to modernity from the early 19th century up to the present day."[13]

Still another cautionary treatment is in the chapter by Uri Lifshin and Jeff Greenberg on how people cope in general with the problem of mortality:

"The classic novel *Frankenstein* grapples with the desire to bring what is dead back to life. …When she wrote [it, author Mary Shelley] was part of a social circle that included the great romantic poets Percy Shelley, and Lord Byron, both of whom confronted in their poems the burden of mortality and the futility of trying to transcend it either spiritually or symbolically. *Frankenstein* offered another, more modern way to try to transcend mortality, a scientific approach, and emphasized the likely monstrous and tragic consequences of this approach to defeating death. At the heart of the novel is the desire to undo death and the question of if it should be done, and if so how – with no satisfactory answer offered. The novel was prescient both in the specific idea of directing modern science toward defeating death, and the more general idea that when science tries to alter basic aspects of our world there are often dire unanticipated consequences of doing so."[14]

It is well that we keep in mind the serious risks of possible mishaps with our developing technologies, as the foregoing authors are adept at warning us. On the other hand, technology, particularly biotechnology, does not consist entirely of "material monstrosities," nor is nature herself perfectly sacrosanct. Indeed, life as currently lived *is also a monstrosity*, in which *nature* inflicts a "turnover of generations" that sacrifices each individual after a period of time, in a process that (as seen, for example, in nursing homes) is not pleasant to watch or contemplate. Our technological progress is arguably heading toward a world which will remedy this, a world in which lifespans can be extended and health maintained indefinitely.

Such a world in turn could be only a starting point for a civilization of benefits and benevolence we can scarcely imagine, conditioned by an abundance of basic essentials for life that advanced technology (coupled with resources such as solar energy and materials from deep space) could provide. Today, however, it is painful to confront the likely prospect that this world is out of reach and will not be ours unless some extraordinary measures could be taken to provide an "ambulance" to a future time when we can enjoy the benefits. One sort of possible confrontation is cryonics – to have one's essential remains, particularly the brain, cooled to low temperature upon clinical death (with treatment as available to minimize freezing damage to tissues) and stored indefinitely. In this way nature's decay process is halted and time is obtained for the hoped-for successful revival to come. Hopes in such an outcome have energized a small group of people for whom the future prospects, at the personal level, are not as bleak as for many others.

Michael Cerullo is a cryonics advocate who is hopeful that today's technology will be successful in one day allowing the revival of people who were adequately preserved at clinical death. (The revival would not necessarily involve the original tissue but the personality elements might be "uploaded" to a future computational device and "run" in a suitable way so the patient would, in effect, awaken and resume life in this setting.) Cerullo has an interesting take on the Frankenstein story and

what "take-home message" it appears Shelley really had in mind:

> "The most obvious interpretation of Frankenstein is as a promethean myth warning against the folly of not considering the consequences of science and technology. …The Frankenstein mythology is frequently used by opponents of life extension to warn of dire consequences of extending life. Yet I would argue that this is a misunderstanding of Shelley's intents and her own viewpoints on life extension. … I think Frankenstein is more straightforwardly interpreted as a warning against the lack of accountability in science rather than any argument geared specifically towards the creation of life or life extension. Shelley wrote long before research review boards and the creation of the Nuremburg code which was enacted after World War 2 to hold scientists to reasonable ethical standards in research. In Shelley's time scientists routinely performed vivisection on animals without a second thought. Thus, if any lesson can be drawn from Frankenstein it is surely that scientists must act with ethical standards when conducting research and be held accountable for their work."[15]

As for Shelley herself, Cerullo notes that she was not at all opposed to the idea of life extension, and even what would today be called cryonics, as shown by an 1826 essay on the case of Roger Dodsworth, Jr., who, it seemed, had been trapped in ice in 1660 while crossing the Alps. Discovered much later (about 1810), the long-frozen body was thawed and restored to life, said the report, and the man identified himself and accurately described his historical setting.[16] Though the tale was soon proved a hoax, Shelley evidently took it seriously when she wrote her essay; an important passage is quoted by Cerullo:

> "Animation (I believe physiologists agree) can as easily be suspended for an hundred or two years, as for as many seconds. A body hermetically sealed up by the frost, is of necessity preserved in its pristine entireness. That which is totally secluded from the action of external agency, can neither have any thing added to nor taken away from it: no decay can take place, for something can never become nothing; under the influence of that state of being which we call death, change but not annihilation removes from our sight the corporeal atoma; the earth receives sustenance from them, the air is fed by them, each [e]lement takes its own, thus seizing forcible repayment of what it had lent. But the elements that hovered round Mr. Dodsworth's icy shroud had no power to overcome the obstacle it presented."[17]

Cerullo adds that Shelley in her essay "discusses many of the existential concerns that would face an individual that was transported into the future and away from the world they knew. But in the end the story shows her fascination with the possibilities of seeing the future."[18]

Aging as a Curable Ailment

Among these possibilities would be a remedy for aging, which can be regarded as a potentially curable ailment, a topic which is addressed in DAAD. Attitudes expressed there are varied, but overall there is a (reassuring) resistance to the idea that death-by-aging is something we must live with and accept. Instead there are two principal approaches which can be taken to physically address the problem. (1) We can work toward treating aging directly, slowing and especially, reversing the process. (2) We can use a "holding" action such as cryopreservation in the event of clinical death (by whatever causes, including aging), to further address the problem later. Both approaches find their advocates in DAAD, along with, as usual, a varied assortment of attitudes. Two chapters in particular (Wang, Sorgner) address aging in different ways, one in terms of therapies that have shown some value, the other in terms of attitudes, in this case calling for recognition of aging as a disease. A third chapter (again, Cerullo) makes a case for a holding action through cryogenic brain preservation. These we consider in turn.

Sinclair Wang has widespread interests in the field of human longevity; for example, he authored a Chinese translation of Robert Ettinger's pioneering cryonics book, *The Prospect of Immortality*. His main focus within this theater is "the applications of microbiology and cell biology for the enhancement of common health and common wealth for all beings." He is "also interested in expanding the envelope of physical science" into turf now occupied by metaphysics through advances in quantum physics.[19] Though positive overall about medicine and its potential for improving the quality of life, Wang is critical of much of the medical establishment today and its underlying philosophy. Instead he advocates a more holistic approach that recognizes, for instance, that much of our health depends on beneficial microorganisms that are hosted in the body and not at all harmful even though genetically "foreign" invaders. Another approach to longevity he favors is stem cell intervention. He concludes his chapter by stressing that increasing longevity and vitality are desirable, but apparently within certain natural limits, beyond which we may not be able to go.

> "The ultimate truth of the human body system, like the universe, is beyond our total rational comprehension. Artificial interferences in order to achieve longevity and vitality are impossible. Nature has provided us two gifts to keep us, and preserve us till our natural lifespan is reached; they are the ecological microbiota and regenerative stem cells. The best use of these two gifts – to recover and regenerate without disturbing or destroying the body's internal system – will make the task not only easy but also natural, to reach our long-desired longevity and vitality."[20]

So, do we have a "natural lifespan," that can be "reached" so that after that point we die, and the eventual lethality of aging, though perhaps amenable to some significant delay, is something we must just accept? Or instead, should we regard aging as a disease like any other, and not rest until we find a complete cure, so we can live indefinitely in perfect, vibrant health, whatever it may take by way of future advances? The latter opinion is held by many futurists (self included!), among them Stefan Lorenz Sorgner, who notes that

> "…Approximately 150,000 people die every day worldwide. 100,000 of them die due to diseases caused by aging-related damages. Only a small percentage dies from HIV/AIDS-related conditions. The excellent website ourworldindata.org confirms this. These findings are linked to the assessment by many transhumanists that aging is a disease. Aubrey de Grey is probably the most prominent representative of this theory … He has analysed the processes generally associated with aging: 1. mutations in genes, 2. mutations of mitochondria, 3. deposits in cells, 4. deposits outside cells, 5. cell loss, 6. loss of the ability of cells to divide, 7. the increase in extracellular protein cross-linking, which decreases elasticity between cells. The first process can lead to cancer, the fourth to Alzheimer's and the fifth to Parkinson's. Nevertheless, primarily diseases are combated, rather than the damages that lead to them and which are identified with general aging processes. …"[21]

Although it might seem like a minor semantic point, public recognition of aging as a "disease" would certainly help to focus efforts toward remedying it, including making research funding more readily available. Sorgner focuses on hindrances to this in his home country of Germany, which also largely apply elsewhere. There a leading philosopher urges that such approaches as gene therapy are desirable when combating *deficiencies*, but not if attempting *enhancements*. It appears then, for example, that a treatment for Hutchinson-Gilford progeria, which kills victims in their teens or earlier with symptoms resembling old age, would no doubt be considered a worthy goal of research. However, suppose one proposed a treatment to restore centenarians to the health and vitality of 20-year-olds, thereby increasing their life expectancy by unprecedented decades. That would be considered "enhancement" and would not similarly be held in favor.

Of course, if it seemed likely that such aging reversal was imminent, many would likely find their objections losing force quickly, and ample funding for further research might then become available. Instead, people today, as in the past, tend to see aging as a "given" of life and, for emotional reasons, are reluctant to characterize something that affects us all as a "disease," though logically there are ample grounds for doing so. At any rate, there is that other side to combating aging, or any other cause of clinical death, which is to carry out biostatic preservation in the event that it happens, so that, if all goes well, future technology can further address the problem, and finally remedy it.

This brings us to cryonics, the principal means used today for biostatic preservation with revival as a goal. Michael Cerullo, in his chapter, "The Case for Brain Preservation and an Examination of Why the Frankenstein Argument Fails," notes that the practice was developed in the second half of the twentieth century and that several companies are now offering the service. There is still uncertainty as to whether the brain preservation is adequate for the goal of revival, but some encouraging-looking results were recently obtained for one variant of the procedure, known as aldehyde-stabilized cryopreservation or ASC, and prizes were awarded. Cerullo assumes for the sake of argument that cryonics will be successful, particularly in allowing whole brain emulation (WBE) from the preserved remains.

A few words about WBE are appropriate here. It is also known as "uploading," a futuristic scenario that advocates think should become possible, perhaps not too distantly. The brain's information would be copied into an advanced computer so the person could be "run" as a program. The program would be interactive and could be supplied with sensory impressions and other information from the outside, or exist in a virtual reality world reminiscent of Second Life but fully immersive. It could also inhabit and control a robot body in the real world, and walk around and move things and generally act like people or other creatures today. In one fashion or other, the consciousness and mental functioning of the original person would continue in a superior, nonbiological substrate. (Those who are disturbed by this scenario can rest their hopes in the possibility of reviving the original brain and body, with missing body parts replaced as needed.) WBE could possibly offer a faster route to revival than reactivating the original body, or at any rate, could offer a faster route toward demonstrating the overall viability of the cryonics idea, if, for example, a mouse brain could be so emulated.

The chapter continues with a discussion of why cryonics is morally justifiable. Some might dismiss the practice as "Frankensteinian"[22] but Shelley was interested in the possibility of life extension through a process like cryonics, as Cerullo noted. There is some discussion of such issues as the possibility of overpopulation if cryonics is successful, leading to "too many people;" such an outcome is far from certain (world fertility rates are showing significant declines, as one counterargument). Going from there, he offers a telling further argument against the "Frankensteinian" dismissal, which well summarizes his whole position.

