ALCOR LIFE EXTENSION FOUNDATION

CRYONICS

JANUARY 2013 • VOLUME 34:1

CHEMICAL BRAIN PRESERVATION AND HUMAN SUSPENDED ANIMATION

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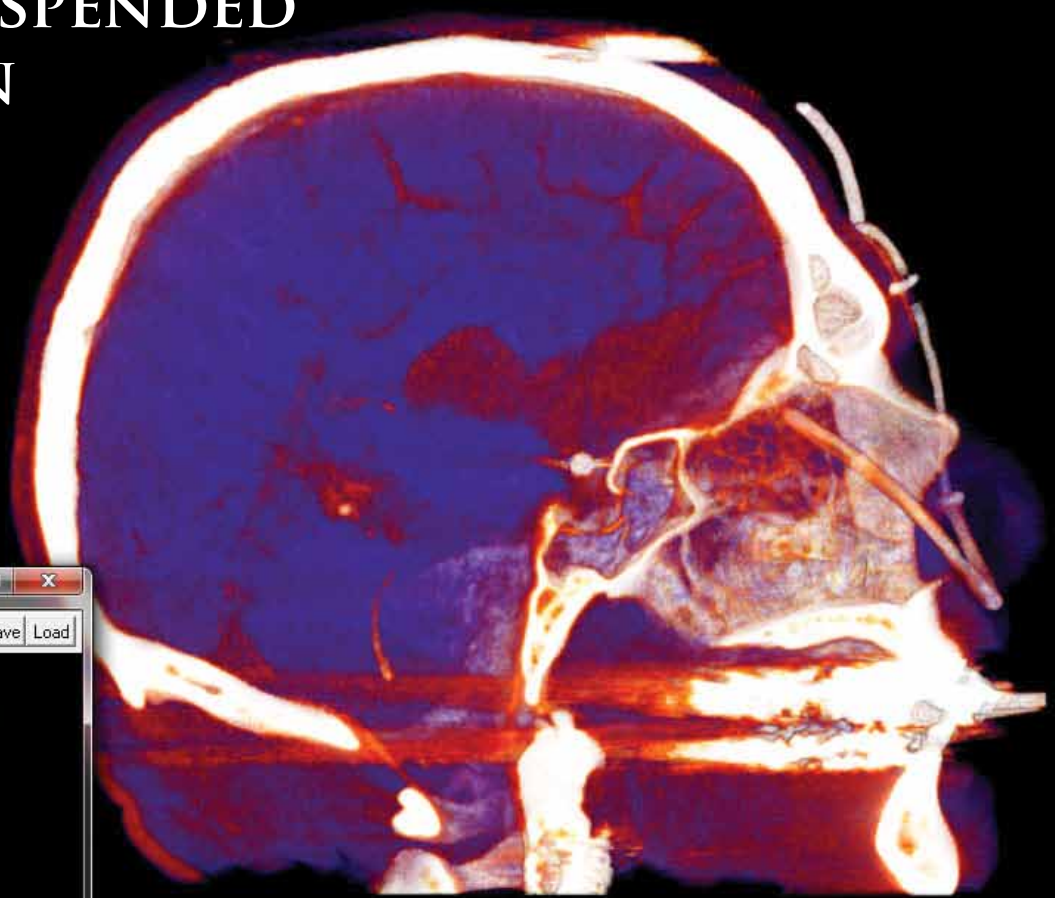

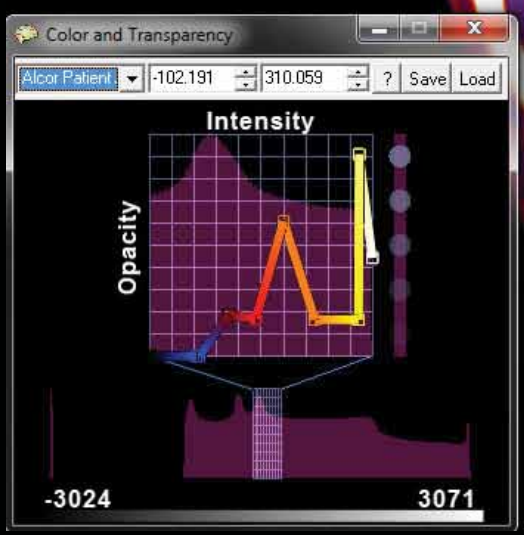

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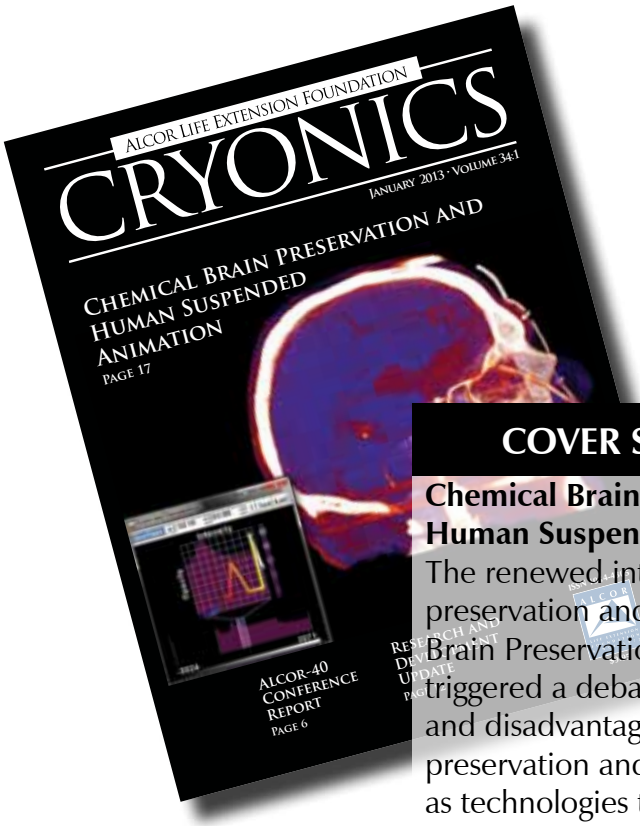

Cover Photo:
CT scan of Alcor patient

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Chemical Brain Preservation and Human Suspended Animation

The renewed interest in chemical brain preservation and the formation of the Brain Preservation Foundation have triggered a debate about the advantages and disadvantages of chemical preservation and cryopreservation as technologies to preserve personal identity for future resuscitation. In this extensive review *Aschwin de Wolf* situates cryonics as an ongoing research program towards reversible human suspended animation and distinguishes it from technologies that merely seek to preserve the ultrastructure of the brain. Unlike chemical brain preservation, contemporary vitrification technologies can be scaled to humans and safely practiced under non-optimal conditions.

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Alcor Life Extension Foundation
CRYONICS

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2013 Annual Giving Program

Alcor provides a wide array of services for you the member, and the general public. We inform and educate, we protect and preserve, and we strive to remain at the forefront of cryonics technology.

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Donations may be made via the Donations button on the Alcor website or by contacting Alcor's Financial Director, Bonnie Magee, at bonnie@alcor.org. Your donation may be made as a lump sum or divided into easy monthly payments. ■

The James Bedford Society

Gifts have played a fundamental role in the cryonics movement since its earliest days. Dr. James Bedford, a man whose extraordinary vision led him to become the first person to be cryopreserved, and the first to make a bequest to a cryonics organization, exemplified the determination of the early pioneers of cryonics. We invite you to follow in his footsteps, and join the James Bedford Society.

The James Bedford Society recognizes those who make a bequest of any size to the Alcor Life Extension Foundation. If you have already provided a gift for Alcor in your estate, please send a copy of your relevant documents to Alcor's Member Communications Director, Lisa Shock.

If you'd like to learn more about setting up a bequest, send an email to lisa@alcor.org or call 877-462-5267 x115 to discuss your gift. ■

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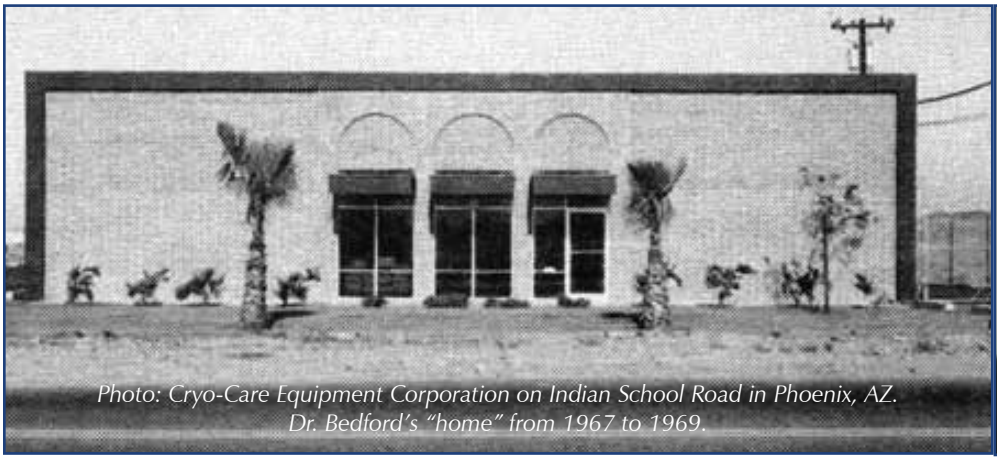

Photo: Cryo-Care Equipment Corporation on Indian School Road in Phoenix, AZ. Dr. Bedford's "home" from 1967 to 1969.

IN PRAISE OF COLD

By Aschwin de Wolf

Some observers believe that cryonics advocates are reluctant to subject their theories to experimental scrutiny because this could damage their (uncritical) belief in future resuscitation. Similarly, one might think that cryonicists would react with a mix of hostility and dismissal to alternative strategies for personal survival. Nothing could be further from the truth. In fact, it is exactly because our personal survival is at stake that forces us to be wary of dogmatism.

For this reason, I have always been interested in chemical fixation as a (low cost) alternative for cryonics. In fact, years before all the talk about the "connectome" and "plastination" I spent considerable time exchanging messages with Michael Perry at Alcor about the technical and practical feasibility of chemical brain preservation. But no matter how open minded I tried to be about this approach, I kept running into the same challenges over and over again.

The challenge that has concerned me the most is whether a delayed start of chemical brain fixation will produce incomplete distribution of the chemical fixative in the brain because of ischemia-induced perfusion impairment. Thinking about the technical problem of "no-reflow" is not the first thing on the mind of someone who first hears about the idea of using chemical fixatives to preserve the brain. In my case, this concern was not just "theoretical." In my lab I have spent many years looking at the effects of cerebral ischemia on cryopreservation and chemical fixation. Last year we decided to broaden our investigations to delayed chemical fixation and we have not been pleased at what we have observed so far. After 1.5 years of room temperature storage the delayed aldehyde fixed brains are falling apart and continue to decompose. In small animals one might imagine that such perfusion impairment could be overcome by *immersing* the brains in the fixative instead but human brains are simply too large. By the time that the fixative would have reached the core of the brain, extensive autolysis will have occurred.

Another complex problem is to identify a fixation and polymerization protocol that fixes all identity-critical parts of the brain. If aldehydes do not completely fix the lipids in the brain, should we add strong oxidizing heavy metals to stabilize lipids? This is possible in theory but, as a general rule, these chemicals are either very expensive or dangerous to use (or both). Even if we are able to identify a chemical fixation protocol for the brain that can do the job, how can we know that such brains are stable for very long periods of time? Should we follow fixation by embedding with a polymer to inhibit residual biochemical activity? To my knowledge, there is no known embedding protocol that is scalable to human brains due to the extreme viscosity of these plastics.

Recently these issues took a more personal nature for me when I had to think really hard about a reasonable but affordable long-term preservation protocol for a companion animal. I spent many days reading the electron microscopy and fixation literature to come up with a protocol that was better than aldehyde fixation and low temperature storage. Adding calcium to the fixative? What about phenol? Post-fixation perfusion of a viscous cryoprotectant to allow storage at subzero temperatures? That is when I really started appreciating the "magic" of cold temperatures.

Absent a vitrification agent, cryogenic temperatures can cause extensive damage to cells. But one thing we know: whatever the nature of this damage, as soon the brain is below the glass transition temperature of -130°C, all water is either frozen or a vitrified rigid solid. We do not have to worry about any damage getting worse over time, or whether some biomolecules have not been fixed. Cold may be "crude" in its effects but it is exactly because no biochemical process can escape inhibition at very low temperatures that makes it such a powerful personal survival technology. ■

ALCOR - 40 CONFERENCE REVIEW

By Chana de Wolf

In honor of its 40th anniversary, Alcor held its first conference in 5 years on October 19-21, 2012, in Scottsdale, Arizona. The program featured a wide variety of topics for presentation, with themes regarding how to improve the odds of a successful cryopreservation and theories of aging and their implications for stopping or reversing aging (as argued by their primary scientific proponents).

Registration to the event opened on Friday and a reception was held where many attendees spent the evening networking and saying hello to old and new friends alike. But the real fun began Saturday morning with the start of the conference.

Greg Fahy, Ph.D.

The Chief Scientific Officer of 21st Century Medicine, Inc. (21CM), Greg Fahy, kicked off the event with an overview of the work being carried out at 21CM in his talk "Progress Toward Reversible Cryopreservation of Complex Systems."

Because cryonics is reliant upon technologies that do not yet exist, it is sometimes likened to religion. "Unlike religion, cryonics must be based on evidence," Fahy began, emphasizing that reversibility is the key component of successful suspended animation.

Incorporating elements of the ongoing "debate" concerning chemopreservation as an alternative to cryopreservation, Fahy questioned chemopreservation and its underlying dependence on mind uploading, arguing that "a map of a city is not the city."

A review of progress in cryopreservation included exciting results in electrophysiological studies of cryopreserved brain slices, including the persistence of LTP in adult rabbit hippocampal slices and recent forays into electromagnetic warming as a way to ensure thermal uniformity across samples during rewarming. Fahy also discussed improvements in cold storage solutions and the long-sought ability to reproduce earlier successful results with M22, Alcor's primary vitrification solution, in the rabbit kidney after 5 long years of complications.

An interesting discussion about shrinking of the brain as a side-effect of cryopreservation highlighted the role of the intact blood brain barrier (BBB) in perfusion of cryoprotectants through the circulatory system to reach the brain. Fahy gave several examples of attempts to open the BBB in order to reduce or eliminate shrinking, including the use of high perfusion pressures, eliminating large polymers such as polyvinylpropinol (PVP) from cryoprotectant solutions, "preloading" of cryoprotectants, and perfusing at higher temperatures – all of which were unsatisfactory. Ultimately, though, the question is whether preventing brain shrinkage improves neural ultrastructure.

Fahy rounded things out with an update on 21CM's "20 year plan." Begun in 2010, their work in whole body vitrification has marched forward with the ultimate goal of reversibility by 2030. Precision perfusion control systems have allowed for unprecedented data collection during whole body vitrification experiments. Currently, the company is focusing on studies of cryoprotectant toxicity to make the next

advance toward reversible cryoprotection of the most complex system of all, the whole organism.

Chana de Wolf, M.S.

Following Greg Fahy was my own presentation of the work being carried out by Advanced Neural Biosciences, Inc. (ANB). ANB is a neural cryobiology research lab founded in 2008 by Chana and Aschwin de Wolf with an emphasis on optimizing protocols for ischemic patients. In particular, ANB has focused on research involving perfusion and cryopreservation of the ischemic brain. In order to do so, a rat model is used to simulate cryonics procedures under realistic conditions.

The main theme of the presentation was that there is a distinct difference between the ice free brain preservation that can be achieved in the lab and the conditions under which a typical cryonics patient is being cryopreserved. In particular, the variable periods of warm and cold ischemia which precede cryoprotective perfusion produce perfusion impairment ("no-reflow") and ice formation in the brain after cryogenic cooling. In the case of cold ischemia we found that remote blood substitution with an organ preservation solution can prolong the period of cold ischemia after which ice free preservation is still possible. Some organ preservations are better than others and we observed the best results with MHP-2 (Alcor's current organ preservation solution). Even after a warm ischemic delay blood substitution still produces better results than not removing the blood prior to cold ischemia, but as the period of warm ischemia increases, so does perfusion impairment and ice formation. I stressed that warm ischemia is not just accelerated cold ischemia, hard to mitigate, and a serious obstacle to good cryopreservation.

We also presented the results of our "field vitrification" research for Alcor. A protocol in which cryoprotective perfusion of the patient is conducted in the field using a simplified protocol followed by shipping on dry ice permits ice free preservation of the brain up to at least 48 hours of dry ice transport. Blood substitution with MHP-2 and shipping at water ice also permits ice free cryopreservation of the brain for at least 48 hours of cold ischemia but the advantage of a field vitrification protocol is that it eliminates cold ischemic injury to the brain and the severe (whole body) edema that usually is seen during cryoprotective perfusion after long periods of cold ischemia.

In closing, I announced the funding we received from the Life Extension Foundation to conduct whole brain electrophysiology (EEG) studies after cooling and vitrification.

Kim Suozzi

After a mid-morning break, Max More explained that he was giving up one of his speaking slots to Kim Suozzi, whom he introduced as a young woman diagnosed with cancer who wished to be cryopreserved at Alcor. Max announced that Alcor would provide services at reduced cost and that staff would be volunteering time to cryopreserve Kim.

Kim Suozzi, who attended the conference with her boyfriend, then spoke about her terminal diagnosis and efforts to raise money in support of her cryopreservation. Only 23 years old, Kim was a psychology student in her senior year at Truman University planning to do graduate work in neuroscience when she was diagnosed with Grade IV glioblastoma (i.e., brain tumor) after experiencing a multiform seizure in March 2011.

Kim had already become interested in transhumanism, the singularity, and cryonics after reading *The Age of Spiritual Machines* by Ray Kurzweil, but thought she still had enough time to consider the cryonics option. When diagnosed, she was reticent to ask her parents for financial support, so she posted her request online instead. After getting "unexpectedly good support," her campaign was picked up by the Society for Venturism, which is currently accepting donations for the Kim Suozzi Charity through their website.

Keegan Macintosh, J.D.

Keegan Macintosh, a young Canadian lawyer and Alcor member since 2011, then presented an in-depth analysis of the Thomas Donaldson legal case entitled "Access to Cryonics: Legal Strategies – Then and Now." Thomas Donaldson, Ph.D., was an Alcor member who, when diagnosed with Grade II astrocytoma, fought for a declaration that he had a constitutionally-protected right to a "premortem cryopreservation." Ultimately, his request was denied by California Superior Court.

In his talk, Macintosh critically analyzed how the case was argued and decided at the appeal level. Macintosh emphasized "meaningful access" to cryonics, explaining that Donaldson's desire for euthanasia via cryopreservation was in order to preserve his brain and personality intact rather than in the state he would be in after his "natural" death. The presented issue was whether Donaldson has a right to premortem cryopreservation, but it was addressed by the courts in terms of assisted suicide.

Because of the very different intentions of these two approaches, Macintosh feels that the issue was considerably confused. He argues that by approaching it as an assisted suicide case, the Court could avoid having to consider the possibility of cryonics ever succeeding. Simply considering relevant state interests, such as preventing suicide and preserving life, should have actually worked for Donaldson's side rather than the State's. Other interests, such as protection of innocent third parties and protection of vulnerable persons and preventing abuse, were not relevant at all.

Macintosh believes that we can learn important lessons from analyzing the Donaldson case. In particular, not to avoid the actual issue at hand. After fast-forwarding to the present and discussing some important changes in physician-assisted-suicide legislation in the U.S., Macintosh argued that a case like Donaldson's may stand a better chance today if these lessons are observed. Interestingly, the successful argument of such a case may be even more probable under the Canadian constitution. In particular, novel arguments could be made under Canada's Charter of Rights and Freedoms that are not available under the U.S. Constitution.

Panel: Long-Term Financial Planning

Rounding out the morning was a useful panel on long-term financial planning

led by Rudi Hoffman, Michael Seidl, and Ralph Merkle.

Rudi Hoffman

Insurance agent and Alcor member Rudi Hoffman introduced the audience to the basics of cryonics funding, including a discussion comparing term vs. permanent life insurance funding options. He highlighted the role life insurance plays in allowing access to cryonics for all and how important it is to emphasize the affordability of cryonics to those considering signing up but who may think that it is available only to the wealthy.

That said, Hoffman acknowledged that technological advances and inflation are inevitable and that cryopreservation costs will increase. He urged new and existing members to take these issues into serious consideration when planning cryonics funding and to obtain inflation-robust coverage beyond today's minimums ($200,000 whole body and $80,000 neuro).

Ralph Merkle, Ph.D.

Ralph Merkle then announced and discussed the Alcor Model Revocable Asset Preservation Trust, recently made available by Alcor to enable cryonics members to preserve their personal assets. In short, Merkle explained, "Your Trust maintains your assets so you 'wake up' with your money as well as your life."

Utilizing an attorney who had written a few wealth preservation trusts for wealthy cryonicists, Alcor drafted a model trust that can be used by most members. Merkle noted that the model trust is used as a starting point to be taken by an individual to his or her attorney to modify to suit their particular situation and purposes. In general, one will need to name a trustee organization (which can be provided by a bank) and three trust advisors (two appointed by the member and one appointed by Alcor). The trust advisors look after the trustee to ensure they do a good job in making financial decisions affecting the trust. Alcor provides continuity after the member's cryopreservation and appoints successor trust advisors.

Importantly, the Alcor model trust is *revocable*, meaning that one may take the money out of the trust at any time. Merkle pointed out that the trust also covers other situations separate from financial decisions, such as whether one has been successfully revived. These decisions are handled by Alcor and the trust advisors, not the trustee.

Ultimately, Merkle reminds us, there is no precedent for a trust intended to maintain personal assets in perpetuity. "It looks like it should work," he said, "but we'll find out."

Michael Seidl, J.D.

The last presenter in the financial planning panel, Alcor board member Michael Seidl spoke briefly but passionately about ways to ensure that funding is available for your cryopreservation when needed. "Cryonicists are adventurers," he said, "but we don't know how long the adventure will take, so we should plan and provision accordingly." Seidl parsed his recommendations into three commandments:

1. Protect your noggin. Think first about providing for your own cryopreservation. Secure funding that will increase over time.
2. Don't give people incentive to frustrate your cryopreservation. A large liquid estate can make people crazy. Leaving everything to Alcor could incentivize interference. Provide for these folks so that this incentive is removed.
3. Give people incentive to support your arrangements. For example, provide a financial incentive for a family member to ensure your cryopreservation.

Panel: Medical Monitoring Devices

A post-lunch panel on the current state of medical monitoring devices was hosted by Aaron Drake, Ben Best, and Martine Rothblatt. As in the previous panel, each person was allotted a few moments to speak about the subject.

Aaron Drake

Alcor's Readiness Coordinator, Aaron Drake, emphasized that a cryonicist's worst fear is dying alone without being able to notify Alcor. Because time is of the essence in getting a patient from bedside to perfusion, Drake explained that Alcor keeps a cloud-based watch list to track potential cases (e.g., members with known health issues). By doing so, Alcor has increased bedside access to dying members from 33% (in the 1990s) to 86%.

Improving upon 86%, Drake said, will require more sophisticated medical monitoring. Lots of devices exist for measuring all sorts of physiological responses. They may be worn on the body or in the fabric of the clothes. Such devices are not only good for Alcor response, but also for getting to a hospital for immediate care.

Ben Best

Ben Best, former President of Cryonics Institute, followed Drake's presentation with a discussion of current monitoring devices that might be useful to cryonics. He began by pointing out that a chain is only as strong as its weakest link, and that "the time until pronouncement [of legal death] needs more resources thrown at it." He is particularly concerned about elderly cryonicists living alone.

While panic-button systems like Life Alert® could be useful, Best thinks it might be better to monitor vital signs (e.g., movement, respiration, heartbeat), which doesn't require the patient to be alert. Desired features of a device would include rapid detection of loss of vital signs, comfortable wear, ability to send messages, low power consumption, wireless, and minimal false alarms.

Lastly, Best described several ongoing commercial efforts such as Athena GTX, NUVANT Mobile, and MyPulse, as well as some cryonics-specific applications in development, but lamented the fact that working, successful devices still have not materialized.

Martine Rothblatt, Ph.D.

Martine Rothblatt, Director of the Terasem Foundation, then spoke about detection of heartbeat cessation. First she reviewed some statistics describing the way our time is spent and leading to the 2.9% probability (1 in 34) that an Alcor member may suffer delayed response (due to lack

of notification of death). The solution to this problem, she said, lies in wireless or Bluetooth external heartbeat detectors or even less sophisticated, wrist-watch style pulse detection devices.

The sometimes low price of these devices lends itself to various economic models that Alcor could implement to generate additional revenue. Rothblatt outlined various models such as: charging for an app and device; giving the app away as a membership benefit; selling or giving away the app and making it modifiable (i.e., not just Alcor-related); and partnering the app and device with one or more PERS (Personal Emergency Response System) companies. PERS is a $125M annual market now, and predicted to be $250M by 2020. If Alcor would take advantage of the 15% annual growth rate of this market, it could generate an additional $1.7M – 27M annually.

Anders Sandberg, Ph.D.

In "Rational Decision Making About Future Technology," philosopher Anders Sandberg talked with us about "handling the unknowable and undecidable." He pointed out that even really smart people make really stupid decisions consistently. As a general rule, humans are reasonably good at handling "human" problems, but as we get further out of our comfort zone, we start getting bad at decision-making.

Sandberg described several approaches to decision-making, such as rationality [rational agents maximize their expected utility; but humans don't have a utility function], irrationality [acting under ignorance and uncertainty isn't irrational – it's how we live our lives], and uncertainty [there are some things we can't or don't know; we can lack knowledge about parameters or about the rules of a system, or even about what is good]. Unprecedented events are important to consider in the light of uncertainty – "the absence of evidence is not evidence of absence," Sandberg said. "A true rational person considers the probability of any event as between 0 and 100%. Just because cryonic resuscitation has not occurred does not mean that it won't."

Max More, Ph.D.

In an effort to educate old and new members alike, Max More lectured the audience on "How to Be an Exemplary Cryonicist." He provided a step-by step outline of the myriad things an Alcor member can do to improve their prospects for an optimal preservation, beginning with health maintenance including regular physical checkups and keeping Alcor informed of changes in medical condition. He stressed the importance of keeping your Alcor paperwork updated, wearing your bracelet, and talking to your friends and family about your cryonics arrangements to build understanding and support. He also advocated relocating to the Scottsdale area, avoiding conflicts in financial arrangements, and planning ahead to keep in pace with inflation and maintain adequate funding.

More discussed the things one can do to improve Alcor's patient care such as giving Alcor access to your medical records and allowing them to perform a CT scan or a sample from the central nervous system to obtain objective feedback about the quality of cryopreservation. Lastly, contributing one's skills or resources to Alcor as a volunteer and starting or attending a local cryonics group meeting are other great ways to stay involved and to improve your chances of an optimal preservation.

Todd Huffman, M.S.

Following the late-afternoon break, Todd Huffman presented "Advances in Neuroscience: Implications for Cryonics." Huffman's focus was on large-scale imaging technologies that can be used to scan and model the brain at various levels of encoding. Particularly interested in neural structure and high throughput light microscopy, Huffman's company 3Scan has developed the Knife-Edge Scanning Microscope (KESM), capable of imaging tissue while slicing it with a diamond blade to create a stack of images that can be put together to create a 3D image.