> "The major point of this chapter is that merely bringing up the story of Frankenstein is no substitute for sound ethical arguments. There are no short cuts to a thorough understanding of the current technology for

> brain preservation and [its] implications. In addition, the ethics of life extension is to a large extent based on empirical facts, many of which are currently uncertain. In another decade, if whole brain emulation is successfully demonstrated in mice, … there will be overwhelming evidence that brain preservation is a life-saving medical procedure. It would require an extraordinary amount of evidence showing harm to society to outweigh an individual's autonomy to choose this procedure if it is available, and no such evidence exists today."[23]

Steps into the Future

In this last major section we consider some far-ranging ideas relating to our anticipated transition from where we are today to the better, brighter world we hope will exist tomorrow. As a starting point we note the possibilities raised by Charles Tandy in asking if we can, in fact, do better than Frankenstein did in the story:

> "Whether Dr. Victor Frankenstein was a mad scientist, a monster himself, is a further question. A generalized interpretation here offered is that the good doctor, mad or not, was lacking in foresight, love, and wisdom. In Shelley's work of fiction, Dr. Frankenstein's creation was both intelligent and conscious. Two hundred years later, we are asking if our non-fictional intelligent technologies will become conscious or remain non-conscious. Either way, ought we not imbue or orient our creations toward love rather than hate? If, in Shelley's thought experiment, Dr. Frankenstein had taught his creature love rather than hate, might things have turned out differently?"[24]

One way we might "orient our creations toward love rather than hate" is explored in Debra Basset's chapter on "digital afterlives." Here the possibilities, far from being "just science fiction," are fully realized today.

> "Some time ago my friend's daughter died suddenly, and I was amazed to find that five years later people were still talking to her on the Internet as though she were still alive. I began to explore how people were using the Internet to stay in-touch with the deceased, and found a plethora of Facebook RIP sites – which had been set up following the death of loved ones – being used to remember, memorialize and communicate with the dead."[25]

Many readers will be familiar with the concept of "avatar," which in modern computer usage signifies "an icon or figure representing a particular person in video games, Internet forums, etc."[26] Potentially this "representation" could allow arbitrary, independent actions so that one's avatar could "speak in one's own voice" (with the help of presently-available voice synthesis, starting with recorded speech) and say whatever comes to mind, in a manner similar to oneself. Appropriate voice hookups with flesh-and-blood humans could allow conversations, which would not end with one's death, so that one could "live on" through such means. The authenticity of one's atavaric representation could be improved by storing more complete information about oneself in a database accessed by the atavar, and the atavar could also have the capacity to assimilate new experiences and thus become a "continuer" of oneself, living an independent existence, or, as noted, carrying on the life of the original after death. Some interesting efforts in the direction of providing for atavaric self-representations are noted by Basset, involving Terasem Movement Foundation, brainchild of transhumanist entrepreneur Martine Rothblatt:

> "The Terasem LifeNaut program based in Vermont, USA allows you to create a 'mind file' to store your cognitive information; a 'safe space to store your life experience' allowing you to 'back yourself up'. The exponential growth of the emerging technologies needed to deliver and support the cyberconsciousness, mindclones, mindware and mindfiles discussed by transhumanist pioneer Martine Rothblatt do not seem far away. Bell and Gray of Microsoft Research agree that it may be possible a 'cyberized' version of you will be able to learn, evolve and eventually take on a life of their own. Rothblatt's research has led to the creation of Bina48, a humanoid robotic head that holds the mindfile of her real-life wife Bina Aspen. This social robot makes various public and media appearances with Terasem's executive director Bruce Duncan, and in 2017 Bina48 was the first robot to complete a college class: Bina48 attended a Philosophy and Love class at Notre Dame de Namur University (NDNU) in California, where she engaged in class discussions and was awarded a college certificate for her participation. Technological advances that enable the creation of digital zombies such as Bina48, raise important questions: Bina48 was created from a living person, but what will happen when the real Bina dies? Will Bina48 remain socially active? Moreover, will the friends and relatives of the real Bina find Bina48 a comfort or a disruption to their grief?"[27]

Basset's focus here appears to be mainly on a "digital zombie" which would somewhat substitute for the original in case of death. The bereaved could take some comfort in communicating with a kind of vicarious representation of a deceased loved one, though deep down they would know it was "just a computer program, with no feelings or consciousness." Or would this always be so? Actually, very unlikely. With further advances in AI and other fields, the "zombie" might more and more closely conform to a conscious being in its own right, with a full panoply

Bruce Duncan with Bina48.
Credit: Terasem Movement Foundation

of feelings and talents, ultimately even far surpassing the human model. Indeed, with the WBE scenario outlined above, it can be argued that our destiny is to become such a program, running in a substrate that is much more suitable for a very extended life than our protoplasmic body, jury-rigged as it was by unconscious natural selection (though remarkable enough in its own right).

We then would become advanced beings, far enhanced beyond our present levels in various desirable ways. Roman V. Yampolskiy and Soenke Ziesche, citing Nick Bostrom, propose some possible guidelines, as a starting point for such enhancements:

- the changes are in the form of addition of new capacities or enhancement of old ones, without sacrifice of preexisting capacities;
- the changes are implemented gradually over an extended period of time;
- each step of the transformation process is freely and competently chosen by the subject;
- the new capacities do not prevent the preexisting capacities from being periodically exercised;
- the subject retains her old memories and many of her basic desires and dispositions;
- the subject retains many of her old personal relationships and social connections; the transformation fits into the life narrative and self-conception of the subject.[28]

Along with opportunities for advancement in the future could come unprecedented means to house or copy ourselves, a topic that is explored in Mark Walker's chapter, with some of the legal conundrums which could arise. Suppose Jones has no problem with the idea that he would survive in a copy of himself, and also is not particularly hindered by moral scruples. He commits a crime, then contrives to have a copy of himself made through advanced nanotechnology (or through an upload), while the original is destroyed. If the law has not been updated to address this possibility, the copy-Jones might claim he is innocent and escape the hand of justice. If, on the other hand, the original is *not* destroyed, would both be guilty? If a copy of an original is made and the original or the copy is destroyed but not both, is that an act of murder? How would inheritance be handled if more than one copy of an heir existed? These and other such conundrums might be resolved, in part, simply by having greatly reduced significance in a future world of abundance, superior enlightenment, and indefinite lifespan.

Such a world would be peopled by those who survive to the times, or are then created. Would any of us be among their number? Those of us who have chosen cryonics are hoping to reach such a world by having our biological remains preserved at clinical death for later revival. What about others, those who died or will die without significant preservation? Is there any hope that they too might someday be resurrected or recreated, somewhat as Russian 19th-century philosopher Nikolai Fedorov imagined?[29] These possibilities are considered by R. Michael Perry (yes, that's me) with some surprisingly optimistic conclusions. Short answer: yes, the long dead could be raised even after so-called information-theoretic death that obliterates identity-critical information, the caveat being that one would have to assume the existence of multiple universes or worlds where resurrections of different variants of a vanished person must happen in parallel.

But a future, however advanced, with whatever prospects for the continuance of the life of its inhabitants, whoever they may be, will not in and of itself guarantee that such life will be meaningful and valuable. Science and technology can give us understanding and the means to realize and sustain our values, but will not manufacture the values in the first place. Something more will be needed, perhaps along the lines of religious traditions of today. Religion, granted its disparagement by many who pride themselves as "rationalist," is, at any rate, intimately focused on values. It is also worth noting that "religion" can be understood in a broader sense than is often assumed today, in which connections with supernatural elements or a God in the traditional sense are not necessarily present. Protestant theologian Paul Tillich defined 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."[30] With this in mind it is plausible that one could be both religious and of a hard-nosed scientific mindset that eschews any claims of miracles or the supernatural; futurists in particular might fit this paradigm. Giulio Prisco explores some possibilities for combining an advanced scientific and technological perspective with religious elements in his chapter, "Turing Church: Hacking

Religion, Enlightening Science, Awakening Technology." A quote from futurist author and religious studies professor Robert Geraci sets the tone for what follows:

> "Popular science authors in robotics and artificial intelligence have become the most influential spokespeople for apocalyptic theology in the Western world... Apocalyptic AI advocates promise that in the very near future technological progress will allow us to build supremely intelligent machines and to copy our own minds into machines so that we can live forever in a virtual realm of cyberspace... Ultimately, the promises of Apocalyptic AI are almost identical to those of Jewish and Christian apocalyptic traditions. Should they come true, the world will be, once again, a place of magic."[31]

There have been some attempts, Prisco notes, to engineer a movement within the spectrum of futurist initiatives in which religious elements are combined with a scientific-technological perspective. One that he and colleagues started a few years ago was the Order of Cosmic Engineers, "a tongue-in-cheek name for a transcendent social movement for the cosmic frontier." It failed, however, because of "our inability to reach a real consensus view of the core concepts, a common vision strongly held by all the founders. Everyone (including me of course) wanted to push their own pet ideas to the forefront, and often de-emphasize or eliminate the pet ideas of others. The main lesson that I learned is that fast design by committee doesn't work for philosophy and religion."[32]

An alternative approach is to have a single originator rather than a committee. In this way a cogent philosophy is produced but so far such initiatives have attracted only a very small following. (Noted are the efforts of Martine Rothblatt, Ben Goetzel, R. Michael Perry, and Dirk Bruere.)

Another approach is, rather than trying to engineer an initiative from scratch, incorporate it into an existing religious tradition. The most successful such initiative to date is the Mormon Transhumanist Association, which gains strength from widely held Mormon beliefs that people, in effect, are "gods in the making," and that science and technology, furthered by hard human effort, could be very important in our progress. Many, however, may not want to affiliate with a mainstream religious movement, whatever the attractions of some particular group or outlook within it.

Prisco notes, as another alternative, a more recent initiative of his own, "Turing Church," named in honor of computer science pioneers Alan Turing and Alonzo Church. Its single ethical prescription is: "Try to act with love and compassion toward other sentient beings." Not actually a "church," it is mainly headquartered on the Internet, "a deliberately disorganized community" for those interested in participating. Prisco describes it as "a minimalist, open, extensible cosmic religion." An important focus of Turing Church is to regard sentient beings in computational terms, which leads to ideas of uploading which are important to many if not all futurists. Prisco is also convinced that "superintelligent, God-like beings control the physical reality that we perceive" and that we will join them one day, in "a partnership … to re-engineer the universe and resurrect the dead."[33] (By way of contrast, the resurrection scenario offered by Perry, above, is without the assumption that God-like beings will assist us, though, of course, not ruling it out entirely.) More generally, Prisco surmises:

> "The task ahead – to adapt religion to transhumanism and our future expansion to the stars – is difficult but important and noble. It is to be expected that most early experiments will stagnate or fail, but I am persuaded that new philosophical and social engineering initiatives will be successful and important for the future of humanity."[34]

Brief Concluding Remarks

By the time *Frankenstein* was written, in the early 1800s, it was clear that science and technology had advanced in ways never achieved before, even if by our standards things were still primitive. It took the brilliant young Mary Godwin Shelley to perceive this and base a novel on what would happen if someone extended this advancement a certain way. She wanted to point out that things might go badly, and we from our perspective of two centuries later can see that indeed things can.

Yet despite all our advances, we are still primitive in one fundamental way: we are chained to our biological substrate with its vulnerabilities, including aging and death. Radical additional progress will be needed to remedy this limitation. Proposed efforts in this direction are sometimes disparaged as "Frankensteinian" but a more proper attitude is clearly to be more positive. We must not stop until we have conquered aging. What will follow after that we cannot be sure of today, but clearly major changes will occur, as we search for new ways of finding meaning and value. Handled properly, it should be a happy search. Cryonics meanwhile offers a simple conceptual way to put our biological systems on hold in event of failure, so we can take part in this happier future. Maybe it is not the only possible way (as I and others have argued); this is controversial, but a case can also be made that it is a good and worthy approach, and better than other practices today for physically addressing the problem of death. ■

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2 MS2; MS3.
3 MS1; MS1, 54; MS3.
4 GF.
5 D, 265; PR.
6 D, 266.
7 D, 267.
8 D, 110.
9 MS1, 270.
10 D, 123.
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12 D, 97-98.
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14 D, 151-52.
15 D, 42-43.
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17 MS4, quoted in D, 43-44.
18 D, 44.
19 D, 16-17.
20 D, 316.
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Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

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

Towards a Biomarker of Aging Based on the Gut Microbiome

Jan, 2019

A low-cost, low-effort way to accurately assess biological age, meaning the burden of molecular damage and the countless harmful cellular reactions to that damage, would greatly speed development of rejuvenation therapies. Ideally researchers would be able to apply a therapy and then within a month obtain a measure of how greatly it affects aging. At present the only reliable way to fully assess means of slowing or reversing aging is to run life span studies, which are slow and expensive in mice, and simply not feasible in humans.