Huffman included several beautiful photos of the 3D images captured by the KESM, from an image of the vasculature of a mouse brain to Nissl stains for cell bodies such as the Purkinje cells of the cerebellum and pyramidal cells of the cortex. 3Scan's current efforts include fluorescence imaging, neural reconstruction algorithms, antibody staining, and embedding. The impact of such technologies on cryonics, Huffman explained, would be in the form of an increase in conventional structural neuroscience data and the ability to reconstruct and evaluate procedures.

Sebastian Seung, Ph.D.

Day One of the conference ended with Sebastian Seung's "Connectomics and Cryonics," followed by a discussion of his talk. Seung began by explaining that connectomics is the application of techniques such as 3D imaging to build high-resolution maps of neural connections. The resulting map is known as the connectome. While working in the field at MIT, Seung met Alcor member and Harvard neuroscientist Kenneth Hayworth. When talking with Hayworth one day, Seung realized the implications of connectomics for cryonics and included some of his thoughts on the subject in his book *Connectome*, which elicited varied reactions.

Starting with the hypothesis that "you are your connectome" (reminiscent of "The Astonishing Hypothesis" of Francis Crick), Seung presented evidence from neuroscience that chemopreservation successfully preserves brain structure as evidenced by reconstructions using serial electron micrographs (EM). He then asked whether memories can be "read" from such connectomes and discussed what kinds of structural information might be important to answering such questions. Ultimately, he concluded that connectivity, including the shapes of neurons and locations of synapses, is what must be preserved in order to construct the identity contained within. But Seung wonders how well cryonics preserves brain structure compared to chemical preservation methods.

To that end, Seung and Hayworth announced the Technology Prize to be awarded by the Brain Preservation Foundation to the first individual or team to demonstrate a technique capable of preserving a human brain for long-term storage with high fidelity. The current contenders for the first stage of the prize

have employed both chemo- and cryopreservation methods, but the required imaging and analyses of these samples has not yet been completed.

Seung's presentation was followed by a relatively long discussion with the audience, which quickly turned into a debate about the merits of chemopreservation and cryopreservation. Topics discussed included the long-term stability of chemopreserved brains and whether the Technology Prize is neutral between both approaches.

Catherine Baldwin, M.S.

In her talk "From Bedside to Clinic: The Evolving Care of Cryopreservation Patients," General Manager of Suspended Animation, Inc. (SA), Catherine Baldwin provided an overview of SA's stabilization capabilities, which she described as "science, technology, and medicine in the service of cryonics." Suspended Animation does patient recovery and stabilization for cryonics organizations, including Alcor. In fact, SA is contracted to perform standby and stabilization for all Alcor patients outside of the state of Arizona.

Baldwin described the stabilization and transport process, beginning with rapid induction of hypothermia followed by cardiopulmonary support (CPS) and administration of medications in preparation for the surgical procedure of cannulation to connect the circulatory system to the perfusion circuit. She stressed that the skills required to carry out these procedures are the same as you find in emergency and medical personnel.

Baldwin started recruiting EMS and surgical personnel early in her employment with SA. Because surgical and perfusion coverage is too expensive on a full-time basis, SA has contracted with companies that provide temporary coverage and now has four on-call cardiothoracic surgeons and eight cardiac perfusionists. Recently, SA has also contracted with a company that provides hospice and skilled nursing on-call. They also have 3 air transportable perfusion (ATP) kits and several vehicles supporting surgery (one on each coast).

In the future, Baldwin expects SA to roll out portable liquid ventilation, requiring only intubation to start efficient internal cooling using the lungs as a heat exchanger. Gene expression profiling is being explored to profile blood from patients using PCR. And finally, Baldwin thinks that by leveraging the network of professionals they've developed, SA will be able to build a network of clinical facility partners that will allow SA to start or carry out cryonics procedures within their facilities.

Aubrey de Grey, Ph.D.

The last segment of the conference focused on alternative theories of aging as argued by their primary proponents. First at bat was Aubrey de Grey, founder of Strategies for Engineered Negligible Senescence (SENS). De Grey believes that aging is the result of cumulative damage caused by normal metabolism. Pointing out that the presenters will disagree on some topics, de Grey stated that he thinks that damage does continue to accumulate in all individuals no matter how old they get.

Traditional approaches to intervention in the aging process include gerontology (i.e., intervene between metabolism and damage to "slow it down") and geriatrics (i.e., intervene between damage and pathology to "patch it up"). Both have been ineffective, and so we must consider another option – the maintenance approach.

The maintenance approach advocates repairing damage directly. It does not require understanding of complicated metabolic pathways leading to damage, but only how to repair the damage itself. "Not necessarily all of the damage," de Grey says, "but enough of it to buy time so we can make it to the point that we can repair more of the damage." His claim is that, unlike the others, the maintenance approach may achieve a big extension of healthy human lifespan quite soon and that it could help people who have reached middle age or older already.

To that end, SENS Foundation does research to implement SENS, including cell therapies and strategies to clean up extracellular "junk" that are in human clinical trials. And though some of these strategies alone have not achieved the clinical endpoints, de Grey believes that what is probably needed are combination therapies to address particular pathologies.

Joshua Mitteldorf, Ph.D.

"In 1997, everyone thought that free radicals were the cause of aging and that antioxidants were the cure. In 2012, we think it seems to be controlled by genes at a very high level and that signaling dysregulation is the problem." Mitteldorf's hypothesis is that aging is not a result of dysregulation of some earlier homeostatic mechanism at all, but that it is programmed into us, and that "we live and die according to a schedule."

He addressed four opportunities to preventing aging: (1) Preserving telomeres; (2) Damping inflammation; (3) Regulation of apoptosis; and (4) Restoring youthful gene expression.

Regarding the first strategy, Mitteldorf explained that telomeres are segments of "nonsense" at the ends of chromosomes that can be lost without causing any damage to the DNA. But DNA replication results in the shortening of telomeres over time, eventually resulting in cell death. An enzyme called telomerase, however, can add base pairs back to the chromosomes. The rationing of telomerase is a programmed death mechanism that evolution exploits to force the sharing of genes. In terms of pushing for telomerase therapies, Mitteldorf said he felt that "we're ready for this" and that he felt very safe doing so. He discussed a number of (expensive) supplements that aim to activate telomerase.

Inflammation is an essential first-line defense against invading pathogens. In youth it is wholly beneficial, but as we get older our bodies begin to target healthy cells rather than just outside pathogens. All of the diseases of old age are associated with higher levels of inflammation. Some drugs that combat inflammation are cheap and easy, such as aspirin, omega-3 fatty acids, curcumin, and ginger. Other approaches to damping inflammation carry substantial tradeoffs, however.

Apoptosis, or cell suicide, is an ancient mode of programmed death found in even the earliest eukaryotes. When the body needs to get rid of diseased cells it does so through apoptosis. But apoptosis is also linked to diseases of old age, including Parkinson's disease, sarcopenia, and glial cell loss. Strategies to limit apoptosis have

very strong tradeoffs. We would need to find a way to make apoptosis "smart" so that it kills the "bad" cells and keeps the "good" ones.

Lastly, Mitteldorf discussed gene expression, which changes as we age. He explained that we do not have the same gene expression profile when we get older as when we were younger and that this makes for a very fertile area of research. There is a major effort underway to understand enough to manipulate the signals that determine gene expression, and if we are successful we may be able to restore youthful gene expression. "It may not be easy,' Mitteldorf concluded, "but my dream is to slow aging from the top down."

Michael Rose, Ph.D.

Rounding out the speakers on aging was Michael Rose, an evolutionary biologist who spoke on "How to Control Your Aging" (or "Looking Good in Liquid Nitrogen").

Rose regards aging as "one of the most completely solved problems in science today." He discussed the theory of the evolution of aging, explaining that some organisms don't age at all and that eukaryotic molecular and cell biology allows for indefinite life without aging, but that "the force of natural selection acting on survival falls with adult age in animals like us." The age of reproduction, he stated, is the key to aging. Experiments carried out in the 1970s delaying the first age of reproduction in fruit flies resulted in substantially slowing the process of aging across subsequent generations. This has allowed us to form a very powerful formal theory of aging.

Looking at other laboratory data, Rose indicated that experiments with medflies in the 1990s suggest that aging is only a transitory phase and that aging, in fact, ceases at some point in late life. After the cessation of aging there is a stabilization of some functional physiological characters while others continue to decline. The resulting plateau in late-life mortality is caused by the decline of natural selection.

Rose then argued that aging is *not* a cumulative process of deterioration, contrary to cell dogmas (and Aubrey de Grey's platform). "Biological immortality evolves," he said. "We've shown that aging stops at the level of the individual, we've shown that we can explain it evolutionarily, and we have experimental proof of such." To control aging we must try to get immortal sooner – to cut off aging – and bring the aging plateau down to a younger age. Rose is interested in using environmental manipulation to effect this change.

Importantly, he asserted, the timing of cessation of aging depends on environment and lifestyle such as the food we eat. The key is to do what is natural for humans, or what we are adapted to. Rose argued that while young people of Eurasian ancestry are well-adapted to evolutionarily recent agricultural lifestyles, at later ages we progressively revert to physiology that is better adapted to the hunter-gatherer lifestyle.

To control your aging Rose suggests (a) adopt the hunter-gatherer lifestyle after 30-40 years of age if Eurasian and earlier (10-25 years) if 'your ancestry is less Eurasian, (b) use the best of modern medicine to lower your mortality level during the last decades of aging and during the plateau, and (c) use autologous tissue repair when it becomes available.

Panel with Mitteldorf, de Grey, and Rose

Wrapping up the conference was an interesting panel discussion with the three aging researchers, Mitteldorf, de Grey, and Rose, mediated by Greg Fahy. Each scientist had an opportunity to ask the others questions and to defend their respective theories in light of data they may not have addressed in their talks.

Mitteldorf wondered how Rose would model real societal changes that have large and lasting impacts on humans. Rose said that the Price equation attempts to take these changes into account, but that it is hard to model such things and that he "didn't wish to underestimate the difficulty of this."

Dr. Fahy then posed a challenge to de Grey and Rose: "Aubrey would say that metabolism is too complicated, and Michael would say something similar. But we've seen that knocking out ONE gene in *C. elegans* can increase lifespan by 10 times. How do you explain that?"

Rose agreed that deleting even "one particularly bad thing" can have significant effects on longevity. "Evolution has already built life-history flexibility," he said. "If you give up one of those major things, like building sperm, you will see great increases in lifespan."

Aubrey de Grey clearly disagreed with Michael Rose and noted that the absence of natural selection does not mean the absence of accumulation of damage.

Many more technical arguments like this were exchanged, but at the end of the panel it became clear that there is no real consensus about what aging is and what would be the most efficient way to stop or reverse it.

Conclusion

In all, Alcor's 40th anniversary conference was an enjoyable weekend for old and new Alcor members alike. The agenda was well-planned and the quality of speakers and presentations was very high. From the science of cryopreservation to the implications of neural network research on cryonics to strategies for preserving your assets as well as yourself, no stone was left unturned and no question unasked. We may not always have the answers, but with meetings like Alcor-40 stimulating discussion and ideas we can better determine where to look for them. ■

Research and Development Update

By Steve Graber

Recent neuro patient imaging via CT scan has shown that we can obtain a highly detailed view of the outcome of cryoprotective perfusion. From this information we believe it is possible to determine with a high level of confidence the exact location and proportion of cryoprotectant perfusion throughout the brain. When we match up the perfusion data against additional case data, such as the time elapsed from pronouncement of death to perfusion, we can generate a deeper understanding of the effects that time has on the quality of brain cryoprotection. This data has the potential to fundamentally change our approach to pre-mortem and immediate post-mortem patient care.

During the first phase of our experiment our expectations for the CT scanning project were much less lofty. We were simply looking to determine the location and placement of acoustic "crackphone" sensors within the skull. Crackphone data collection and the subsequent analysis and reporting of fracturing events are an integral part of our cooldown process prior to long term care. We feel it is important to determine the position of the crackphone elements because these fracturing events are recorded and analyzed during patient cooldown. All reasonable attempts at correct placement are taken by the surgeon during the cryoprotection procedure but knowing the exact placement is not possible during surgery. In addition, there is typically considerable shrinking of the brain during the procedure, which can affect the location of the elements. A secondary goal for us was to determine if a CAT scan can be performed while the patient cephalon is secured within our standard aluminum neuro storage canister. Once we started analyzing the data it became apparent that we were seeing much more than we had anticipated.

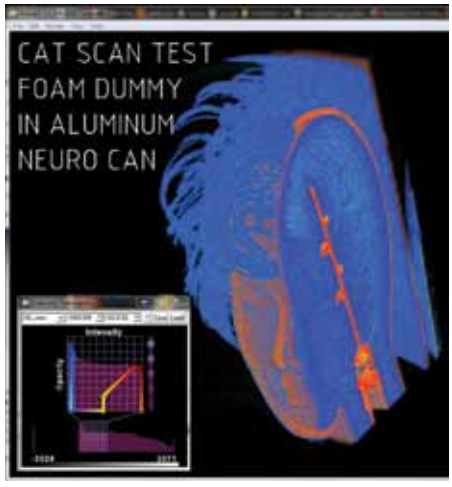

Figure 1: Cross section of dummy head showing expanding foam in blue and center support in orange. CLUT manipulation tool (inset) which allowed this image to appear from the data. Less dense materials (foam and hair in blue) to the left side with more dense plastics to the right.

The software I used was the open source, freely available, 3D MRI and CAT scan viewer 'mricroGL'. In order to view our DICOM images in mricroGL I first converted the DICOM data into the native mricroGL NIfTI format, using the dcm2nii.exe program. Once the conversion process was completed I was able to open and view the acquisition series images in 3D format.