Thus a fair amount of effort is presently devoted to the development of biomarkers and combinations of biomarkers that might one day serve this purpose. In this preprint paper, researchers outline their work on the use of the gut microbiome as a basis for a biomarker of aging. It is known that characteristic changes occur in the microbiome with age, many of them detrimental and associated with the development of age-related disease, but there is a high degree of variability between individuals and study populations. Thus these results will certainly need a much broader replication as a part of any further development.

Quote

Although infant microbiome succession is well studied and can be used to assess the risks of various health conditions, its transition to adult microbiome is less understood. More so, composition variability attributed to geographic location, medical history, diet, and other factors make it hard to analyze adult microbiomes as effectively as those of infants. Age-related studies of human microbiome have failed to produce a straightforward theory of gut flora aging.

Some studies indicate decreasing biodiversity in the elderly gut. However, that is not the case for all data sets, and elderly healthy people may have microbiomes as diverse as the younger population. Other findings include changes in specific taxa abundance in aging microbiota. Such bacterial genera as Bacteroides, Bifidobacterium, Blautia, Lactobacilli, Ruminococcus have been shown to decrease in the elderly, while Clostridium, Escherichia, Streptococci, Enterobacteria increase. However, these patterns are not strictly established as results vary greatly across different studies. This may be attributed to different methodologies as well as unbalanced data sets that may contain people of different lifestyles.

Despite these complications, the consensus is that the elderly gut has lower counts of short chain fatty acid (SCFA) producers such as Roseburia and Faecalibacterium and an increased number of aerotolerant and pathogenic bacteria. Such shifts can lead to dysbiosis, which in turn contributes to the onset of multiple age-related diseases.

The standard way of separating the gut microbiome into three chronological states – child, adult, and elderly microbiomes – lacks a clear set of rules. Among them, adult microbiome remains the greatest mystery. It has no established succession stages, as in newborns, and does not normally reflect gradient detrimental processes typical for an old organism. This poses a question whether normal adult microbiome progresses at all or it is in a state of stasis. Considering the aging process is gradual and involves accumulation of damage and other deleterious changes (as also indicated by a number of biomarkers such as DNA methylation clocks), it is logical to suppose that gut microbiome succession is also gradual. However, attempts to use microbiome-derived features to predict chronological age have been inconclusive.

Here, we developed a method of predicting the biological age of the host based on the microbiological profiles of gut microbiota using a curated dataset of 1,165 healthy individuals. Our

predictive model, a human microbiome clock, has an architecture of a deep neural network and achieves the accuracy of 3.94 years mean absolute error in cross-validation. The performance of the deep microbiome clock was also evaluated on several additional populations. This approach has allowed us to define two lists of 95 intestinal biomarkers of human aging. We further show that this list can be reduced to 39 taxa that convey the most information on their host's aging. Overall, we show that (a) microbiological profiles can be used to predict human age; and (b) microbial features selected by models are age-related.

Link: https://doi.org/10.1101/507780

Protein Aggregation versus Infection Hypotheses of Alzheimer's Disease

Jan, 2019

The amyloid hypothesis has dominated the past twenty years of failed attempts to build therapies to treat Alzheimer's disease. However, it is only very recently that immunotherapies and other methods of reducing amyloid-β levels in the aging brain have started to show signs of working. As a consequence, the field is in a state of some upheaval when it comes to choice of strategy going forward. Alternative views of Alzheimer's and its development have emerged and gained enough support to raise sufficient funds to compete. In the long run, this is all to the good, I think. A diversity of approaches always beats out a top-down monoculture when it comes to finding viable paths forward. The open access paper noted here examines a few different hypotheses that have risen to prominence.

Quote

In this review, we focus on four Alzheimer's disease (AD) hypotheses currently relevant to AD onset: the prevailing amyloid cascade hypothesis, the well-recognized tau hypothesis, the increasingly popular pathogen (viral infection) hypothesis, and the infection-related antimicrobial protection hypothesis. In briefly reviewing the main evidence supporting each hypothesis and discussing the questions that need to be addressed, we hope to gain a better understanding of the complicated multi-layered interactions in potential causal and/or risk factors in AD pathogenesis.

As a defining feature of AD, the existence of amyloid deposits is likely fundamental to AD onset but is insufficient to wholly reproduce many complexities of the disorder. A similar belief is currently also applied to hyperphosphorylated tau aggregates within neurons, where tau has been postulated to drive neurodegeneration in the presence of pre-existing Aβ plaques in the brain.

Although infection of the central nervous system by pathogens such as viruses may increase AD risk, it is yet to be determined whether this phenomenon is applicable to all cases of sporadic AD and whether it is a primary trigger for AD onset. Lastly, the antimicrobial protection hypothesis provides insight into a potential physiological role for Aβ peptides, but how Aβ/microbial interactions affect AD pathogenesis during aging awaits further validation. Nevertheless, this hypothesis cautions potential adverse effects in Aβ-targeting therapies by hindering potential roles for Aβ in anti-viral protection.

Unlike familial AD, sporadic AD may evolve from a combination of various genetic and environmental factors. Neuroinflammation, tau pathogenesis, and viral infection have all been implicated to play important roles in AD; however, these factors do not appear to be pathogenic triggers that are specifically relevant to AD. Thus, specific causal mechanisms that drive AD onset have yet to be clearly defined, which may lead to the identification of new therapeutic targets. It is now widely accepted that sporadic AD is a complicated syndrome.

Link: https://doi.org/10.1186/s40035-018-0139-3

Impressions from the January 2019 Juvenescence Gathering

Jan, 2019

The JP Morgan Healthcare conference took place in San Francisco this past week. The conference is less interesting in and of itself, but it is the spur for any number of other short gatherings of various biotech investment and business interest groups. So in the middle of last week, Jim Mellon and the other Juvenescence principals were in town to host their second annual showcase for startups working on aging, and the BioAge and Felicis Ventures folk hosted the overlapping Extending Human Lifespan event on the same day. I had to miss that second one, as I was presenting Repair Biotechnologies at the Juvenescence event to a small crowd of other entrepreneurs, angel investors, and venture capitalists of varied allegiances, and stayed for the whole event to see the other presentations.

Many of our fellow travelers associated with SENS rejuvenation research and Methuselah Foundation spheres were present to meet and greet: the SENS Research Foundation folk; much of the Oisin Biotechnologies team; Doug Ethell of Leucadia Therapeutics; Frank Schüler of Forever Healthy Foundation; a number of angel investors I've interacted with in the past while we were interested in the same companies; and many others arriving and leaving as they moved between events.

One thing that caught my eye is that the theme of diversity and new hypotheses in Alzheimer's research (or outright rebellion against the past two decades of relentless focus on clearing amyloid via immunotherapies, present it as you will) has robustly made its way to the commercial development stage. Leucadia Therapeutics were presenting their latest work on ferrets as an

animal model to illustrate that the development of Alzheimer's occurs due to blocked drainage of cerebrospinal fluid though the cribriform plate. Related company Enclear Therapies was not present, but was a topic of discussion given that their founders have very similar thoughts on filtration of cerebrospinal fluid. Maxwell Biosciences principals presented their work on the LL-37 antimicrobial peptide as a test of the microbial theories of Alzheimer's disease, in which infection is provoking greater aggregation of amyloid and inflammation to accelerate other aspects of the condition. An attempt at intervention is perhaps the best way to clear up questions of causality here: do we see microbial infections in the Alzheimer's brain because they are an important cause, or because immune dysfunction in general tends to be more advanced in these patients?

A further contingent of startups at the Juvenescence event were similarly of interest for having a good shot at answering scientific questions very much faster than the academic community can, due to the influx of resources from the venture community. Elevian falls into this category, with their work on GDF11. Early work on parabiosis, joining the circulatory systems of an old and young mouse, pointed to GDF11 as a possible factor in conveying benefits to the old mouse. There is now some debate over why parabiosis works, however, casting doubt on the argument of beneficial factors in young blood. Similarly, there has been some back and forth in the research community regarding whether or not past work on GDF11 is as it appears to be, but the Elevian staff claim to have resolved the conflicts. In many cases, the best way to resolve a debate of this nature is to just forge ahead and try to build a therapy; that effort can pull in much greater funding more rapidly than the academic community can manage via the usual channels available to researchers.

Another item that caught my attention, and seems worthy of consideration, is that the infrastructure and drug discovery companies in our space of treating aging as a medical condition are the furthest ahead in terms of building out relationships with venture concerns, obtaining larger funding, and breaking ground on their larger and later projects. This may reflect the focus of groups like Juvenescence from the past couple of years, their approach to establish an initial presence in a field. Examples of this trend include In Silico Medicine and Ichor Therapeutics' portfolio company Antoxerene, both of which offer faster, cheaper discovery of small molecule drugs for any sort of use, but both of which happen to have founders very interested in aging and longevity over and above any of the myriad other uses for their technologies. In Silico Medicine in particular is clearly advancing by leaps and bounds in Asia as they gather support from the high-end venture groups there.

(I'll confess that I've never found the development of lower level biotechnological infrastructure all that interesting as a topic. Obviously it is vital, and acceleration of technological progress is achieved by making common tasks easier, faster, and cheaper. Someone has to do it, invest in it, and focus on it, but that someone will never be me. I am far more interested in specific implementations of rejuvenation therapies, the development groups who might end up using the infrastructure to build a given treatment).

San Francisco is ever a hub of connections for the venture and technology spaces. It is the base of operations and home for a sizable number of high net worth individuals, agents for other high net worth individuals, fund partners deploying sizable amounts of capital, successful founders turned angel investors, successful angel investors turned founders – all rubbing shoulders, bumping into one another at the supermarket, and two degrees of separation removed at most. It is through this very connected network that interest in the biotechnologies of rejuvenation has been spreading these past fifteen years, pushed along by the presence of the SENS Research Foundation in the Bay Area. This occurred slowly at first, given that the focus was initially philanthropic funding of research rather than startups, but much more rapidly these past few years now that the first rejuvenation biotechnology startups are arriving on the scene.

At a small gathering after the Juvenescence event, those attending included an older AI-focused entrepreneur-turned-investor who has a growing interest in biotechnology, and a recently successful young founder from the technology space who is now taking life science classes to get up to speed on what he considers to be his next area of interest. The next day I met with an angel investor who attended the Juvenescence event, and who is cheerfully incorporating biotech companies into his previously tech-company-heavy portfolio. This dynamic is similarly reflected in venture firms such as Y Combinator, Felicis Ventures, and (closer to our community) Kizoo Technology Ventures led by Michael Greve, among others. They are transitioning into biotechnology, and the interest in doing something about aging is a driving motivation for many involved. For others, it is the realization that successful rejuvenation therapies will lead to a market so enormous as to make a pittance of near everything that has come before. Self-interest is a machine to be harnessed in these matters: while fundamental research is very cheap, later commercialization and distribution of medical therapies to millions of patients is enormously expensive. We need the deep pockets to enter this space, and to pull in all of their allies and other interested parties, if we are to see a reasonable rate of progress in moving rejuvenation therapies from lab to clinic.

The only other alternative is some form of major, lasting revolution in the regulatory environment, as that is the dominant cause of cost and delay. Therapies could be brought to market just as safely as they are today at a fraction of the present cost; the majority of cost and time imposed by the FDA, EMA, and the like is entirely unnecessary, some of it the debris of regulatory capture used by larger pharmaceutical entities to suppress competition, some of it the consequences of bureaucrats going to any lengths to avoid negative press, even by the means of preventing most new technologies from ever being approved.