One of my main software tasks was to develop color lookup tables (CLUTs) for each of the materials I desired to view within the images, and for that I started with the 'Dummy in a Can' series. Within a short time I had successfully revealed the dummy head within the aluminum canister (fig.1). Furthermore I was able to determine the inner workings of the dummy head and, with some quick analysis came to the conclusion that due to the expanded foam and plastic insert detected within the structure, at least she is not a complete air-head. The aluminum can is almost impossible to completely eliminate from the viewer but with adequate cropping and slicing capabilities I was able to reveal the 'patient' inside the can, including detailed variations in the foam density, the air bubbles within the foam, and the "patient's" hair.

During a subsequent trip to the medical imaging lab we were able to successfully image specific components of our M22 cryoprotectant. That event is what led to our greatest progress, which I will address later in this article.

Following the aluminum can analysis I next converted and opened up the first of the patient scan data series. At this point I was able to successfully determine the placement of the crackphone elements, as well as location of the burhole and nasopharangeal thermocouples.

Below are a series of screen-captures which have been chosen to represent the 3D imaging process. These images were taken of two patients, A-1546 and A-1088. Due to the fact that A-1546 was pronounced on the east coast he/she experienced approximately 18 hours of delay from pronouncement to cryopreservation. It should be noted that by all of our standard measures with the exception of travel time, patient A-1546 was an almost ideal case who underwent a very successful

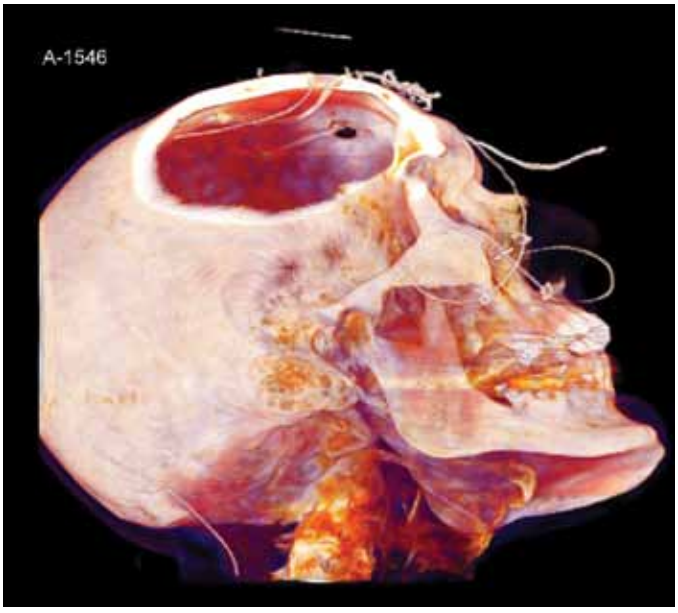

Figure 2: Crackphone element and Thermocouple placement – A 1546.

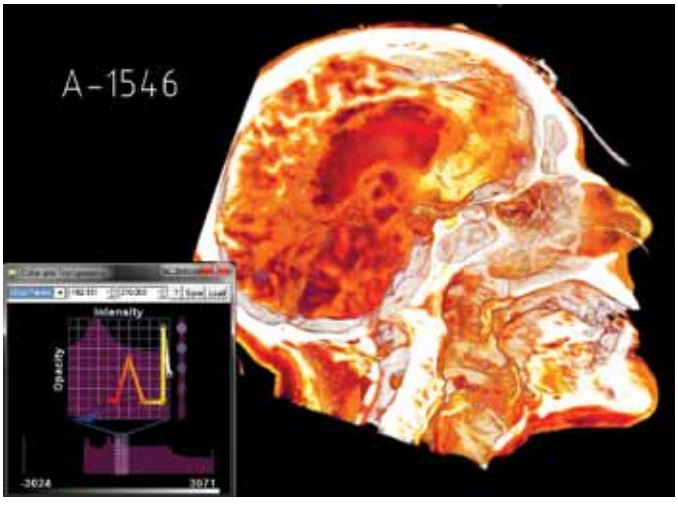

Figure 3

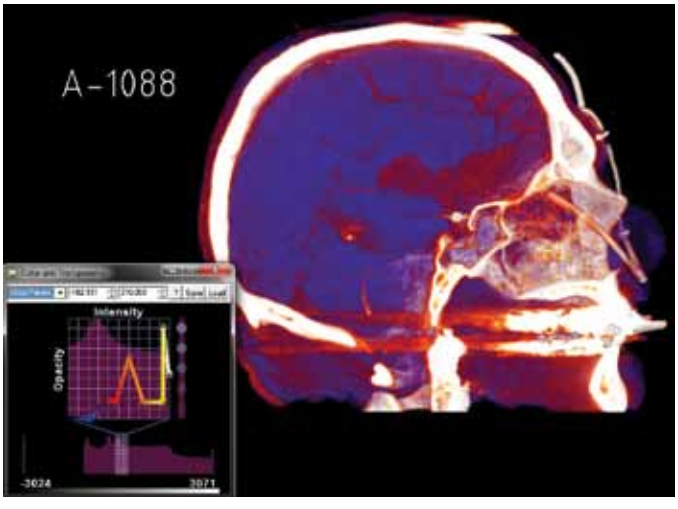

Figure 4

cryopreservation. Patient A-1088 unfortunately legally died of a sudden, massive hemorrhagic stroke on the east coast and did not undergo a cryoprotection.

These flat images don't fully express the actual 3D visualization (rotation in real-time) of our images at the native DICOM scanning resolution of ~0.3mm. This delivers an impressive level of detail which can only be fully appreciated using the mricroGL or some other data program.

With a CLUT setting optimized to highlight dense objects in white and yellow, and less dense matter in red and blue I used the 'Slice' tool to remove a small section of the skull (fig.2.) We can easily make out the crackphone wires and the thermocouple wire traversing through the burholes into the brain cavity. The nasopharyngeal TC location is a complete surprise, having been pushed so far into the nasal cavity that the tip of the probe ends up all the way into the throat under the jaw. Variations in brain density are starting to be visible in the red and blue range. NOTE: Color designations are entirely arbitrary.

As you read this, you might be asking yourself "Why weren't we doing this a long time ago?" The answer is that we had to wait for large computers to shrink down to desktop machines, and for software to be written that we could afford.

A sagittal section of A-1546 (fig.3) directly through the mid-line highlights some very interesting density variations throughout the brain. I have inset the CLUT adjustment control window to help explain the density range, opacity and colorizing in this image. This particular cross-section also highlights the position of the mid-line crackphone as a white dot at the top center of the brain. White and yellow are once again the densest region while orange/red is mid-density and blue is least dense. My initial expectation was to see a fairly uniform density map throughout the brain but it appears not the case in this patient. I will draw more detailed conclusions further in my report after showing our non-perfused brain using the same CLUT settings.

For reference, here is a sagittal section through the mid-line (fig. 4) this time of patient A-1088, who was a recent straight freeze. The placement of the nasophyrangeal probe is clear. X-ray scattering from metal denture fixtures shows up as white and orange/red noise horizontally across the bottom of the image. The terminal hematoma is visible in fig. 4 as a red shape spread throughout the brain cavity behind the nasal passages.

Homogeneity of electron density is evident throughout the brain of A-1088. When compared to the identically composed, sectioned and CLUT displayed image of A-1546 (fig. 3) it is clear that there is great disparity in overall density between these two brains. A-1546 shows a significantly greater electron density than A-1088 throughout the majority of the brain, but there are areas

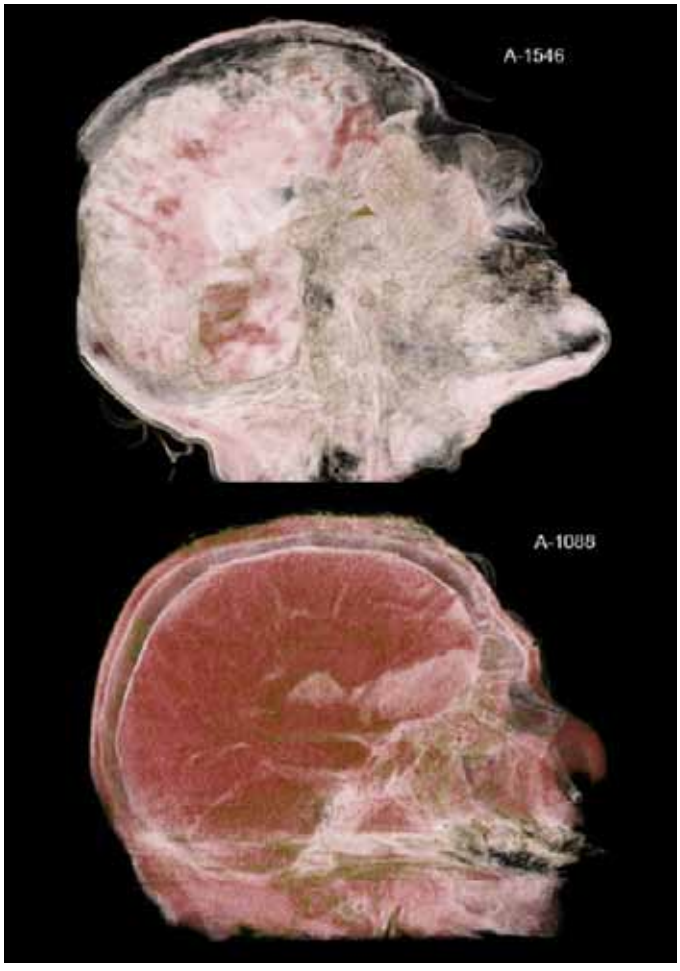

Figure 5: Another image showing a comparison of electron density using identical CLUT settings. In this image the hematoma in the frontal lobe of A-1088 appears in white. Bone opacity has been lowered to zero. White is still more dense than red. We can very clearly see a significant difference in relative density between our two subjects.

of lower density which refute this generalization. Overall the A-1546 brain is much more electron dense and we believe this to be evidence that perfusion did occur, at least in certain areas. It is important to note that we do not feel that homogeneous perfusion of cryoprotectant was achieved across the entire brain. This may be due to the fact that patient A-1546 was pronounced out of state and experienced a travel time of 18 hours from pronouncement to the beginning of the cryoprotective ramp in the Alcor O.R.

In September 2012 we CT scanned in high resolution a variety of specific chemical compounds which are common in the M22x1.25 vitrification solution. We created a package of 5 cryogenic vials individually containing water, ethylene glycol, formamide, M22x1.25 and a last one containing dimethyl sulfoxide. Once these 'marker' scans were brought back to Alcor I was able to isolate and enhance the absorbtion and scattering properties for the contents

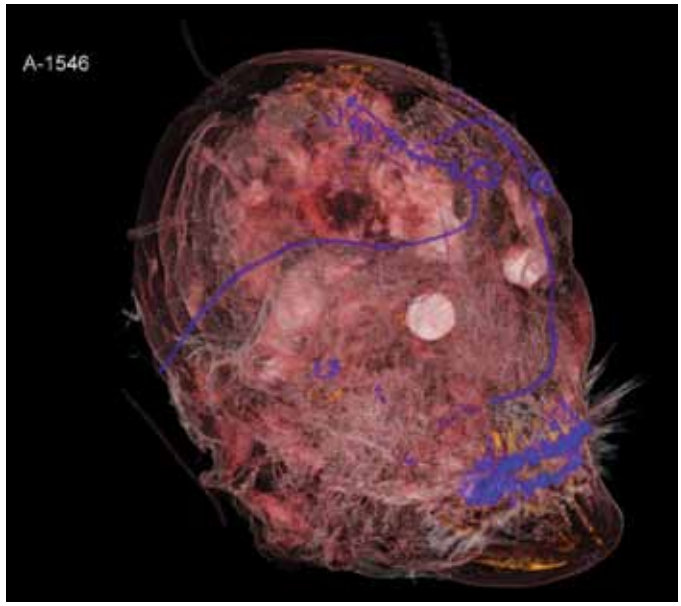

Figure 6: In this image blue is most electron-dense, followed by yellow, to red, and white is least dense. I have selectively removed the majority of the skull's electron density by taking its opacity to 0 and highlighted the metallic crackphone and thermocouple wires to determine their placement within the skull. Additional details appear at this specific density including staples, teeth, and two structures deep within the skull which appear to be sockets for the jawbone.

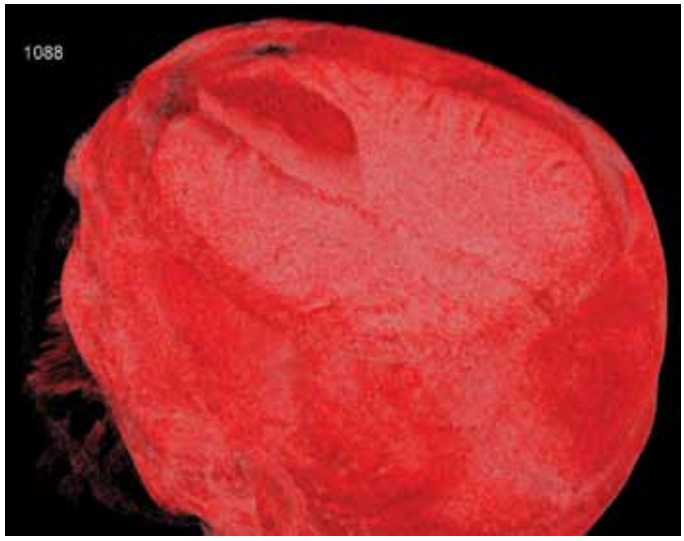

Figure 7: A variation on the slice tool. This one was taken in the transverse direction, and clearly shows the location of the brain hematoma of patient A-1088. Although it's hard to believe, the CLUT parameters used to achieve this image are the same as used for a previous image of A-1546 (fig. 6). The structures highlighted by the software at these particular electron densities are completely different.