I'm certainly in favor of great upheaval in the development of medical therapies, but tearing down the present edifice is a vast project, and arguably one that will be much less costly and difficult to undertake given the existence of the first rejuvenation therapies and the public demand for more.

A final thought on investors and the science of rejuvenation: most of the newcomers are still finding their way to an understanding of the science in this space. They cannot yet tell the difference between projects likely to produce significant gains in human life span, those based on repair of the damage that causes aging, and those that cannot in principle produce large gains, those based on, say, upregulation of stress responses, such as mTOR inhibitors. Investors are guided by potential for financial gains, but that metric is not in fact a great way to tell the difference between better and worse approaches to aging. The typical competently run medical biotechnology company is acquired or goes public before the final determination of effectiveness of their programs; perhaps somewhere just after the first human trial, or even prior to that when the market is hot. Companies can do this after showing marginal benefits, or even just potential for marginal benefits, with a therapy that will never produce large or reliable benefits in larger patient populations, and yet still realize large gains for the early investors. So this is a challenge, and an opportunity for patient advocates to make a difference – to help guide those people chasing gains into obtaining those gains by backing better rather than worse technologies.

Nattokinase and Reversal of Atherosclerotic Lesions

Jan, 2019

Atherosclerosis is one of the great killers. Fatty deposits form in blood vessel walls, narrowing and weakening the vessels. Eventually something ruptures, and the result is a stroke or heart attack, but even absent that the condition can narrow vessels sufficiently to cause fatal coronary artery disease. Even with modern medicine, the condition is inexorable: the toolkit doesn't yet include a way to more than slightly reverse the buildup of these plaques, and medical professionals must focus on ways to incrementally slow the progression of atherosclerosis rather than delivering any true cure.

One of the side-effects of starting a company, Repair Biotechnologies, that is working on a way to reverse atherosclerotic plaque, is that I've been doing a great deal more reading on the topic of atherosclerosis than I would otherwise have done in the course of writing Fight Aging! Thus I turn up interesting items from the past few years that I missed at the time because I lacked the context to understand why they were worthy of notice, or just didn't have the sort of focus on atherosclerosis that I have at the moment. The papers I'll share today fall into this category, providing evidence for nattokinase, a very simple and readily available supplement, to have a surprisingly large effect on atherosclerotic lesions in humans. After six months of treatment, a third of the lesions were removed.

A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia

Quote

All enrolled patients were from the Out-Patient Clinic of the Department of TCM at the 3rd Affiliated Hospital of Sun Yat-sen University. Using randomised picking method, all patients were randomly assigned to one of two groups, nattokinase (NK) and statin (ST) group. NK Group-patients were given NK at a daily dose of 6000 FU and ST Group-patients were treated with statin (simvastatin 20 mg) daily. The treatment course was 26 weeks. Common carotid artery intima media thickness (CCA-IMT), carotid plaque size and blood lipid profile of the patients were measured before and after treatment.

A total of 82 patients were enrolled in the study and 76 patients completed the study. Following the treatments for 26 weeks, there was a significant reduction in CCA-IMT and carotid plaque size in both groups compared with the baseline before treatment. The carotid plaque size and CCA-IMT reduced from 0.25±0.12cm² to 0.16±0.10cm² and from 1.13±0.12mm to 1.01±0.11mm, repectively. The reduction in the NK group was significantly profound, a 36.6% reduction in plaque size in NK group versus 11.5% change in ST group. Both treatments reduced total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG).

Nattokinase: A Promising Alternative in Prevention and Treatment of Cardiovascular Diseases

Quote

Nattokinase (NK), the most active ingredient of natto, possesses a variety of favourable cardiovascular effects and the consumption of Natto has been linked to a reduction in cardiovascular disease mortality. Recent research has demonstrated that NK has potent fibrinolytic activity, antihypertensive, anti-atherosclerotic, and lipid-lowering, antiplatelet, and neuroprotective effects. This review covers the major pharmacologic effects of NK with a focus on its clinical relevance to cardiovascular disease.

This size of effect on atherosclerotic lesions is big enough to be suspicious, given that nattokinase is a supplement in common use, and the dose used is not outrageously large. We seem to be seeing a lot of that sort of thing these days, however; sometimes significance goes unnoticed, but equally sometimes it is an issue with the study that will be corrected later. It is hard to tell which without meaningful further effort. Does bisphosphonate treatment actually extend life expectancy by five years, and did this really go unnoticed despite its widespread use in older people? Is fisetin actually a significantly effective senolytic

compound in humans despite being widely used; did the very high senolytic dose in comparison to the usual supplement dose successfully hide this property? How did nearly twenty years of earnest development and use of the chemotherapeutic dasatinib go past without anyone noticing that it killed enough senescent cells to improve health and measures of aging in mice and people? And so forth.

Over the past few decades, hundreds of millions of dollars (at the very least) has been spent on clinical trials to try to reverse atherosclerosis – to give existing repair systems in the body sufficient breathing space or increased capacity, allowing them to break down the fatty deposits that form in blood vessels. The sponsors of any of those trials would have been ecstatic to find a reliable reversal of atherosclerotic plaque that was half the size of that noted in the nattokinase trial here. One might take a look at a 2012 review paper that surveys the degree to which treatments at the time could achieve the goal of reversing atherosclerosis. A reversal of 15-20% in an unreliable fraction of patients was about the best that could be done. Most approaches were considerably less effective than that. Not a lot has changed in this high level picture since then.

At present the dominant approach to treatment of atherosclerosis is reduction of blood cholesterol, the cholesterol attached to LDL particles, or LDL-C. Statins are the long-standing approach, and are now being joined by even more effective treatments such as PCSK9 inhibitors. This slows down atherosclerosis by (a) lowering overall cholesterol, and thus freeing up some fraction of the macrophage cells that would otherwise have had to shovel it out of blood vessel walls, but more importantly (b) lowering oxidized cholesterol, which is very damaging to macrophages. When considering atherosclerosis and its treatments it is important to consider macrophages: they are drawn to the fatty lesions, and their task once there is to mine cholesterol from the lesion, ingest it, and hand it off to HDL particles that carry it back to the liver for excretion. This is called reverse cholesterol transport.

Atherosclerosis exists because macrophages become overwhelmed, mostly by oxidized cholesterol, but also by the sheer volume of cholesterol, or by an overly inflammatory environment. They become agitated, call for help, become foam cells (some of which become senescent, causing further issues) or die. Most of a plaque is made up of the debris of dead macrophages, and the plaque itself is a self-expanding disaster area that calls ever more macrophages to their doom. Reducing the LDL-C slows down this feedback loop, but it cannot do much for existing plaques. There is some regression (the aforementioned 15-20% at best) because macrophages are given some breathing room, but plaques continue to grow at the new slower pace, and people continue to die.

There has been a considerable amount of work over the years on alternatives to lowering LDL-C. Researchers have tried all sorts of ways to improve the ability of macrophages to mine cholesterol and send it back to the liver. They have tried increased numbers of HDL particles (which are formed from APOA1 protein). They have tried altered forms of APOA1 found in some human populations that are associated with lower levels of atherosclerosis. They have tried the introduction of artificial HDL particles to swell the numbers. They have tried upregulation of the ABCA1 and ABCG1 proteins that perform the actual handoff of cholesterol molecules to APOA1. There is more in the same vein.

All of these things work pretty well in mice; the current best approaches produce 50% reversion of atherosclerotic lesions in animal studies. Yet all of those tried in humans, meaning the HDL and APOA1 approaches, have failed miserably in clinical trials. What this means is that there is something that the research community doesn't yet understand in the low-level detailed differences between human and mouse reverse cholesterol transport. That is a big roadblock for anyone turning up to propose some form of enhanced cholesterol transport as a therapy, even if intending to try one of the varied effective-in-mice approaches that hasn't yet been trialed in humans.

In this context, one can see that evidence for a common supplement to manage 36% reversion of lesions in humans is both welcome and jarring. It will certainly have to be replicated before many researchers in the LDL-C-focused side of the scientific community are likely to take it all that seriously. Any simple, easily obtained improvement should be welcome. Nonetheless, it is still only reversion by a third. The disease will still progress, and will still kill people. The research community has to do better than this.

Towards Reliable, Low-Cost Tests for the Earliest Stages of Alzheimer's Disease

Jan, 2019

The research community has moved quite determinedly these past few years towards practical, low-cost tests for early Alzheimer's disease. Even with the limited means available to patients today, an early warning might be used to delay the aggregation of amyloid-β that takes place in the initial stages of the condition, before the appearance of cognitive impairment. Lifestyle changes such as weight loss and improved fitness, antiviral therapies, and control of chronic inflammation should all make some difference, given what is known of the mechanisms of Alzheimer's disease. Looking ahead, better options may soon be available. Senolytics, for example, may make a difference, and further means of directly reducing amyloid-β levels in the aging brain are starting to emerge. These therapies might be better applied in the early stages of the condition, rather than later, when the disease process is beyond their ability to control.

Early treatment through the clinical community requires some form of early diagnosis – so early treatment is very dependent on the existence of standard, widely accepted tests that can be readily and cheaply applied. While it is certainly possible to assess amyloid-β in cerebrospinal fluid, and has been for many years, that requires a lumbar puncture. It is expensive, painful, and certainly not the sort of thing people would willingly undergo once a year. Today's selection of research results from recent months covers a number of lines of work in which researchers are making progress towards an improved set of tests that might determine progression towards Alzheimer's disease.

Blood test detects Alzheimer's damage before symptoms

Quote

A simple blood test reliably detects signs of brain damage in people on the path to developing Alzheimer's disease – even before they show signs of confusion and memory loss. The test detects neurofilament light chain, a structural protein that forms part of the internal skeleton of neurons. When brain neurons are damaged or dying, the protein leaks out into the cerebrospinal fluid that bathes the brain and spinal cord and from there, into the bloodstream.

Finding high levels of the protein in a person's cerebrospinal fluid has been shown to provide strong evidence that some of their brain cells have been damaged. But obtaining cerebrospinal fluid requires a spinal tap, which many people are reluctant to undergo. Here, researchers studied whether levels of the protein in blood also reflect neurological damage. To find out whether protein blood levels could be used to predict cognitive decline, the researchers collected data on 39 people with disease-causing variants when they returned to the clinic an average of two years after their last visit. The researchers found that people whose blood protein levels had previously risen rapidly were most likely to show signs of brain atrophy and diminished cognitive abilities when they revisited the clinic. "It will be important to confirm our findings in late-onset Alzheimer´s disease and to define the time period over which neurofilament changes have to be assessed for optimal clinical predictability."

New discoveries predict ability to forecast dementia from single molecule

Quote

A new study shows that harmful single tau molecules take different shapes that each correlates to a distinct type of larger assembly that will form and self-replicate across the brain. Researchers had already established that the structure of larger tau assemblies determines which type of dementia will occur – which regions of the brain will be affected and how quickly the disease will spread. But it was unknown what specified these larger structures. The new research reveals how a single tau molecule that changes shape at the beginning of the disease process contains the information that determines the configuration of the larger, toxic assemblies. This finding suggests that characterization of the conformation of single tau molecules could predict what incipient disease is occurring – Alzheimer's or other types of dementia.

The team is trying to translate these findings into clinical tests that examine a patient's blood or spinal fluid to detect the first biological signs of the abnormal tau, before the symptoms of memory loss and cognitive decline become apparent. The researchers are also working to develop treatments to stabilize shape-shifting tau molecules, prevent them from assembling, or promote their clearance from the brain.

A biomarker in the brain's circulation system may be Alzheimer's earliest warning

Quote

The blood-brain barrier is a filtration system, letting in good things (glucose, amino acids) and keeping out bad things (viruses, bacteria, blood). It's mostly comprised of endothelial cells lining the 400 miles of arteries, veins, and capillaries that feed our brains. Some evidence indicates that leaks in the blood-brain barrier may allow a protein called amyloid into the brain where it sticks to neurons. This triggers the accumulation of more amyloid, which eventually overwhelms and kills brain cells.

"Cognitive impairment, and accumulation in the brain of the abnormal proteins amyloid and tau, are what we currently rely upon to diagnose Alzheimer's disease, but blood-brain barrier breakdown and cerebral blood flow changes can be seen much earlier. This shows why healthy blood vessels are so important for normal brain functioning." Blood-brain barrier leaks can be detected with an intravenously administered contrast substance in concert with magnetic resonance imaging. Brain microbleeds, another sign of leakage, also can be picked up with MRI. A slowdown in the brain's uptake of glucose, visible via PET scan, can be a another result of blood-brain barrier breakdown.

Scientists pave the way for saliva test for Alzheimer's disease

Quote

Researchers examined saliva samples from three sets of patients, those with Alzheimer's disease, those with mild cognitive impairment, and those with normal cognition. Using a powerful mass spectrometer, they examined more than 6,000 metabolites – compounds that are part of our body's metabolic processes – to identify any changes or signatures between groups. "In this analysis, we found three metabolites that can be used to differentiate between these three groups. This is preliminary work, because we've used a very small sample size. But the results are very promising. If we can use a larger set of samples, we can validate our findings and develop a saliva test

of Alzheimer's disease. So far, no disease-altering interventions for Alzheimer's disease have been successful. For this reason, researchers are aiming to discover the earliest signals of the disease so that prevention protocols can be implemented."

The Epigenetic Clock Does Not Reflect Long-Term Physical Activity Differences in Twins

Jan, 2019

Epigenetic clocks are a weighted algorithmic combination of specific DNA methylation markers, those that exhibit characteristic changes with age. The various iterations of the clock have a strong association with chronological age, and appear to reflect biological age as well, in that people with more pronounced age-related disease and populations with higher mortality rates tend to have a higher epigenetic age than their healthier peers. Since the clock was reverse engineered by analysis of DNA methylation and age data, there remains the question of what exactly it is measuring. There is no comprehensive map to definitively link changes in epigenetic markers with the progression of the causes of aging.

Thus it is presently hard for researchers to make good use of the clock in speeding up the development of potential rejuvenation therapies; given a result, there will be uncertainty over what the result means. Numerous studies have been carried out on the epigenetic clock and specific medical conditions and therapies. Some of the results are troubling, such as the one here. If one can take twins who have a lifetime of very different exercise habits behind them, and find that they have roughly the same epigenetic age, that is a challenge. The epidemiological and animal data on exercise, even the modest levels of physical activity discussed here, strongly indicates that it has a robust, measurable effect on mortality rate and risk of age-related disease. If that doesn't show up in the epigenetic clock, we must come back once again to ask just what is it that the clock measures.

Quote

Advances in the fields of molecular biology have produced novel promising candidate biomarkers and their combinations that may be considered as biological aging clocks. So far, one of the most promising new aging clocks is DNA methylation (DNAm) age, also known as the "epigenetic clock". DNAm age is a multi-tissue age estimate based on DNA methylation at 353 specific age-related CpG sites. It is determined with a special algorithm, which is publicly available. The epigenetic clock appears to be associated with a wide spectrum of aging outcomes, most consistently mortality. Discrepancy between DNAm age and chronological age, i.e., higher "age acceleration" predicts all-cause mortality.

So far, it is also not clear whether the genetic component in variation of DNAm age changes over a life span. On the other hand, some environmental exposures and behaviors such as infections, diet, alcohol use, smoking, and work exposures predispose to age-related diseases and increase probability of death. Only part of the individual variation of life expectancy can be accounted for using known and measured characteristics and exposure. An epigenetic clock could provide insights into the mechanisms behind why some individuals age faster than others and are more prone to age-related diseases and accelerated decline in physical function.

Physical activity is a potentially modifiable behavior that could slow down the rate of cellular and molecular damage accumulation and blunt the decline in physiological function with increasing age. The purpose of the study was to estimate the magnitude of genetic and environmental factors affecting variation in DNAm-based age acceleration in young and older monozygotic (MZ) and dizygotic (DZ) twins with a focus on leisure time physical activity.

The relative contribution of non-shared environmental factors was larger among older compared with younger twin pairs [47% versus 26%]. Correspondingly, genetic variation accounted for less of the variance in older compared with younger pairs [53% versus 74%]. We tested the hypothesis that leisure time physical activity is one of the non-shared environmental factors that affect epigenetic aging. A co-twin control analysis with older same-sex twin pairs (seven MZ and nine DZ pairs, mean age 60.4 years) who had persistent discordance in physical activity for 32 years according to reported/interviewed physical-activity data showed no differences among active and inactive co-twins, DNAm age being 60.7 vs. 61.8 years, respectively. Results from the younger cohort of twins supported findings that leisure time physical activity is not associated with DNAm age acceleration.

Link: https://doi.org/10.1186/s13148-019-0613-5

Small Molecules Convert Supporting Cells in Damaged Brain Tissue into New Neurons

Feb, 2019

Researchers here present an interesting approach to regeneration of the brain. Rather than spur greater creation of new neurons, or delivering neurons via cell therapy, they find a way to persuade supporting cells near damaged areas to convert themselves into neurons. They have not yet demonstrated that this will work in animals to restore lost function. In situ cell reprogramming is a part of the field that has a lot of promise, but much of the experimentation has yet to be accomplished. "Reprogramming" covers a wide range of possible goals, from minor changes to encourage cells into greater activity or altered behavior within

their type, to the more radical adjustments such as change of type or inducement of pluripotency. It remains to be seen which of these approaches will turn out to be viable in the near term of the next decade or so.

Quote

A simple drug cocktail that converts cells neighboring damaged neurons into functional new neurons could potentially be used to treat stroke, Alzheimer's disease, and brain injuries. A team of researchers identified a set of four, or even three, molecules that could convert glial cells – which normally provide support and insulation for neurons – into new neurons. The team previously published research describing a sequence of nine small molecules that could directly convert human glial cells into neurons, but the large number of molecules and the specific sequence required for reprogramming the glial cells complicated the transition to a clinical treatment.

In the current study, the team tested various numbers and combinations of molecules to identify a streamlined approach to the reprogramming of astrocytes, a type of glial cells, into neurons. By using four molecules that modulate four critical signaling pathways, they could efficiently turn human astrocytes – as many as 70 percent – into functional neurons. The resulting chemically converted neurons can survive more than seven months in a culture dish in the lab. They form robust neural networks and send chemical and electrical signals to each other, as normal neurons do inside the brain.

The researchers had previously developed a gene therapy technology to convert astrocytes into functional neurons, but due to the excessive cost of gene therapy – which can cost a patient half a million dollars or more – the team has been pursuing more economical approaches to convert glial cells into neurons. The delivery system for gene therapies is also more complex, requiring the injection of viral particles into the human body, whereas the small molecules in the new method can be chemically synthesized and packaged into a pill.

Link: http://science.psu.edu/news-and-events/2019-news/Chen2-2019

John W. Campbell, Editor of Astounding Science Fiction, Described Actuarial Escape Velocity in 1949

Feb, 2019

Some of the voices of the past can appear entirely contemporary, because they saw further and with greater clarity than most of their peers. John W. Campbell, editor of Astounding Science-Fiction Magazine, died of heart disease at age 61 in 1971. In 1949 he wrote an editorial on the future of medicine, aging, and longevity that wouldn't seem out of place today. He anticipated what we presently call actuarial escape velocity, or longevity escape velocity, the idea that gains in life span through progress in medical technology allow greater time to benefit from further gains – and eventually, we are repaired more rapidly than we are damaged, escaping from aging. These commentaries of past years, printed on paper, often vanish into the void. Fortunately this one remains.

As was the case for Timothy Leary in the 1970s, Campbell in 1949 overestimated what could be achieved with the technology of his near future. They were not the first to do so. Thus those of us who have advocated and raised funds for the rejuvenation biotechnology of today must have an argument as to why this decade is different, why we are not doomed to a certainty of aging to death just like Leary and Campbell. That argument must be detailed, robust, and heavily scientific.

That argument exists! Look no further than the SENS rejuvenation research programs and the extensive supporting evidence for the effectiveness of working to repair the root cause molecular damage of aging. This approach is different from the hypothetical approaches to intervene in aging that were proposed in the past – though Campbell is closer to it than Leary. The SENS thesis on aging predicted that senolytics to clear senescent cells from old tissues would be effective as a means of rejuvenation, and now we are finding that this is in fact the case. Senolytics robustly turn back all manner of measures of aging and age-related disease in animal studies. Implementing the rest of the SENS agenda, to repair or work around the molecular damage at the root of aging, is the way to demonstrate that, yes, it is different this time around.

Oh King, Live Forever!... – Astounding Science-Fiction Magazine, Vol. 43, No. 2, April, 1949

Quote

At some point in the history of the world and the history of medical science, a point will be reached such that a child born at that time can, if he chooses – and has reasonable luck so far as mechanical damage goes – live practically forever. This point in time will be some forty or more years before the perfection of the full requirements for continuous life – and this point may already have passed, without our knowing it.

For it is inherent in the nature of things that the critical birth-period can not be known until after the event – until after the perfection of the final techniques. Modern medical techniques have been developed to a high point – and on an exponential curve of progress, as is normal in an advancing science – with a view to keeping children and young adults happy, healthy and reasonably sane. The rise in the average-age-at-death statistics has been largely influenced by the diminution of infant and young-adult mortality; medical science has been

devoting the greater measure of its efforts to that end of the problem.

Now, with an increasingly older population group, with increasing masses of people in the older age brackets as their biggest problem, systemic failure type medical problems, rather than acute infectious problems will predominate. Heart disease takes the place of diphtheria; cancer replaces tuberculosis. Childbirth fever is vanquished – the problem is hardening of the arteries. Pediatrics is a well-advanced science; gerontology, its opposite number, is practically an unexplored field.

The first achievements of an advancing study of "old age and why is it" will naturally be concentrated on the typical conditions that kill the aged – systemic failure troubles such as heart and artery breakdowns. Of course, the only real cure for the systemic failures of the aged is the very simple and obvious one – youth. Not chronological youth, but metabolic youth. Research must be done on that problem, and is being done. The efforts being made at any time will, of course, be basically palliative – treatments that are primarily symptomatic. The obvious symptom of trouble is heart disease; the cause is old age. The medical profession assures itself that it isn't out to find the secret of eternal youth – simply to cure heart disease. But if it succeeds in cleaning up all the symptoms, one by one, the sum total of the results must, necessarily, be metabolic youth.

Some of the more forthright researchers are headed directly toward the more all-inclusive goal of extended maturity – i.e., extended youth. The two groups of researches will, inevitably, meet on a middle ground of success, sooner or later. For the present and near-future, say twenty years hence, we can expect some very real extensions in active life span, before the onset of the symptoms which, collectively, are termed "old age", and, simultaneously, a successful attack on the more outstanding problems of old age. The combined effect may be to extend the useful period of life as much as thirty years. Certainly not a figure to be confused with "eternal youth" – but pleasant none the less.

During the next succeeding years, incidentally, progress may well be at a faster rate. If the maturity extension techniques are applied to the research workers themselves – naturally! – the experience and ability gained in the previous years of work will be available to aid in further advances. Instead of spending thirty-five years learning how, and then twenty-five years doing research, a man with an added thirty years of life would be a far more efficient unit of civilization; a non-producer for thirty-five years, he could be a producer for fifty-five!

And the great problem really can't be very extreme: the human metabolism is already so nearly perfectly balanced that it takes many decades of very slow accumulation of imbalances to bring on old age. So small a factor of failure certainly should be correctable – and a small advance should mean a large improvement. With the accumulated knowledge and techniques of the previous research, the second twenty years of work might well see a further extension of maturity by another couple of decades.

The first advance of thirty years would be no "eternal youth" treatment. But – science tends to advance exponentially. That thirty-year reprieve might give just the time needed for research to extend your life another forty years. And that forty years might ... We don't know, nor can we guess now, when in time that critical point will arrive – or has arrived. But somewhere in history there must come a point such that a child born then will be just passing maturity when the life-extension techniques will reach the necessary point. They will grant him a series of little extensions – each just sufficient to reach the next – until the final result is achieved. I wonder if that point has been passed? And my own guess is – it has.