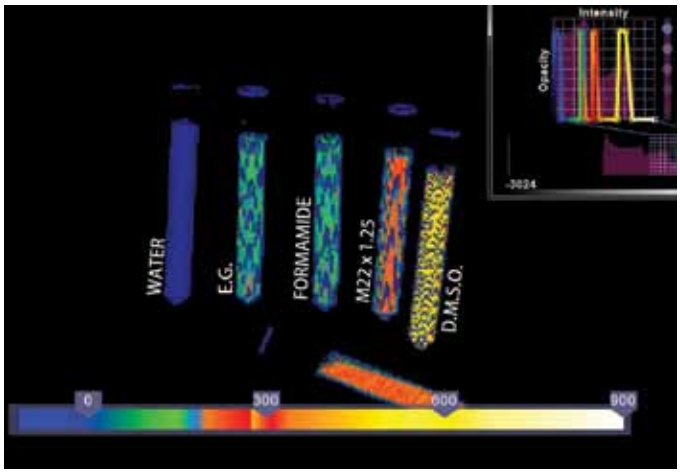

Figure 8: CT visualization of specific chemical compounds and the corresponding color lookup table (CLUT)

of the five individual nunc tubes in my CT Visualization software. I then created a "CLUT Map" and saved it to disk.

The new CLUT map was applied to our earlier patient CT Scans and the initial results from this additional analysis effort have proven quite extraordinary. These findings were significant enough that I created a short video which was displayed during breaks at the Alcor 40th anniversary conference. Inside of each patient's scan file is revealed a great wealth of information which we believe should be able to potentially determine success, failure, or some combination thereof of the Alcor perfusion procedure. We believe we have the ability to visualize perfusion. This is important because we can then compare it against a number of external variables including but not limited to: hours of warm or cold ischemia, travel time, effects of various post mortem medications, etc. The end result is that we may be able to definitively answer some important questions. Is perfusability adversely affected over long transport times? etc... We are in the very early stages of research with this technique but it holds a lot of promise.

As you read this, you might be asking yourself, "Why weren't we doing this a long time ago?" The answer is that we had to wait for large computers to shrink down to desktop machines, and for software to be written that we could afford. Also, we just didn't know; there's not a lot of brain cryoprotection being done, and we're apparently the first people to ever look. ■

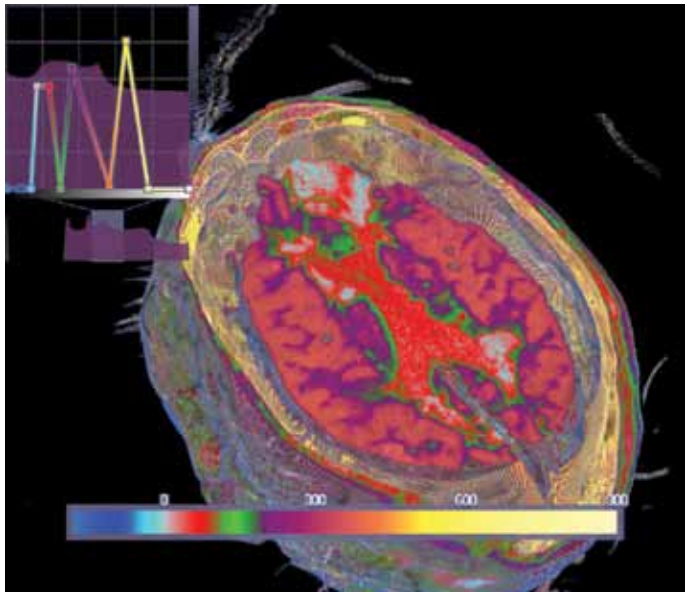

Figure 9: From the video shown at the 2012 Alcor Conference: A brain CT Scan of an Alcor patient with an 18 hour travel time from pronouncement of death to perfusion. The CLUT created for this image was based upon our CT Scan of specific chemicals found in M22 cryoprotectant. Dark Blue to Light Blue colors are most likely water ice and frost while White to Red are quite possibly blood and cerebrospinal fluid. Colors from Green to Light Yellow are Cryoprotectants.

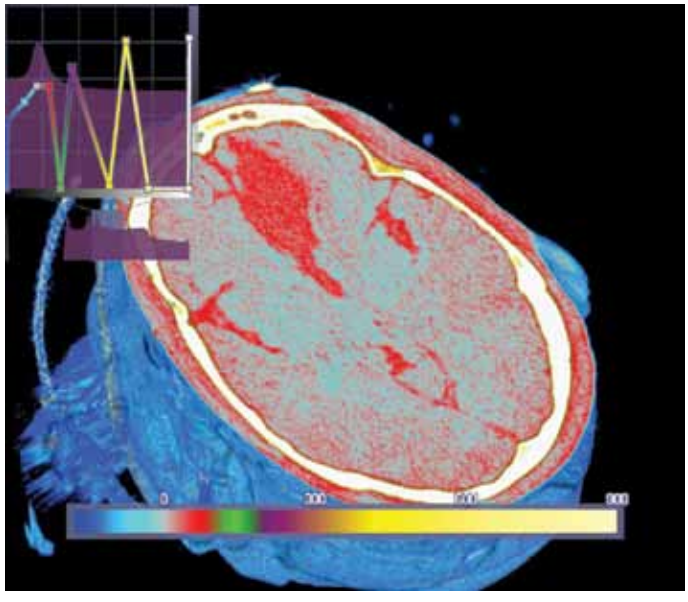

Figure 10 - From the video shown at the 2012 Alcor Conference: Brain CT Scan of an Alcor patient with a straight freeze. This CLUT is basically identical to the one in Fig. 9 above.

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Chemical Brain Preservation and Human Suspended Animation

By Aschwin de Wolf

Executive Summary

Scientific and practical considerations strongly support cryopreservation rather than chemopreservation for the stabilization of critically ill patients. Technology for achieving solid state chemopreservation of brains larger than a mouse brain does not yet exist. Chemical fixation is irreversible without very advanced technologies. Chemical fixation permits no functional feedback or development pathway toward reversible suspended animation. By contrast, cryopreservation seeks to maintain viability of the brain as far downstream as our capabilities and resources permit – an approach that reflects our view of cryonics as an extension of contemporary medicine. Cryopreservation preserves more options in that a cryopreserved brain could be scanned in future, or later chemically fixed, but the process of chemical fixation cannot be reversed and replaced by just low temperature storage. The cost benefits of chemopreservation over cryopreservation are exaggerated, largely because the standby and treatment procedures for effective chemopreservation would be just as extensive as for cryopreservation, if not more so, even assuming that highly toxic chemicals could be worked with safely in the field. Chemopreservation is being inherently tied to mind uploading, an association that is likely to limit its acceptance as a form of experimental critical care medicine by apparently requiring acceptance of the idea of substrate independent minds.

Introduction

The formation of the Brain Preservation Foundation and the recent publication of Sebastian Seung's book *Connectome*[1] have given rise to a renewed interest in chemical preservation as a means of personal survival. Alcor welcomes these developments and has even attempted to donate to the Brain Preservation Technology Prize to stimulate validation of both cryopreservation and chemopreservation as preservation technologies.[2] In fact, in 2008 Alcor received a grant to conduct a preliminary investigation into chemopreservation.[3] In addition, Alcor staff member Mike Perry published an extensive article about low-cost alternatives for cryonics[4] and Aschwin de Wolf published the first technical review of chemopreservation as an alternative method of biostasis in *Cryonics* magazine.[5]

A common denominator in our research and writings has been the recognition that chemical preservation may constitute a viable alternative to cryopreservation on a theoretical level but that scientific and practical considerations strongly support cryopreservation for the stabilization of critically ill patients. In this article we will further explore these issues and also respond to some of the recurrent arguments that have been made in favor of chemical brain preservation.

One seemingly paradoxical position that will be clarified in this article is that Alcor aims for better preservation technologies than can be offered through chemical preservation but is also more optimistic about the resuscitation of patients preserved under suboptimal conditions with older cryopreservation technologies.

Suspended animation

What distinguishes the long-term objective of Alcor from chemopreservation proposals is that we are not satisfied with preservation of the ultrastructure of the brain alone. The aim of Alcor is to keep the patient viable by contemporary medical criteria as far into our procedures as possible.[6] There are a number of reasons for this choice.

The most important of these reasons is that restoring function after reversal of our procedures is the most credible test of the efficacy of our procedures. We are reluctant to settle for preservation of ultrastructure alone because this goal can always trigger objections that we are failing to preserve crucial identity-encoding parts of the brain. This is not just a theoretical concern. Recent discussions about chemical preservation of the "connectome" (pattern of connections between brain cells) have made it quite evident that absent functional recovery of the brain, there is no shortage of arguments that seek to show that chemical preservation will fail to produce the desired outcome. Some of these arguments invoke rather unorthodox views about how memory is encoded in the brain (such as the necessity of locking neurotransmitters in place).[7] However, absent a test showing that memory is preserved after reversal of the preservation procedure, we will not be able to progress beyond a debate in which different perspectives compete without empirical resolution.

Another important reason why Alcor seeks to maintain viability of the brain as far downstream as our capabilities and resources permit is that we view cryonics as an extension of contemporary medicine and allowing unnecessary damage would contradict this perspective. Contemporary chemopreservation methods depend on extensive cross-linking of proteins and this cannot be reversed by contemporary

"Obviously brain preservation technologies based on methods used to prepare tissue for electron microscopy (chemical fixation, staining and embedding) have a natural advantage when the evaluation method is electron microscopy."

medical technologies. In a sense, one could argue that chemopreservation has to "kill" the brain to preserve it. Although even in "ideal" cryonics cases we are not yet able to sustain viability throughout all parts our procedures, Alcor's research efforts and resources are dedicated to attacking this limitation from all angles (rapid cooling during stabilization, development of low toxicity vitrification agents, intermediate temperature storage, etc.).

Yet another argument of seeking reversible preservation procedures is that we want to minimize the time the patient has to be retained in low temperature care. The shorter the period the patient has to be maintained in biostasis the less risk there is that social and financial challenges will force cryonics providers to discontinue care of their patients. Another benefit of minimizing injury prior to long term care is that earlier resuscitation may reduce the amount of alienation for the resuscitated patient.

Finally, a more general argument can be offered in favor of this approach. The conventional case for cryonics rests on the expectation that we (a) can cure the terminal disease the patient suffered from prior to cryopreservation; (b) will have available credible rejuvenation technologies to prevent the patient succumbing to another age-associated illness; and (c) will be able to repair the damage associated with the cryopreservation process itself. Since most of the scientific skepticism concerns the damage being done by biostasis methods themselves, eliminating this form of damage would further strengthen the case for human cryopreservation.

Reversible cryopreservation would constitute true suspended animation for humans. At Alcor we believe that a credible cryonics organization should aim for perfecting human suspended animation. If we can achieve reversible cryopreservation, the objection that our patients sustain too much damage in our procedures can be effectively countered and the remaining debate will be about the technical feasibility of rejuvenating the patient and restoring them to good health. As currently conceived chemopreservation is fundamentally incapable of securing viability of the brain and cannot be brought under the rubric of evidence-based medicine.

Our friends in the future

A common objection to cryonics has been that future generations may have little interest in resuscitating cryopreserved patients. At Alcor we do not want to rely solely on the goodwill of future generations and we have set a substantial amount of funding aside to deal with this issue ourselves. Still, the first thing we should recognize, as former Alcor President Michael Darwin has pointed out,[8] that friendship should come from both sides. Preservation technologies that transfer many challenges and puzzles to people in the future may not make us many friends. If the term "friends in the future" has any meaning at all it should require minimizing the burden on future generations and even provide them an incentive for wanting to resuscitate us. This understanding informs Alcor's decision to offer the best procedures possible and not to send off a compromised brain to an unknown future based on just a series of logical arguments.

Limits of connectome preservation

How do we know if our procedures are good enough? As discussed above, if we can demonstrate that a person (or relevant animal) can survive our procedures intact without loss of identity and memory, this will inspire confidence. But how can advocates of chemical preservation of the connectome know that what they are doing is good enough?

If one confines oneself to structural preservation of the connectome, it is always possible to object that "just" preserving the connectome is not enough. One could argue that we also would need to preserve detailed information about all different kinds of neurons, the molecular state of synapses ("synaptome"), ion channels, microtubules, neurotransmitters, extrasynaptic interactions and so forth. The most extreme position would be to argue that for meaningful brain preservation complete preservation of the brain (or a molecular brain scan) would be required. Now some of these objections can be countered by arguing that the biochemical basis for brain functioning and short-term memory does not need to be preserved to preserve the individual. But such arguments may not completely satisfy critics who believe there is more to identity preservation than the connectome. Without functional tests, biostasis proposals will remain a source of criticism for people who want more robust empirical corroboration for the efficacy of the proposed procedures.

The prevailing proposal is to subject an experimental animal brain to a series of procedures and then re-construct the brain through 3D imaging technologies. And here is where we think there is a formidable challenge for chemical preservation. Because functional tests are not possible in cross-linked brains, the only available reference for looking at the efficacy of chemopreservation is to compare the results of this procedure against images that have been obtained through chemical preservation as well! Granted, electron microscopy has taught us a lot about brain anatomy but we cannot say for sure whether the procedures employed to prepare specimens for electron microscopy (irreversibly) damage specific areas of the brain that are crucial for memory and identity. In neural cryobiology, on the other hand, it is possible to subject the cryopreserved brain tissue to both a viability test and (subsequently) to ultrastructural examination.

The response of people advocating chemopreservation as a means of personal survival is to supplement their arguments with a substantial amount of philosophy to make their point. But philosophical arguments are no substitute for empirical evidence and the only empirical evidence that will be persuasive to critical observers is to seek functional recovery. Absent that, cynics will continue to invoke the existence of some "platonic" fragile brain that no preservation technique can salvage.