A Ribosomal DNA Epigenetic Clock is an Unexpectedly Accurate Measure of Age

Feb, 2019

Epigenetic clocks are a weighted combination of DNA methylation at specific sites on the genome. Modern processing power allowed the association between these algorithms and aging to be reverse engineered, but it remains an open question as to what exactly is being measured. What underlying processes of aging are reflected by these characteristic epigenetic changes? All of them? Some of them? Some more than others? No-one knows in certainty, though the specific genes and proteins involved offer some suggestions. Until researchers have a better idea on that front, it is hard to use these clocks in the way we all want them to be used: to greatly speed up development of rejuvenation therapies. If it was possible to take a measure, apply a therapy, and then within days or a month at most take a second measure, and on that basis declare whether or not a particular approach works, then the assessment of potential methods of rejuvenation could proceed quite rapidly indeed.

Epigenetic clocks are evolving as researchers explore this association between DNA methylation and aging. The most interesting aspect of the new clock noted below is that only a tiny portion of the genome is involved. Even though it is apparently very similar in diverse species, to me this sounds like there is an even greater risk that the clock only measures a small slice of the many important processes of aging, and thus won't be all that helpful for the development of rejuvenation therapies. In a world without the ability to intervene in specific processes of aging, all of those processes in any given individual tend to be aligned with one another. But if just one of those processes is reversed – such as by clearance of senescent cells – then assessment will become a problem if epigenetic clocks behave unpredictably in this sort of scenario.

In practice, what is going to happen is that measures of aging and rejuvenation will be developed in parallel to the development of rejuvenation therapies. Perhaps epigenetic clocks will be increasingly calibrated to report on the outcome of clearance of senescent cells, for example. This seems likely, as the industry will want something more than just counts of cells and reversal of symptoms for one specific age-related disease to show that they are affecting the course of aging in a profound way. But that tailored epigenetic clock may well turn out to be useless for, say, assessing the effects of cross-link breaking on the progression of aging. Nothing is simple in biochemistry. We might hope for a universal assessment of age to turn up sometime soon, to speed up research and development, but it may well be that the only practical way to build such a measure is to first make significant progress in all of the areas of the full SENS program of rejuvenation therapies.

Uncovering a "smoking gun" of biological aging

Quote

Researchers looked at ribosomal DNA (rDNA), the most active segment of the genome and one which has also been mechanistically linked to aging in a number of previous studies. They hypothesized that the rDNA is a "smoking gun" in the genomic control of aging and might harbor a previously unrecognized clock. To explore this concept, they examined epigenetic chemical alterations (also known as DNA methylation) in CpG sites, where a cytosine nucleotide is followed by a guanine nucleotide. The study homed in on the rDNA, a small (13 kilobases) but essential and highly active segment of the genome, as a novel marker of age.

Analysis of genome-wide data sets from mice, dogs, and humans indicated that the researchers' hypothesis had merit: numerous CpGs in the rDNA exhibited signs of increased methylation – a result of aging. To further test the clock, they studied data from 14-week-old mice that responded to calorie restriction, a known intervention that promotes longevity. The mice that were placed on a calorie-restricted regimen showed significant reductions in rDNA methylation at CpG sites compared with mice that did not have their caloric intake restricted. Moreover, calorie-restricted mice showed rDNA age that was younger than their chronological age.

The researchers were surprised that assessing methylation in a small segment of the mammalian genome yielded clocks as accurate as clocks built from hundreds of thousands of sites along the genome. They noted that their novel approach could prove faster and more cost effective at determining biological and chronological age than current methods of surveying the dispersed sites in the genome. The findings underscore the fundamental role of rDNA in aging and highlight its potential to serve as a widely applicable predictor of individual age that can be calibrated for all mammalian species.

Ribosomal DNA harbors an evolutionarily conserved clock of biological aging

Quote

The ribosomal DNA (rDNA) is the most evolutionarily conserved segment of the genome and gives origin to the nucleolus, an energy intensive nuclear organelle and major hub influencing myriad molecular processes from cellular metabolism to epigenetic states of the genome. The rDNA/nucleolus has been directly and mechanistically implicated in aging and longevity in organisms as diverse as yeasts, Drosophila, and humans. The rDNA is also a significant target of DNA methylation that silences supernumerary rDNA units and regulates nucleolar activity.

Here, we introduce an age clock built exclusively with CpG methylation within the rDNA. The ribosomal clock is sufficient to accurately estimate individual age within species, is responsive to genetic and environmental interventions that modulate life-span, and operates across species as distant as humans, mice, and dogs. Further analyses revealed a significant excess of age-associated hypermethylation in the rDNA relative to other segments of the genome, and which forms the basis of the rDNA clock. Our observations identified an evolutionarily conserved marker of aging that is easily ascertained, grounded on nucleolar biology, and could serve as a universal marker to gauge individual age and response to interventions in humans as well as laboratory and wild organisms across a wide diversity of species.

Request for Startups in the Rejuvenation Biotechnology Space, 2019 Edition

Feb, 2019

I am a little late with the 2019 list of projects in rejuvenation biotechnology that I'd like to see startups tackling sometime soon. In my defense, this year I have a startup of my own to keep up with, and the first part of 2019 was a wall to wall series of conferences alternating between the US and Europe. It continues to be the case that this is a new industry of near endless potential, yet little of that potential is under active development. This is the state of affairs despite the arrival of hundreds of millions of dollars in venture funds managed by the like of Juvenescence, Life Biosciences, and so on. The research community remains packed full of low-hanging fruit, potential approaches to rejuvenation that are barely even hidden; anyone with a modest knowledge of the field knows where they are. Anyone without that modest knowledge can find out easily enough – just send an email to Aubrey de Grey and the rest of the SENS Research Foundation crowd and ask for introductions. There has never been a better time to start a company focused on one or more aspects of rejuvenation biotechnology.

No More New Senolytics for a Little While

I know that many of you out there have the Best Idea Ever when it comes to ways to destroy senescent cells – but I think it best for everyone to sit back and let the existing set of senolytic therapies work their way closer to the clinic first. New senolytic companies are now competing with a dozen different approaches that are several years further along in their process of development. It is true that the world is a very large place, containing a great many old people who would benefit from senolytics, and there is plenty of room for a dozen competing ways to remove senescent cells as a part of a large medical ecosystem of rejuvenation. That said, there is the very real threat that failures on the part of any of the leading companies in this space will throw a pall over the funding environment. Start a senolytics company now, and you are at the mercy of Unity Biotechnology's trial results. This isn't fair, and Unity's programs are no reflection on the other, largely better approaches to clearance of senescent cells, but this is the way the world works. If Unity stumbles, investors will become nervous.

Deliver Existing Low Cost Senolytics to the Aged Masses

The most noteworthy point in all of the past five years of senolytic development is that the first compounds used as proof of principle in animal and human studies are actually pretty good at their job. They are also cheap and easily available. The dasatinib and quercetin combination, fisetin, and piperlongumine all have quite compelling animal data to support their senolytic effects, and all are very cheap. Why then are tens of millions of people in the US alone still suffering from arthritis and other inflammatory age-related conditions that have senescent cell accumulation as a significant cause? Why is it that no-one has yet stepped up to start a logistics company to improve all these lives considerably with one dose of senolytics that would cost something like $50-100 to manufacture and deliver at scale, and could be sold for twice that? This is a rare confluence of profit and public service.

Tailored Biological Age Assessment

Epigenetic clocks to assess biological age rather than chronological age are great in the abstract – except that no-one knows exactly what they measure, and thus they are useless at the present time for assessing the outcome of specific approaches to rejuvenation, such as senolytics. The technology is now far enough along that it is in principle possible to build a company based on supplying suitably tailored biological age assessment approaches that can be used to assess the results of a senolytic therapy, or other meaningful approach to aging. It is my belief that measures of biological age must be developed hand in hand with the therapies as they emerge, and only then can they be made useful. This is work that is presently not being accomplished in the for-profit marketplace, and thus here is opportunity.

A Competitor for Revel Pharmaceuticals in Glucosepane Cross-link Breaking

Revel Pharmaceuticals is the only company working on glucosepane cross-link breaking, emerging from the only lab that is working in a significant way on glucosepane cross-link breaking. These cross-links are a significant cause of loss of skin elasticity and loss of blood vessel elasticity. A success here will be as big as senolytics. I've spoken to more than one researcher who is either interested in this area, or has worked on this area, and would take funding to move ahead with their approach to the problem. So where are the competitors for Revel? This will be the next big thing in true rejuvenation therapies, I predict.

A Platform for Bacterial Enzyme Discovery to Break Down Metabolic Waste Targets

While I'm issuing predictions, here is another: the process of screening bacterial species from soil and seawater samples to find useful enzymes will prove to be far more cost effective than the present, or even machine-learning-enhanced, small molecule drug development process when it comes to establishing ways to break down harmful molecular waste in the human body. This is particularly true given the major advances in culturing bacterial species achieved in the past few years. So far as I know, no-one has started a company specifically to develop this approach as a platform for the many, many potential rejuvenation therapies that could result. There are a score of amyloids, numerous oxidized lipids, and countless components of lipofuscin to deal with just as a starting point. Companies such as LysoClear and Revel Pharmaceuticals found their lead compounds via mining the bacterial world, but have not made their process into a platform; the next generation of companies in this space should.

Make a Start on Interdiction of Telomere Lengthening as a Universal Cancer Therapy

Work in the laboratory to block lengthening of telomeres by telomerase is quite advanced – either close or ready to make the leap to a startup company. Someone should get out there, license one of these approaches, and get started on the process of bringing it to the clinic. The truly effective cancer therapies of the near future, those that will supplant immunotherapy because they are cheaper, more general, and more effective, will be based on suppression of telomere lengthening. All cancers must lengthen their telomeres, no cancer can avoid doing so, and if it is blocked, the cancer will wither. Any cancer, no matter what type, could be defeated by this single form of therapy, once implemented.

The Three Pillars of Immune System Rejuvenation

There are three vital initial components to the rejuvenation of the immune system, and this is a sufficiently important goal that there should be far more than the small number of companies presently working in this space. Firstly, the aged thymus must

be regenerated in size and function; more competitors and more competing approaches than those of Repair Biotechnologies, Intervene Immune, and Lygenesis would be welcome. Secondly, a way to clear out and replace the damaged and malfunctioning cells of the aged peripheral immune system that does not involve the harsh, high-risk approaches of hematopoietic stem cell transplant and high dose chemotherapy. A kinder, more gentle targeted cell killing strategy that can be used in older, frail individuals is needed. Thirdly, the industry needs a way to introduce a new, functional, youthful hematopoietic stem cell population that, again, is kinder and more gentle than present transplant procedures, and can thus be used with older patients. Success in any one of these three will produce sizable gains, enough to help usher in the other two.

A Cell Therapy Platform to Reliably Deliver and Engraft New Stem Cell Populations

Stem cell decline is a major feature of aging. Existing stem cell therapies do little to nothing to address this issue. Aged stem cell populations must be supplemented or replaced with new, youthful stem cells. The surrounding niche and signaling must be adjusted to prevent the new cells from lapsing into inactivity. Platforms are needed that allow these goals to be achieved for arbitrary stem cell populations, or even just a majority of the most important stem cell populations. This is a path to delivering major gains in late life health and function.

An 80/20 Solution for Robust Gene Therapy

The community needs a gene therapy platform that works most of the time and for most tissues with minimal alteration, provides a high degree of cell coverage, and a high degree of configurable targeting by cell or tissue type. Perhaps this can be built atop the leading viral vector type, AAV, or perhaps it will emerge from some of the programmable gene therapy approaches, such as that of Oisin Biotechnologies. Regardless, it is very much needed. There is so much that could accomplished right now, today, if it wasn't necessary to build every new gene therapy completely from scratch, with years of work going into ways to obtain sufficient cell coverage, and to bypass the biggest obstacles, such as the patient's immune system. In the future, gene therapy will largely replace small molecule drugs for most uses – but that requires a great increase in the efficiency of development. The first 80/20 platforms that are good enough for most uses will drive the creation of an enormous amount of value.

Fix the Problems with Medical Tourism

Enhancement therapies, such as rejuvenation therapies, will be used by a hundred times as many people as presently undergo medical procedures. There are far more individuals who want to be enhanced than who have a medical condition and are at the point of needing treatment in the present system. The nature of the medical tourism industry will change dramatically given the much larger population of potential customers that will exist in a world of many novel enhancement therapies. There is an enormous opportunity here to solve the scattered, fraud-ridden nature of the existing marketplace, and to realize the full potential of regulatory arbitrage in responsibly bringing new therapies into trials and the clinic. Many companies presently opt to take therapies into their first human trials in Australia because the cost is half or less of running through the standard process in the US or Europe. There is no reason why, in other jurisdictions, the cost couldn't be a tenth of that in the US and Europe, and a therapy deployed to the clinic entirely via medical tourism. That sort of competition is the only way to reduce the weight of the ball and chain of regulatory waste that holds back progress.

Methods of Outright Mitochondrial Repair

Loss of mitochondrial function occupies a central position in the declines of aging, implicated as a contributing cause of many age-related conditions. While mitochondrially targeted antioxidants that make the situation incrementally better are a going concern, with several products in the marketplace, much better approaches will be needed to deal with the issue of mitochondrial damage and decline with age. An implementation of the MitoSENS strategy of allotopic expression as a backup source of vital mitochondrial proteins, carried out for at least most mitochondrial genes, for example. Barring that, delivery of replacement mitochondria into tissues, perhaps engineered to be resistant to the signaling and damage that causes a general malaise in mitochondrial function and quality control. Or ways to robustly and completely restore the normal, youthful processes of mitophagy and mitochondrial fission in old tissues. This is a big problem and ambitious solutions are needed.

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

Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry

A Swarm of Slippery Micropropellers Penetrates the Vitreous Body of the Eye

Zhiguang Wu1, Jonas Troll, Hyeon-Ho Jeong, Qiang Wei, Marius Stang, Focke Ziemssen, Zegao Wang, Mingdong Dong, Sven Schnichels, Tian Qiu, and Peer Fischer

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Abstract

The intravitreal delivery of therapeutic agents promises major benefits in the field of ocular medicine. Traditional delivery methods rely on the random, passive diffusion of molecules, which do not allow for the rapid delivery of a concentrated cargo to a defined region at the posterior pole of the eye. The use of particles promises targeted delivery but faces the challenge that most tissues including the vitreous have a tight macromolecular matrix that acts as a barrier and prevents its penetration. Here, we demonstrate novel intravitreal delivery microvehicles—slippery micropropellers—that can be actively propelled through the vitreous humor to reach the retina. The propulsion is achieved by helical magnetic micropropellers that have a liquid layer coating to minimize adhesion to the surrounding biopolymeric network. The submicrometer diameter of the propellers enables the penetration of the biopolymeric network and the propulsion through the porcine vitreous body of the eye over centimeter distances. Clinical optical coherence tomography is used to monitor the movement of the propellers and confirm their arrival on the retina near the optic disc. Overcoming the adhesion forces and actively navigating a swarm of micropropellers in the dense vitreous humor promise practical applications in ophthalmology.

From the Introduction

Ocular drug delivery plays an important role in ophthalmology and is used to treat diseases ranging from diabetic retinopathy, glaucoma, to diabetic macular edema. Although topical administration is currently available to treat diseases in the anterior of the eye including the cornea, ciliary body, and the lens, delivery to the posterior part of the eye via topical administration, systemic administration, and intravitreal injection is very ineffective and difficult because of the lacrimal fluid–eye barrier and the retina–blood barrier. To overcome these difficulties, nanoparticles have been injected into the eye, and their passive diffusion toward the retina has been investigated. Passive diffusion, however, suffers from long diffusion time and decreased activity of the biomedical agents. Moreover, it is systemic and therefore comes with an increased risk of side effects. It therefore still remains challenging to achieve targeted delivery with intravitreal administration.

Here, we report the first micropropellers that can penetrate the vitreous humor and that can reach the retina. The propellers are helical in shape, with the diameter that is comparable to the mesh size of the biopolymeric network of the vitreous and are functionalized with a perfluorocarbon surface coating that minimizes the interaction of the propellers with biopolymers, including collagen bundles that are present in the vitreous. The coating is inspired by a liquid layer found on the carnivorous Nepenthes pitcher plant, which presents a slippery surface on the peristome to catch insects. The nontoxic silicone oil and fluorocarbon coatings are also used as slippery surfaces in medical applications. Under the wireless actuation of an external magnetic field, the coated micropropellers not only show controllable propulsion but also can be driven as a large swarm over centimeter distances through the eyeball and can reach the retina within 30 min. The micropropellers are imaged with standard optical coherence tomography (OCT).

Source: http://advances.sciencemag.org/content/4/11/eaat4388, accessed 29 Dec. 2018.

A Continuous-Time MaxSAT Solver with High Analog Performance

Botond Molnár, Ferenc Molnár, Melinda Varga, Zoltán Toroczkai, and Mária Ercsey-Ravasz

***Nature Communications* volume 9, Article number: 4864, 19 Nov. 2018.**

Abstract

Many real-life optimization problems can be formulated in Boolean logic as MaxSAT, a class of problems where the task

is finding Boolean assignments to variables satisfying the maximum number of logical constraints. Since MaxSAT is NP-hard, no algorithm is known to efficiently solve these problems. Here we present a continuous-time analog solver for MaxSAT and show that the scaling of the escape rate, an invariant of the solver's dynamics, can predict the maximum number of satisfiable constraints, often well before finding the optimal assignment. Simulating the solver, we illustrate its performance on MaxSAT competition problems, then apply it to two-color Ramsey number $R(m, m)$ problems. Although it finds colorings without monochromatic 5-cliques of complete graphs on $N \leq 42$ vertices, the best coloring for $N=43$ has two monochromatic 5-cliques, supporting the conjecture that $R(5, 5)=43$. This approach shows the potential of continuous-time analog dynamical systems as algorithms for discrete optimization.

From the Introduction

Digital computing, or Turing's model of universal computing is currently the reigning computational paradigm. However, there are large classes of problems that are apparently intractable on digital computers, requiring resources (time, memory, and/or hardware) for their solution that scale exponentially in the input size of the problem (NP-hard). Such problems, unfortunately, are abundant in sciences and engineering, for example, the ground-state problem of spin-glasses in statistical physics, the traveling salesman problem, protein folding, bioinformatics, medical imaging, scheduling, design debugging, Field Programmable Gate Array routing, probabilistic reasoning, etc. It is believed that in order to make progress on solving such problems one might have to look beyond computation with digital Turing machines. Analog computing and quantum computing present two promising and possibly revolutionary approaches, complementing complementary metal–oxide–semiconductor technology in solving certain types of hard computational problems. However, quantum computing currently faces fundamental physics and engineering challenges that still need to be solved, leaving analog computing as a possibly more feasible option. …

One quintessential family of intractable problems that could potentially be tackled with special purpose analog devices are Boolean satisfiability problems, both in their decision (SAT) and optimization forms (MaxSAT). … [MaxSAT] has the same formulation as SAT (or *k*-SAT), but the task is to maximize the number of satisfied clauses. It is harder than SAT as one cannot guarantee in polynomial time the optimality of the solution (unlike for SAT), for problems that do not admit full satisfiability. … SAT and MaxSAT have a very large number of applications, with SAT solvers becoming an important back-end technology. Applications include scheduling, planning and automated reasoning, electronic design automation, bounded model checking, design of experiments, coding theory, cryptography, and drug design.

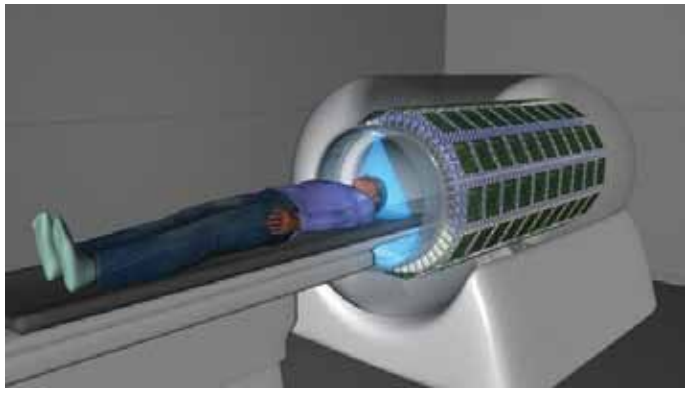
A continuous-time deterministic system (CTDS) based on ordinary differential equations (ODEs), was recently proposed as an analog SAT solver …. It was designed such that all the SAT solutions appear as attractive fixed points for the dynamics while no other attractors exist trapping the dynamics. For hard problems its behavior becomes chaotic, showing that problem hardness and chaos are related notions within this context, and thus chaos theory can be used to study computational complexity. …

Here, we present an extension of the CTDS such as to solve MaxSAT problems. The idea is based on the observation that the CTDS makes no assumptions about problem satisfiability and thus, even for unsatisfiable SAT problems, the dynamics will still minimize the number of unsatisfied clauses. What we need to determine, however, is the likelihood of the optimality of the best solution found by analog time t, as function of t, which we achieve heuristically, by analyzing the statistics of a dynamical invariant, the escape rate. … We conclude with a discussion on analog solvers and their realization in hardware.

Source(s): https://www.nature.com/articles/s41467-018-07327-2, accessed 27 Feb. 2019.

World's First Full-Body Medical Scanner Generates Astonishing 3D Images

Reported by Rich Haridy, newatlas.com, 19 Nov 2018



The new EXPLORER full-body scanner promises faster and more detailed medical imaging. (Credit: UC Davis).

After over a decade of development, the world's first full-body medical scanner has produced its first images. The groundbreaking imaging device is almost 40 times faster than current PET scans and can capture a 3D picture of the entire human body in one instant scan. Called EXPLORER, the full-body scanner combines positron emission tomography (PET) and X-ray computed tomography (CT). Following years of

research, a prototype, primate-sized scanner was revealed in 2016. After expansive testing, the first human-sized device was fabricated in early 2018. Developed in a collaboration between scientists from UC Davis and engineers from Shanghai-based United Imaging Healthcare, the very first human images from the scanner have finally been revealed. The results are being described as nothing short of incredible and the research team suggests EXPLORER could revolutionize both clinical research and patient care.

"The level of detail was astonishing, especially once we got the reconstruction method a bit more optimized," says Ramsey Badawi, chief of Nuclear Medicine at UC Davis Health. "We could see features that you just don't see on regular PET scans. And the dynamic sequence showing the radiotracer moving around the body in three dimensions over time was, frankly, mind-blowing. There is no other device that can obtain data like this in humans, so this is truly novel."

The new EXPLORER scanner offers remarkable improvements over current imaging systems. As well as offering faster scans, producing a whole-body image in as little as 20 to 30 seconds, the device is effectively up to 40 times more sensitive than current commercial scanning systems. This means the scanner can produce detailed images using significantly lower doses of radiation tracers than are currently needed. The higher sensitivity also allows clinicians to image certain molecular targets that are beyond the limits of current scanning systems.

"The tradeoff between image quality, acquisition time and injected radiation dose will vary for different applications, but in all cases, we can scan better, faster or with less radiation dose, or some combination of these," says Simon Cherry, from the UC Davis Department of Biomedical Engineering.

Perhaps the most exciting and novel application of this new scanning system is its ability to capture entire body images in single momentary scans. Current PET systems are fundamentally slow and inefficient due to the necessity of having to scan single slivers of the body at one time. Over a long stretch of 30 or 40 minutes all these smaller images are aggregated into a larger 3D image, however this significantly limits the ability of clinicians to measure the effects of something moving across the entire body in real time.