The Brain Preservation Technology Prize

In 2010 the Brain Preservation Foundation established the Brain Preservation Technology Prize. The Prize seeks to validate chemical preservation and/or cryopreservation of the brain for personal identity preservation, and develop protocols to apply these technologies to large mammalian brains. Although the Prize is open to both chemical and cryobiological preservation methods, the endpoint for evaluating the quality of preservation involves advanced 3D electron microscopic imaging techniques. Obviously brain preservation technologies *based* on methods used to prepare tissue for electron microscopy (chemical fixation, staining and embedding) have a natural advantage when the evaluation method *is* electron microscopy. Cryopreservation methods are at a comparative disadvantage because they are designed to achieve different preservation objectives than preparation for electron microscopy. To succeed, Prize competitors using cryopreservation must successfully load cryoprotectant chemicals into a whole brain, cool to cryogenic temperatures, unload cryoprotectant chemicals, and then still perform the chemical preservation steps necessary to prepare tissue for electron microscopy. An advantage cryopreservation has is that Prize officials are permitting cryopreservation competitors to perform the chemical preservation steps on small tissue pieces after whole brain cryopreservation.

A specific concern for Brain Preservation Technology Prize competitors using cryopreservation is that cryopreserved brains are currently very dehydrated. Due to this dehydration, which typically persists even after cryoprotectant removal, it is not yet clear that cryopreserved brains can be effectively evaluated by the Prize organizers. To be specific, the criterion for success is preservation of the connectome, which requires two things: preservation of synapses and preservation of enough information to infer the pattern of connections between them. Neural cryobiology researchers believe that they can achieve good ultrastructural preservation of the brain but dehydration compactifies the neuropil, reduces space between structures, and makes the tissue so dark in the electron microscope that it is hard to actually observe the synapses. So if a quick scanning method doesn't discern all synapses that are actually there, it will fail. There are techniques for doing electron microscopy at cryogenic temperatures in the vitrified state, but these depend on the tissue being sliced *before* vitrification. Making slices out of a whole vitrified brain while vitrified is a tough problem. It is easier to make thin slices out of a whole brain that's been turned into solid plastic because the resin used is designed for being cut into thin slices for microscopy. So plastination has a natural advantage in this competition — in terms of processing for the tests rather than in actual results.

We have no doubt that the designers of the prize sought to design a neutral prize, but it is challenging to develop a prize that is truly neutral in term of evaluation. For example, if the prize used viability as a criterion, cryopreserved brains would be at a great advantage. In fact, the effects of using aldehydes and powerful oxidizers would render the chemopreserved brains dead by even the most charitable functional criteria. It is our belief that a prize that aims to corroborate the case for personal survival technologies should embrace both ultrastructure and viability.

What is plastination?

While the term chemopreservation has been used to describe the idea of chemical fixation as an alternative to cryopreservation, many proponents of the idea of chemical brain preservation use the more narrow term 'plastination.' Plastination is usually described as a technique first developed by Gunther von Hagens in 1977 to preserve body parts for anatomical or educational purposes. This is a rather "harsh" technique, which requires dehydration by alcohol and *replacement* of the lipids by a polymer. To our knowledge, there are no credible peer reviewed ultrastructural studies of brains plastinated in such a manner.

"At Alcor, we believe that a credible cryonics organization should aim for perfecting human suspended animation."

What most writers have in mind when they use the word "plastination" as a means of biostasis is a procedure in which chemical fixation with an aldehyde is followed by treatment with osmium tetroxide and resin embedding. While previous proposals for chemical brain preservation only discuss the use of fixatives such as formaldehyde to crosslink and immobilize proteins, the addition of osmium tetroxide and resin (plastic) embedding provide greater long-term stability. Osmium tetroxide stabilizes unsaturated lipids in the cell membrane, and replacement of cell water with a solid polymer resin stops diffusion of molecules in a manner similar to cryopreservation. While theoretically sufficient, the empirical sufficiency of these measures for preserving identity-critical information for centuries is not currently known, and may require complex accelerated aging studies. Another reason for including the two additional steps of osmium tetroxide fixation and resin embedding is to prepare the brain for slicing and scanning for resuscitation in the future.

Whatever "plastination" method is chosen, the consequence will be that the brain is rendered non-viable by contemporary medical criteria. In fact, chemical fixation and osmium tetroxide are routinely used with the explicit aim of killing life and irreversibly stopping biochemical activity.

The cost of chemical brain preservation

One of the proposed advantages of chemical preservation of the brain is to be its comparatively low cost compared to human cryopreservation. It can be admitted that an isolated chemically preserved brain reduces long term space requirements compared to a typical Alcor neuropatient. The space saving, however, is modest since the annual storage cost for a neuropatient is only a few hundred dollars per year. A chemically fixed brain can be removed from the skull and may not require a dedicated (low temperature) storage environment. In reality, however, we do not expect most people to be comfortable with the idea of long-term brain preservation without any kind of institutional structure. (Would you want your chemopreserved brain to be sitting unsecured on the shelf of a person who has no contractual obligation or means to protect you and eventually revive you?) So the real cost difference may more reflect reductions in storage space and long-term maintenance than elimination of organizations that protect these brains and initiate resuscitation.

Whether the cost of resuscitation of chemically preserved brains will exceed that of cryopreserved patients will depend on the *method* of resuscitation. If biological or mechanical cell repair machines are used to restore function, the costs of chemopreservation may actually be higher because the informational and logistical requirements of restoring a brain to its *pre*-cross-linked state may be even more daunting than that of a "straight frozen" brain. An alternative for brain repair is to slice the brain, scan it, and upload it to a computer. Such a revival scenario may be substantially less expensive than repairing a cryopreserved brain but it cannot be taken for granted that such revival attempts will constitute meaningful resuscitation of the individual. In addition, this method, destructive mind uploading, is possible for cryopreserved brains as well.

The expected cost of preparing the brain for long term chemical preservation cannot be separated from the issue of acceptance of the procedure. If chemical brain preservation is not accepted by mainstream medicine it will not be available as an elective hospital-based procedure. Like cryonics, chemopreservation should be practiced as a form of emergency medicine. As such, it will require the same kinds of "standby" and "stabilization" procedures to prevent post-arrest deterioration of the brain. In cryonics, professional teams capable of performing stabilization procedures rapidly and effectively cost tens of thousands of dollars to bring to the bedside. The cost to deploy teams to restore circulation and perfuse solutions after clinical death would be no different for chemical preservation, and they would be even more critical for preservation to be successful.

An additional complication for chemical brain preservation is the toxicity of the necessary chemicals to the team and surrounding personnel. In simple terms, chemicals powerful enough to bind and inactivate biological molecules must by their nature be very reactive and toxic to living people. (This is in contradistinction to chemicals used for cryopreservation, which are practically innocuous by comparison.) The initial steps of chemical preservation require perfusion with aldehyde fixative chemicals such as formaldehyde, glutaraldehyde, or acrolein. Even fumes of these chemicals at low concentration are powerful irritants to eyes and lungs. They could not be used in an ordinary hospital room or hospice setting. (Being similar to embalming fluid, aldehyde fixatives could possibly be used in a mortuary.) After initial stabilization with aldehyde fixatives, a chemopreservation patient would have to be transported to a dedicated facility for treatment with even more toxic chemicals such as osmium tetroxide and plastic resin monomers. Osmium tetroxide is a volatile and extremely powerful oxidizer, and epoxy resin monomers are mutagenic carcinogens. In addition to being very dangerous, these chemicals are also expensive and would bring the costs of chemical brain preservation closer to the costs associated with vitrification solutions in cryonics.

If chemical brain preservation were to be accepted as a routine hospital-based procedure, costs would be reduced because of economies of scale and the reduced need to deploy standbys and stabilize patients in the field. However, it is doubtful that one form of preservation would be accepted and the other would be rejected. As a consequence, if acceptance would reduce costs, this would happen to both chemical preservation and low temperature preservation of the brain.

The no-reflow phenomenon

One of our biggest concerns about offering chemopreservation as a practical means of stabilizing critically ill patients is that if the procedure is practiced in non-ideal circumstances, the effects could include progressive decomposition of brain tissue *despite* chemical fixation. In terms of tolerance of warm and cold ischemic delays, chemopreservation is a lot more demanding. Since the 1960s it has been recognized by many biomedical researchers that even short periods of warm circulatory arrest can produce perfusion impairment in the brain.[9] Any credible chemopreservation proposal requires access to the vessels of the patient. This means that in the case of delays due to warm and cold ischemia, there will be incomplete distribution of the fixatives. In fact, the recognition of this challenge is a standard part of textbooks on preparing specimens for electron microscopy.

Ischemia-induced "no-reflow" is a problem for both chemopreservation and cryopreservation, but even more so for chemopreservation. In the case of cryopreservation, incomplete distribution and equilibration of a cryoprotectant can produce ice formation, but long term care at cryogenic temperatures will stabilize the tissue with no further degradation. In the case of chemopreservation, the absence of low temperatures could permit ongoing degradation of poorly fixed and embedded tissue.

While it is possible that resin embedding (solidification) would halt autolysis, the ischemia- induced perfusion impairment that prevents complete distribution of aldehydes would also prevent adequate perfusion of the organic solvents and monomers for resin embedding. (Whether resin embedding could be achieved by perfusion even under ideal conditions is still an open question.)

Chemopreservation as emergency medicine?

Even if chemical brain preservation would be accepted as a routine hospital procedure there will still be many cases in which this procedure will have to be applied on short notice outside of the hospital or after long delays. For example, people can experience sudden cardiac arrest in the street, die in their sleep, or be involved in a traumatic accident in a remote area. In these circumstances chemical preservation will have to be conducted after a (prolonged) period of circulatory arrest. As discussed above, delayed chemical fixation will most likely fail to completely fix all areas of the brain as a consequence of perfusion impairment. This major inadequacy of chemopreservation leaves cryopreservation as an irreplaceable biostasis technology for cases of unexpected cardiac arrest. ***Cold is the only biostasis-inducing agent that can rapidly penetrate tissue regardless of its state of injury.***

Practicing chemical fixation as emergency medicine raises another complex logistical issue. One part of the procedures is to perfuse the brain with the dangerous chemical osmium tetroxide (or any other oxidizing agent that can stabilize lipids). We wonder whether it is possible to establish a protocol that would permit a safe environment to conduct this procedure in the field. While it is true that osmium tetroxide does not necessarily need to be administered in the field, and aldehyde fixation would buy enough time to transport to dedicated facilities, even the practice of emergency aldehyde fixation would create much greater health hazards than the practice of remote blood substitution in cryonics, or even field cryopreservation. As far as we are aware, even the most "toxic" solution used in cryonics (the vitrification agent) is less dangerous than the least toxic solution (formaldehyde and/or glutaraldehyde) envisioned for chemopreservation.

Solid state chemopreservation is not applicable to human brains at present

The clinical application of chemo-preservation is still hypothetical because technology for fixing and plastic embedding whole human brains doesn't exist yet. At the time of writing, the chemopreservation technology competing for the Brain Preservation Technology Prize uses external diffusion to introduce osmium tetroxide and resin into a mouse brain by soaking it in various solutions for more than 250 hours. Since diffusion time varies as the square of distance, a similar soaking protocol applied to a human brain would require six years. As a practical matter, such a protocol would almost certainly fail because of resin polymerization during the long soaking time. Rather than diffusion, perfusion protocols that circulate all chemicals through the vascular system appear essential for solid state chemopreservation of large mammalian brains. Such protocols have yet to be developed, and face considerable obstacles of viscosity and blood-brain barrier penetration.

The "Prehoda fallacy"

The impossibility of conducting functional assays in chemically preserved brains is one of our concerns and reflects our aim to develop technologies that are reversible with contemporary technologies. On the other hand, a dominant perspective in the advocacy of chemical brain preservation is that perfect preservation is a necessary condition for medical acceptance of cryonics or chemopreservation.

One of the most prevalent objections to cryonics among the educated public and scientists is that absent proof of reversible cryopreservation cryonics should not be offered to the public. One of the most outspoken representatives of this kind of reasoning was the author Robert Prehoda. In 1969 Prehoda published the book *Suspended Animation: The Research Possibility That May Allow Man to Conquer the Limiting Chains of Time.*[10] In this visionary book, he covered a variety of means to extend the maximum human life span including, but not limited to, chemical anabiosis, human hibernation, suspended animation, and controlling the aging process. Despite his participation in the 1967 cryopreservation of James Bedford (who is still a patient at Alcor) he was opposed to offering cryopreservation before the technology was perfected. He reiterated this stance in a 1969 interview in which he said: "I am still opposed, as I was before Dr. Bedford's death, to freezing people at the present time because this money should be spent on research. Any human freezing is premature and without scientific basis until a mammal can be revived from the frozen state."[11]

Prehoda's objection to offering cryopreservation continues to be made in either a strong or a weak version. In its strongest form it is argued that it is not "scientific" to offer cryonics services as long as reversible cryopreservation of a whole mammalian organism has not been demonstrated. Such claims are often presented in the form that there is no scientific "proof" that cryonics will work. A weaker version of the argument also exists in which it is claimed that without evidence of reversible cryopreservation the general public and scientists have good reason to reject it.

These views rest on a fundamental misunderstanding of the rationale of cryonics and do not recognize the distinction between the objective of science and the objective of medicine. The objective of science is to generate knowledge about the physical world by testing hypotheses. The objective of medicine is to treat people (or non-human animals) by using the best knowledge from science and practical experience available. Medicine is inherently "messy" because it cannot avoid acting on incomplete information in conjunction with a (subjective) assessment of risk. For example, if a person is in overall good health most people would not support subjecting this person to an experimental treatment with potential severe adverse effects for a minor illness. On the other hand, if a person is born with a highly lethal single gene mutation, more risky experimental treatments could be justified. What distinguishes cryonics from conventional medicine is not decision making under uncertainty but the temporal separation of stabilization and treatment.