Source(s): https://newatlas.com/full-body-scan-explorer-medical-imaging/57303/, accessed 27 Feb. 2019.

Reframing Superintelligence Comprehensive AI Services as General Intelligence

K. Eric Drexler

Future of Humanity Institute, University of Oxford
Technical Report #2019-1 (2019), 01 Jan 2019

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Abstract

Studies of superintelligent-level systems have typically posited AI functionality that plays the role of a mind in a rational utility-directed agent, and hence employ an abstraction initially developed as an idealized model of human decision makers. Today, developments in AI technology highlight intelligent systems that are quite unlike minds, and provide a basis for a different approach to understanding them: Today, we can consider how AI systems are produced (through the work of research and development), what they do (broadly, provide services by performing tasks), and what they will enable (including incremental yet potentially thorough automation of human tasks).

Because tasks subject to automation include the tasks that comprise AI research and development, current trends in the field promise accelerating AI-enabled advances in AI technology itself, potentially leading to asymptotically recursive improvement of AI technologies in distributed systems, a prospect that contrasts sharply with the vision of self-improvement internal to opaque, unitary agents.

The trajectory of AI development thus points to the emergence of asymptotically comprehensive, superintelligent-level AI services that – crucially – can include the service of developing new services, both narrow and broad, guided by concrete human goals and informed by strong models of human (dis)approval. The concept of comprehensive AI services (CAIS) provides a model of flexible, general intelligence in which agents are a class of service-providing products, rather than a natural or necessary engine of progress in themselves.

Ramifications of the CAIS model reframe not only prospects for an intelligence explosion and the nature of advanced machine intelligence, but also the relationship between goals and intelligence, the problem of harnessing advanced AI to broad, challenging problems, and fundamental considerations in AI safety and strategy. Perhaps surprisingly, strongly self-modifying

agents lose their instrumental value even as their implementation becomes more accessible, while the likely context for the emergence of such agents becomes a world already in possession of general superintelligent-level capabilities. These prospective capabilities, in turn, engender novel risks and opportunities of their own.

Further topics addressed in this work include the general architecture of systems with broad capabilities, the intersection between symbolic and neural systems, learning vs. competence in definitions of intelligence, tactical vs. strategic tasks in the context of human control, and estimates of the relative capacities of human brains vs. current digital systems.

From the Preface

The writing of this document was prompted by the growing gap between models that equate advanced AI with powerful agents and the emerging reality of advanced AI as an expanding set of capabilities (here, "services") in which agency is optional. A service-centered perspective reframes both prospects for superintelligent-level AI and a context for studies of AI safety and strategy.

Taken as a whole, this work suggests that problems centered on *what highlevel AI systems might choose to do* are relatively tractable, while implicitly highlighting questions of *what humans might choose to do with their capabilities*. This shift, in turn, highlights the potentially pivotal role of high-level AI in solving problems created by high-level AI technologies themselves.

The text was written and shared as a series of widely-read Google Docs released between December 2016 and November 2018, largely in response to discussions within the AI safety community. The organization of the present document reflects this origin: The sections share a common conceptual framework, yet address diverse, overlapping, and often loosely-coupled topics. The table of contents, titles, subheads, summaries, and internal links are structured to facilitate skimming by readers with different interests. The table of contents primarily [consists] of declarative sentences, and has been edited to read as an overview. … I have made only a modest effort to harmonize terminology across the original documents. I thought it best to share the content without months of further delay.

Source(s): https://www.fhi.ox.ac.uk/reframing/, file:///C:/Main/AI/Drexler/Reframing_Superintelligence_FHI-TR-2019-1.1-1.pdf, accessed 27 Feb. 2019.

Brg1 Promotes Liver Regeneration after Partial Hepatectomy via Regulation of Cell Cycle

Baocai Wang, Benedikt Kaufmann, Thomas Engleitner, Miao Lu, Carolin Mogler, Victor Olsavszky, Rupert Öllinger, Suyang Zhong, Cyrill Geraud, Zhangjun Cheng, Roland R. Rad, Roland M. Schmid, Helmut Friess, Norbert Hüser, Daniel Hartmann, and Guido von Figura

Scientific Reports **volume 9, Article number: 2320 (2019) 20 Feb. 2019.**

Abstract

Brahma-related gene 1 (Brg1), a catalytic subunit of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, is known to be involved in proliferative cell processes. Liver regeneration is initiated spontaneously after injury and leads to a strong proliferative response. In this study, a hepatocyte-specific Brg1 gene knockout mouse model was used to analyse the role of Brg1 in liver regeneration by performing a 70% partial hepatectomy (PH). After PH, Brg1 was significantly upregulated in wildtype mice. Mice with hepatocyte-specific Brg1 gene knockout showed a significantly lower liver to body weight ratio 48 h post-PH concomitant with a lower hepatocellular proliferation rate compared to wildtype mice. RNA sequencing demonstrated that Brg1 controlled hepatocyte proliferation through the regulation of the p53 pathway and several cell cycle genes. The data of this study reveal a crucial role of Brg1 for liver regeneration by promoting hepatocellular proliferation through modulation of cell cycle genes and, thus, identify Brg1 as potential target for therapeutic approaches.

From the Introduction

The liver has a unique regenerative capacity to regain its size, architecture, and function in response to the loss of mass caused by a variety of injuries. This regenerative capacity provides the basis for a potentially satisfying clinical outcome for patients after a serious hepatic injury, cancer resection, or living donor liver transplantation. The regenerative capacity is often reduced when concomitant liver disease, such as liver fibrosis or non-alcoholic fatty liver disease (NAFLD), is present. To promote liver regeneration therapeutically, it is therefore important to decipher the molecular mediators that regulate liver regeneration.

Liver regeneration starts with a well-organised and complex series of signals, which are generated by cytokines and growth factors. The use of the rodent partial hepatectomy (PH) model described originally by Higgins and Anderson resulted in a better understanding of the three sequential and critical steps leading to liver regeneration. Firstly upon PH, hepatocytes exit

their quiescent and highly differentiated state in order to rapidly re-enter the cell cycle (priming phase). Secondly, with the help of mitogens, hepatocytes enter the cell cycle and progress beyond the restriction point to G1 phase and M-phase in order to proliferate and compensate for the removed mass (proliferation phase). After approximately two cell cycles of hepatocyte replication, cells terminate proliferation under the control of negative factors (termination phase). Finally, liver mass is restored to the size before hepatectomy, and liver morphology is gradually rearranged.

Epigenetic mechanisms are a relevant regulatory component of many biological processes, including organ regeneration. A crucial epigenetic regulator is the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, a large multi-subunit chromatin remodelling complex, that consists of approximately 15 subunits. The mammalian SWI/SNF complex family is further subdivided into two major complexes, the brahma related gene 1 (Brg1)-associated factor complex (BAF) and the polybromo Brg1-associated factor (PBAF) complex. While the catalytic subunit Brahma (Brm) is used only for BAF complexes, Brahma related gene 1 (Brg1) is a subunit of both mammalian SWI/SNF complexes. Recently, an important role for this complex could be shown for liver regeneration. It was revealed that the subunit Arid1a plays a prominent role in the context of liver regeneration by impairing liver regeneration, mainly due to a positive modulation of target gene transcription that represses proliferation. However, the exact function of the SWI/SNF complex and, in particular, its catalytic ATPase subunits in liver regeneration remain unclear.

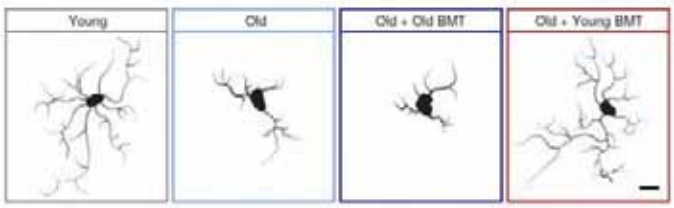
The aim of this study was to investigate the role of Brg1 in hepatocytes during liver regeneration in mice and to analyse molecular signaling pathways modulated by Brg1. By using a mouse model with hepatocyte-specific knockdown of Brg1, this study reveals an important function of Brg1 during liver regeneration by promoting hepatocellular proliferation through modulation of cell cycle genes.

Source(s): https://www.nature.com/articles/s41598-019-38568-w, accessed 27 Feb. 2019.

Young Bone Marrow Transplantation Preserves Learning and Memory in Old Mice

***Communications Biology* volume 2, Article number: 73 (2019) 20 Feb. 2019.**

Melanie M. Das, Marlesa Godoy, Shuang Chen, V. Alexandra Moser, Pablo Avalos, Kristina M. Roxas, Ivy Dang, Alberto Yáñez, Wenxuan Zhang, Catherine Bresee, Moshe Arditi, George Y. Liu, Clive N. Svendsen, and Helen S. Goodridge



Microglia in brains of old mice have larger cell bodies with fewer and shorter branches than those in young mice. But microglia of old mice who received bone marrow transplants (BMT) from young mice resembled those of young mice; transplants from older mice didn't have that effect. Microglia play an important role in brain health. Credit: Cedars-Sinai / Communications Biology

Abstract

Restoration of cognitive function in old mice by transfer of blood or plasma from young mice has been attributed to reduced C–C motif chemokine ligand 11 (CCL11) and β2-microglobulin, which are thought to suppress neurogenesis in the aging brain. However, the specific role of the hematopoietic system in this rejuvenation has not been defined and the importance of neurogenesis in old mice is unclear. Here we report that transplantation of young bone marrow to rejuvenate the hematopoietic system preserved cognitive function in old recipient mice, despite irradiation-induced suppression of neurogenesis, and without reducing β2-microglobulin. Instead, young bone marrow transplantation preserved synaptic connections and reduced microglial activation in the hippocampus. Circulating CCL11 levels were lower in young bone marrow recipients, and CCL11 administration in young mice had the opposite effect, reducing synapses and increasing microglial activation. In conclusion, young blood or bone marrow may represent a future therapeutic strategy for neurodegenerative disease.

From *Science Daily*:

A new study has found that transplanting the bone marrow of young laboratory mice into old mice prevented cognitive decline in the old mice, preserving their memory and learning abilities. The findings support an emerging model that attributes cognitive decline, in part, to aging of blood cells, which are produced in bone marrow.

"While prior studies have shown that introducing blood from young mice can reverse cognitive decline in old mice, it is not well understood how this happens," said Helen Goodridge, PhD, associate professor of Medicine and Biomedical Sciences at Cedars-Sinai and co-senior author of the study. "Our research suggests one answer lies in specific properties of youthful blood cells."

If further research confirms similar processes in people, the findings could provide a pathway for designing therapies to

slow progression of neurodegenerative diseases, including Alzheimer's, that affect millions of Americans, Goodridge said.

In the study, published in the journal *Communications Biology*, 18-month-old laboratory mice received bone marrow transplants from either 4-month-old mice or mice their own age. Six months later, both transplanted groups underwent standard laboratory tests of activity level and learning, plus spatial and working memory. Mice that received young bone marrow outperformed mice that received old bone marrow. They also outperformed a control group of old mice that did not get transplants.

The research team then examined the hippocampus, a region associated with memory, in the mice brains. Recipients of young bone marrow retained more connections, known as synapses, between neurons in the hippocampus than did recipients of old bone marrow, even though they had about the same number of neurons. Synapses are critical to brain performance.

Further tests showed a possible reason for the missing synapses. The blood cells made by the young bone marrow reduced the activation of microglia, a type of immune cell in the brain. Microglia support neuron health but can become overactive and participate in disconnection of the synapses. With fewer overactive microglia, neurons would remain healthy and more synapses would survive.

Source(s): https://www.nature.com/articles/s42003-019-0298-5, https://www.sciencedaily.com/releases/2019/02/190220103341.htm, accessed 27 Feb. 2019.

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.
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