Evidence-based medicine is inherently conservative and the idea of cryonics extends this conservatism to end-of-life decisions. The fact that society has exhausted all means of curing critically ill

patients does not mean that future medicine will not be able to treat this patient. The objective of cryonics is to ensure that a patient is stabilized to reach that future with as little additional damage as possible. The fact that current cryopreservation methods are not reversible and cause (additional) damage cannot be used as an argument against this reasoning because the argument that treatments may be available for presently terminal illnesses can also be extended to cover the damage associated with the cryopreservation process. The "Prehoda fallacy" consists of not recognizing the point that a procedure that aims to take advantage of *future* developments in science by definition cannot be experimentally demonstrated by *contemporary* science. Exercising our best judgment in this matter is neither "scientific" nor "unscientific" although one can question whether the reasoning involved is coherent or not.

This of course does not mean that science should not play a role in making such decisions. Certainly it should. The cryonics proposal can be submitted to the test of whether it contradicts known laws of physics or exceeds realistic computational abilities required for cell repair. More specifically, reasonable expectations about future medicine can be strengthened by improvements in cryopreservation or cell repair technologies. And, of course, we can generate experimental evidence to choose between alternative biostasis methods such as the use of cold temperatures or chemical fixation. But ultimately, cryonics cannot be "proven" in the conventional sense of the word because if all components of the proposal (curing the terminal disease, reversing cryopreservation, and rejuvenation) could be demonstrated now, cryonics would be redundant. We can make efforts to minimize this element of uncertainty but eliminating it completely may never be possible as there may always be diseases and traumatic insults that contemporary technologies cannot treat. In this sense, the acceptance of uncertainty in conjunction with reasonable expectations about future technological development is an intrinsic element of cryonics.

The reason why we highlight this fallacy is that we have observed a milder form among advocates of chemical brain preservation. Although lip service is being paid to the rationale of cryonics, the argument seems to be that technical feasibility is an important reason for scientists to reject cryonics. Such a perspective seems quite reasonable but it fails a basic reality check. Most scientists who comment on cryonics in public have made little effort to educate themselves about the procedure and often make uninformed statements about cryobiology and the ultrastructural effects of cerebral ischemia that even contradict the established knowledge in those fields of research. And when cryonics organizations introduce new procedures (such as vitrification) that aim to eliminate a scientific objection, the criticism simply moves to another part of the procedure. The residual element of uncertainty that characterizes cryonics can always be exploited to claim that the procedure lacks scientific proof. Eliminating ice formation or fracturing, or demonstrating preservation of the connectome will not satisfy critics who use these kinds of arguments to shield more subjective psychological and social objections to cryonics. Successful preservation of the connectome may win over some doubters but it is not likely that it will move chemopreservation and/or cryonics into the mainstream until these psychological and social objections can be effectively countered.

"Cold is the only biostasis-inducing agent that can rapidly penetrate tissue regardless of its state of injury."

What constitutes preservation?

Insistence on demonstrated preservation of the connectome as a condition for offering a bio-preservation method to the terminally ill could backfire. Actually, we don't know if the connectome is either necessary *or* sufficient. As long as it, and whatever else that is essential, if anything, can be *inferred* from the preserved brain (and the rest of the body) restoring the original healthy state should be possible.[12] This argument does not just apply to biostasis procedures that introduce known and predictable forms of damage but also applies to any patient who suffers some degree of ischemia prior to preservation. In fact, a perfect preservation of an ischemic brain might be classified as not being successful if it does not conform to the preservation of the connectome of a control brain. But whether this dooms such preservations to failure depends on whether the original state can be inferred from what was preserved, which itself is a function of the degree and duration of ischemia.

We believe that a research program aimed at demonstrating under which conditions the original structure can be inferred from the injured brain could be at least as persuasive as a program to demonstrate successful preservation of the connectome of non-compromised brains. Demonstrating the scope and limits of such reconstructions will also corroborate the premise of cryonics that using a preservation technique that itself adds damage is not necessarily a dead end provided there is systematic knowledge of how this preservation method alters the structural and functional properties of the brain.

Neural archeology and suspended animation

There is a wide gap between the aim of moving toward reversible human cryopreservation and the state of the brain of many cryopreservation patients. It might be tempting to conclude that a commitment to developing true human suspended animation implies a pessimistic outlook on the prospects of resuscitating patients that were preserved under suboptimal conditions with older technologies. In our view, such a perspective ignores the important point that one can aim for the best preservation technologies possible but at the same time hold that advanced "neural archeology" might be able to infer the original state from a brain with severe damage.[13] What makes Alcor's perspective unique is that we share both the belief that our procedures should be subjected to the most rigorous testing possible with the goal of perfecting

preservation technologies but that we also recognize that our understanding of the limits of "inferability" will remain incomplete as long as our scanning, computational, and repair technologies evolve. There is no question that providing the best technologies that we can offers the best prospects of resuscitating our patients in the future but this argument cannot be used to categorically claim which patients are beyond repair and which are not.[14] In our opinion, the perspective that informs many advocates of chemopreservation sets the bar too low and too high.

Are there advantages to chemical brain preservation?

One of the envisioned advantages of chemopreservation over cryopreservation is that plastinated brains do not require continued maintenance or even organizational continuity. This may be true but there are a number of qualifications that need to be discussed. As discussed above, this advantage only applies to brains that were preserved under ideal conditions. In non-ideal conditions, the brain will most likely experience regional or global autolysis over time. Strictly speaking, we do not even know anything about the fate of well-preserved brains after very long periods of time and it might still be the case that even these brains benefit from storage at low (non-freezing) temperatures.

While it is technically feasible that such brains do not need a permanent storage facility like cryonics patients, it is hard to imagine chemopreservation being offered without the existence of an organization that is committed to the fate of such patients and maintains sufficient funding for future resuscitation attempts.

It cannot be denied that cryopreservation patients require ongoing replenishment of liquid nitrogen to keep them at low temperatures but this does not mean that cryonics patients would be adversely affected by short interruptions of liquid nitrogen deliveries. Calculations at Alcor predict that it will take at least three months of non-delivery of liquid nitrogen before the brains of patients would start dangerous warming. If such a scenario is due to supplier unavailability (such as a refusal to

Resin Embedding of Mouse Brains

In 2012 a group from the Max-Planck Institute for Medical Research in Germany published a method for resin embedding an entire intact mouse brain suitable for electron microscopy*. This group is also one of the announced competitors for the Brain Preservation Technology Prize. Their recently-published method may qualify for the Stage 1 (small brain) portion of the Prize.

They achieved a technical tour-de-force because a mouse brain is much larger than the tiny milligram size previously required for tissue pieces to be prepared for electron microscopy. However their basic approach is still the same as traditional methods for preparing small tissue pieces. First, proteins are chemically fixed by perfusing an aldehyde solution through the whole animal. Second, the brain is removed and then soaked in solutions containing osmium tetroxide to fix and stain membranes. Third, the brain is soaked in organic solvents to replace water. Finally the brain is soaked in solutions of resin monomer molecules that eventually polymerize, turning the tissue completely solid.

Except for the first protein fixation step, this approach relies completely on passive diffusion (soaking) rather than perfusion. According to the paper, to resin embed a mouse brain, the time required for the soaking steps is:

5 x 8 hours (buffer rinses)
3 x 48 hours (wbPATCO osmium stain)
4 x 12 hours (acetone dehydration)
3 x 12 hours (resin monomer infiltration)
---
268 hours total

Calculation of the time that theoretically would be required to perform these steps on a human brain is sobering. A human brain is 1500 grams / 0.5 grams = 3000 times more massive than a mouse brain. Taking the cube root of 3000, that translates to 14 times greater diameter than a mouse brain. Using the rule that diffusion time scales quadratically with distance, the extrapolated preparation time for a human brain would be

14 * 14 * 268 hours = 52,528 hours

which is six years. In practice, the process would likely stop early in the resin soaking phase as monomers polymerized in the outer layers of the brain, increasing viscosity and preventing deeper infiltration.

Development of fundamentally new technology – technology using perfusion for all phases – is required before resin embedding can be seriously considered for biostasis of large mammalian brains.

*S. Mikula, J. Binding, W. Denk, Staining and embedding the whole mouse brain for electron microscopy, Nature Methods, published online 21 October 2012; doi:10.1038/nmeth.2213

deliver to Alcor) Alcor could purchase and transport liquid nitrogen from elsewhere, start producing liquid nitrogen itself, or (temporarily) switch to other means of maintaining cryogenic temperatures.

In case cryonics patients cannot be maintained in dewars at all, emergency chemopreservation will be an option. This can be achieved by either perfusing the formerly cryopreserved patients or by slicing the brains and using passive diffusion to chemically fix them.

The most negative scenario would be a prohibition of cryonics and forced burial of patients. While not impossible, it is doubtful that in such an environment chemically fixed brains will be permitted to exist. Both cryopreservation and chemopreservation would have to continue as underground operations.

preservation that identified mechanical or biological cell repair technologies as the means of resuscitation. What is unfortunate about the almost exclusive focus on mind uploading is that it not only requires potential supporters to take seriously the idea of chemical preservation of the brain but also commit to the idea of substrate independent minds.

It is no surprise that the defense of mind uploading depends on mainly philosophical arguments because at this point these are the only *possible* arguments to defend it. While the arguments in favor of mind uploading deserve critical scrutiny, we think that ultimately the feasibility of this approach is an empirical matter and cannot be settled by thought experiments or analogies.[15] For example, both proponents and skeptics of mind uploading accuse each other of not being consistent "materialists."

than chemical brain preservation, we strongly support any technologies that draw attention to the inadequacies of contemporary practices surrounding death. Throughout history the medical definition of death has been subject to continuous revision as medical and resuscitation technologies have advanced.[16] There can be no doubt that many people who are written off by today's medicine will simply be considered critically ill in the future.[17] Both cryonics and chemical brain preservation constitute a means to stabilize patients to reach that future. In the coming years we may see additional proposals to stabilize critically ill patients such as "room temperature vitrification" or biostasis induced by advanced nanotechnology. Clearly, the idea that death should be defined relative to today's medical capabilities is no longer adequate and needs to be replaced

"Even the most "toxic" solution used in cryonics (the vitrification agent) is less dangerous than the least toxic solution (formaldehyde and/or glutaraldehyde) envisioned for chemopreservation."

Chemopreservation and mind uploading

One of the lessons that we have learned in cryonics is that it is not helpful to make the idea more controversial than necessary. Cryonics (or chemical brain preservation) is already controversial enough on its own and we do not see the benefit of associating it with ideas such as immortalism, transhumanism, mind uploading, or any political ideologies. This is not just a strategic or public relations consideration but reflects our view of offering cryonics as a form of experimental critical care medicine.

In many ways the promotion of chemical brain preservation has been characterized by many of the PR mistakes that characterized the beginning of cryonics. In particular, we are concerned that, instead of remaining agnostic about resuscitation methods including mind uploading, chemical brain preservation is now closely associated with this one method.

There is something decidedly *ad hoc* about this association. One could just as well imagine a campaign for chemical brain

In fact, by subjecting the preservation method to empirical scrutiny but using philosophical arguments to corroborate the resuscitation method, we think that the Brain Preservation Foundation conveys a mixed perspective about validation of personal survival technologies. The kinds of cell repair technologies that are envisioned for the resuscitation of cryonics patients are highly advanced, but do not require a shift in thinking about human biology and identity. Mind uploading, on the other hand, is neither conceptually necessary for resuscitation of chemically preserved brains nor does it constitute an appealing idea to gain more support for chemopreservation.

Toward a new definition of death

In this article we have critically investigated the claims in favor of chemopreservation, and its (envisioned) advantages over cryopreservation. While, everything carefully considered, we believe that cryopreservation is more suitable for robust scientific validation and presents a more versatile, practical, and safe option

by a concept of death that recognizes that clinical death can only be considered irreversible if identity-critical information has been erased beyond recognition.[18] ■

This article greatly benefited from the encouragement and contributions of Max More and Brian Wowk. I also want to thank the Alcor R&D Committee for carefully reviewing earlier versions of this article.

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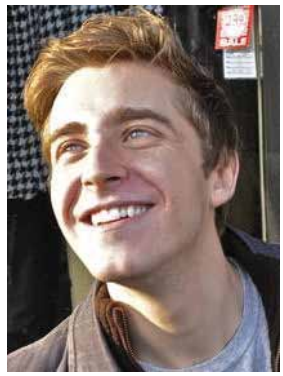
RETRACTION

The original paper version of this article included the results of an experimental model to understand the effects of ischemia on perfusion fixation of the rat brain. Subsequent comments and questions prompted me to omit them from the current (online) version because these results raise complex methodological issues about modelling perfusion fixation of the ischemic human brain in a rat model and I believe that those cannot be done justice without changing the nature of the article. The author wishes to convey that these results are part of an ongoing research project and using them as an illustration of the potential consequences of conducting perfusion fixation in the ischemic human brain would be premature. Excluding these preliminary results does not affect the general arguments made in this article and restores its intended aim as an opinion piece. Omitting them should not be interpreted as an endorsement of the idea of perfusion fixation of ischemic human brains as a life extension strategy.

IN PERPETUITY



WHO SPEAKS FOR THE DEAD?

By Keegan Macintosh

Do the dead have rights, *in the proper sense of the word?* That is to say, when someone is obligated to do something with a dead person, like bury them, for whose benefit are they doing it? *For the dead?* Or for the living?

You might well ask, is this really important? In short, yes. The person to whom the obligation is owed is the person who may sue for enforcement of that right, and their identity may also *determine the remedies* which are available to them (be it money, compulsory performance of or abstinence from a particular act). So, the question of whose rights are engaged in dealing with the dead is fundamentally important from the cryonics patient advocate's perspective.

An illustration: If you make a contract with someone, both of you intending that a substantial portion of what you have promised to do will only be done after (and in fact as a result of) your legal death, and vice versa that a substantial portion of what they have promised to do will likewise only be done after your legal death: who has promised what to whom?

While you remain alive, the answer seems quite obvious. But once you are dead, you are no longer a person. You, sadly, are not an entity recognized by law. You are your estate. Your estate has legal personality of a kind, but it is probably better to think of your estate as a medium. And, as such, it really isn't about you anymore — it's about your stuff, and who gets it. Yes, you can (and should, and hopefully do) have a will that references your cryonics arrangements, but practically speaking, the interest that your estate has in that contract you made for things to be done for you after you died, is the fact that something about that contract could result in more stuff for the estate's beneficiaries. That's really all the estate can care about, because the real, live person who was capable of having immaterial (or better still, "non-pecuniary") interests in the contract is now gone.

But wait? How can the cryopreservation agreement (cat's out of the bag — that contract was about cryonics after all) result in more stuff for the estate? Your cryonics service provider *(CSP)* didn't promise to give anything, or pay anything. You, the patient promised to give something, and in fact cleverly entered into other contracts with other people to automatically transfer money to your CSP upon your legal death. So how could the cryopreservation agreement possibly represent a source of "stuff" for the estate? Well, that's because there were really two layers of promises — two sets of obligations in *every contract. The top layer,* or primary obligations, are what you actually bargained for. The secondary obligations are what the other party must do (or rather, pay) if they do not perform their primary obligations. These secondary obligations are the damages, and they are a part of the contract from the very beginning without anything being written about them.

So, the potential pecuniary ($) interest your estate has in the cryopreservation agreement, since your estate is just a medium that can only really have an interest in things and stuff, is in the *failure* of your CSP to do what it promised to do for you. And unfortunately for you, in cryonics there are no do-overs.

Hence why it is important to know who speaks for you when you are dead. The beneficiaries of your will, however friendly to your arrangements and well-intentioned they are, have no vested, personal, legal interest in the CSP's performance of its primary obligations to you under the cryopreservation agreement. The executor of your will, on the other hand, has certain obligations to carry out promises made by you when you were alive, and (sometimes) to ensure that your body is dealt with as you directed by will or other instrument. The executor may even have an obligation to ensure that you *remain* interred as directed. But how long must they keep vigil? When they, too, are dead, does their executor now watch over the both of you? At a certain point (if not right away) this clearly becomes

impossibly impractical. Alternately, if your CSP's custody of your body was effected by a consent to body donation for research (which is the more robustly enforceable method, generally), even your executor has essentially no standing with respect to your body. And this is good, because above all else we trust that our CSPs want the same thing we want — and I have no reason to believe that is anything but true. But what if, someday down the road when your executor and next-of-kin are now in the dewar next to you, your CSP's performance dips demonstrably below the threshold of "good faith best efforts"? Is there anyone who can claim authority to move you or to enforce performance of your CSP's primary obligations under the cryopreservation agreement?

The above is not an exhaustive analysis by any measure. I write it hoping only that it will illustrate how peculiarly vulnerable cryonics patients are under the laws currently applying to them. What I plan to do with this column is explore intersections of law and cryonics & life extension (and there are many), and one theme I expect to visit frequently is cryonics patient advocacy. This is the issue of "who speaks for the dead" adverted to above, though in truth it starts long before legal death, and is more about how the dead or incapacitated can speak for themselves through legally recognized documentary evidence of their intentions: wills, trusts, powers of attorney (financial and health care), advance directives, consents to body donation, etc. However, all of these need agents to carry them out, and others still may seek to tear them down, so the more complex questions deal with how to build checks and balances into your supplementary cryonics documents and otherwise incentivize compliance of possible threats.

One specific topic I plan to look at soon: Just how uniform is the Uniform Anatomical Gift Act in its implementation by the various States? Are body donation consent forms executed under the authority of the UAGA enforceable outside America?

Another, somewhat related question: If a cryonicist executes a valid will in Oregon, moves to California, and dies there without executing a new will, but the original will does not comply with the formalities of execution applying in California, is the will valid — and if so, is it valid for all purposes, or only some? This is the domain of private international law, aka "conflict of laws," which refers to how one legal jurisdiction deals with foreign legal elements: foreign parties, parties asking for application of foreign law, or foreign judgments. This is a particularly complicated area, but one which cannot be ignored, since so many cryonicists do not live in the same legal jurisdiction as their cryonics organization.

Another theme I will be exploring in this column is access to cryonics and other forms of life extension. In the case of cryonics, impediments to access can take the very blatant form of a law directly prohibiting it, or essential procedures thereof, or else operate indirectly, like mandatory autopsy provisions. Access to cryonics is also context-specific — taking on a very different meaning for someone diagnosed with a brain-threatening disorder, for instance. As such, the availability of legal assistance in dying is a topic which might be dealt with under this heading, and whether the practical benefits accruing to those patients outweighs the risks, both individually and to cryonics generally. How the law defines death, and public policy debates over whether to move to new definitions for reasons quite separate from cryonics, also fall neatly here.

Access to life extension, more generally, is also interesting to examine from a legal perspective. Are the current models of regulation applying to drug development sufficiently flexible to accommodate the advent of SENS-type rejuvenation therapies? One could say that cryonics aspires to being ordinary health care someday, at which time we can expect that it will be subject to some form of regulation. What should it look like? And how can cryonics organizations today best self-monitor and self-regulate to ease that eventual transition?

Finally, constitutional rights instruments have immense potential as tools for securing meaningful access to cryonics and other forms of life extension. However, the content and implementation of these fundamental rights documents vary throughout the world. Cryonics has fairly deep roots in America, but are we certain there is no better soil on Earth in which it might flourish?

All of the above areas of law overlap and interact, and there are other relevant ones that I have not mentioned (insurance law, notably), and no doubt a few I am not yet even aware of. I also plan to report on live cases of interest, as they arise.

One last, but significant point: due to variations between the laws of different jurisdictions (even within a single nation) you cannot simply assume that paperwork designed to work in one jurisdiction will work as intended in yours. You need to find a cryonics-friendly advisor where you live and have them review your cryonics arrangements, and revise them if necessary to work in your home jurisdiction. You are fighting for your life — you cannot afford to wear ill-fitting armor. ■

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Alcor Member Forums

Discussion board of the Alcor Life Extension Foundation

Discuss Alcor and cryonics topics with other members and Alcor officials.

- The Alcor Foundation
- Cell Repair Technologies
- Cryobiology
- Events and Meetings
- Financial
- Rejuvenation
- Stabilization

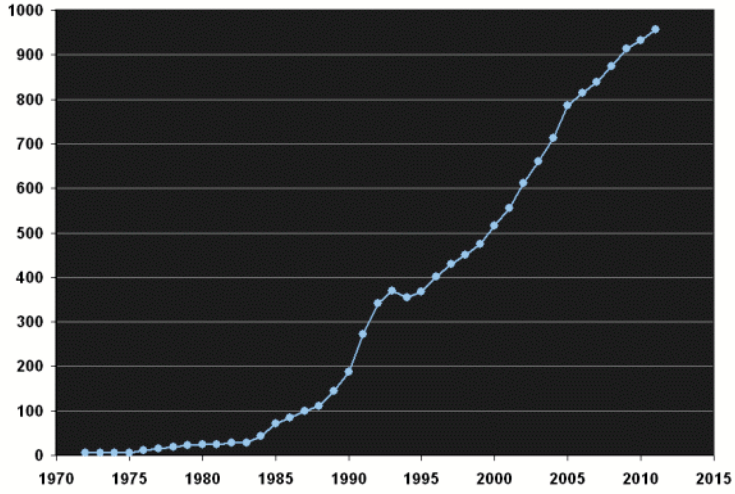
Other features include pseudonyms (pending verification of membership status) and a private forum.

http://www.alcor.org/forums/

Membership Statistics

2012	01	02	03	04	05	06	07	08	09	10	11	12	
Members	956	959	963	967	968	974	974	975	975	982			**982**
Patients	110	110	111	111	111	111	112	112	112	112			**112**
Associate	0	0	0	8	9	13	16	20	21	24			**24**
Total	1066	1069	1074	1086	1088	1098	1102	1107	1108	1118			**1118**

As of October 31, 2012, Alcor had 982 cryopreservation members, 24 associate members, and 112 patients.



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There's no debating the power of **omega-3** fatty acids. From support for **heart health** and **brain function** to help with **inflammation**, their broad-spectrum benefits have been firmly established in a wealth of studies.[1-9]

To ensure the purest, most stable, and easy-to-tolerate fish oil supplement, **SUPER OMEGA-3 EPA/DHA** is *molecularly distilled*. This proprietary technology ensures any environmental pollutants are reduced to extremely low levels. The result? Our fish oil enjoys a **5-star rating** for **purity**, **quality**, and **concentration** from the **International Fish Oil Standards** program (**IFOS**)—the highest possible ranking from the world's *premier* testing laboratory.

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Fish oils (and other fatty acids) have a tendency to oxidize, rendering them nutritionally inferior. Scientific studies show that when added to fish oil, ***sesame lignans*** safeguard against oxidation and direct fatty acids toward pathways that help with inflammatory reactions.[10]

To further emulate the benefits of a **Mediterranean diet**, **Super Omega-3** delivers standardized, high-potency ***olive fruit extract***. Research shows that **fish oil** combined with **olive oil** helps with inflammation better than fish oil alone.[11]

Olive also contains the compounds ***hydroxytyrosol***, ***tyrosol***, and ***oleuropein***. Together these nutrients counter the action of free radicals, delay aging in specialized skin cells, prevent undesirable LDL oxidation, and help maintain normal platelet activation.[12-15]

Super Omega-3 (4 regular size softgels) supplies the equivalent content of **6 tablespoons of extra virgin olive oil**. Take two softgels twice daily with meals.

A bottle containing 120 softgels of **Super Omega-3 EPA/DHA with Sesame Lignans and Olive Fruit Extract** retails for $32. If a member buys four bottles, the price is reduced to **$21** per bottle. If **10 bottles** are purchased, the cost is **$18.68** per bottle. (Item # 01482)

Just one serving of SUPER OMEGA-3 EPA/DHA with Sesame Lignans & Olive Fruit Extract provide:

EPA Pure+™ Extract (eicosapentaenoic acid)	**1400 mg**
DHA Pure+™ Extract (docosahexaenoic acid)	**1000 mg**
Olive Fruit Extract [std. to 6.5% polyphenols (39 mg), 1.73% hydroxytyrosol/tyrosol (10.4 mg), 0.5% verbascoside/oleuropein (3 mg)]	**600 mg**
Sesame Seed Lignan Extract	**20 mg**

A SMALLER SOFTGEL for easier swallowing!

Some members have requested we make **Super Omega-3** available in a smaller capsule for easier swallowing. We have accomplished this by making **half-size** softgels available.

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For those with sensitive stomachs, **Super Omega-3** is also available with **enteric coating** and retails for **$34**. If a member buys four bottles, the price is reduced to **$23.25** per bottle. If **10 bottles** are purchased, the cost is **$21** per bottle. (Item # 01484)

To order the most advanced fish oil supplement, Super Omega-3 EPA/DHA with Sesame Lignans and Olive Fruit Extract (with or without enteric coating), call 1-800-544-4440 or visit www.LifeExtension.com

Ratings based on results of the 2012 ConsumerLab.com Survey of Supplement Users. More information at www.consumerlab.com.

CAUTION: If you are taking anti-coagulant or anti-platelet medications, or have a bleeding disorder, consult your healthcare provider before taking this product.

Contains fish (anchovy, mackerel), sesame, and corn.

Supportive but not conclusive evidence shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.

IFOS™ certification mark is a registered trademark of Nutrasource Diagnostics, Inc. These products have been tested to the quality and purity standards of the IFOS™ program conducted at Nutrasource Diagnostics, Inc.

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MEETINGS

About the Alcor Foundation

The Alcor Life Extension Foundation is a nonprofit tax-exempt scientific and educational organization dedicated to advancing the science of cryopreservation and promoting cryonics as a rational option. Being an Alcor member means knowing that—should the worst happen—Alcor's Emergency Response Team is ready to respond for you, 24 hours a day, 365 days a year.

Alcor's Emergency Response capability includes specially trained technicians and customized equipment in Arizona, northern California, southern California, and south Florida, as well as many additional certified technicians on-call around the United States. Alcor's Arizona facility includes a full-time staff, and the Patient Care Bay is personally monitored 24 hours a day.

ARIZONA

Flagstaff:

Arizona without the inferno. Cryonics group in beautiful, high-altitude Flagstaff. Two-hour drive to Alcor. Contact eric@flagstaffcryo.com for more information.

Scottsdale:

This group meets the third Friday of each month and gatherings are hosted at a home near Alcor. To RSVP, visit http://cryonics.meetup.com/45/.

At Alcor:

Alcor Board of Directors Meetings and Facility Tours – Alcor business meetings are generally held on the first Saturday of every month starting at 11:00 AM MST. Guests are welcome. Facility tours are held every Tuesday and Friday at 2:00 PM. For more information or to schedule a tour, call D'Bora Tarrant at (877) 462-5267 x101 or email dbora@alcor.org.

The Alcor Volunteer Network, Scottsdale Chapter has a variety of meetings on topics including: member education, training, community outreach, and fundraising. To RSVP, visit: http://www.meetup.com/AVNScottsdale/members/

CALIFORNIA

Los Angeles:

Alcor Southern California Meetings—For information,call Peter Voss at (310) 822-4533 or e-mail him at peter@optimal.org. Although monthly meetings are not held regularly, you can meet Los Angeles Alcor members by contacting Peter.

San Francisco Bay:

Alcor Northern California Meetings are held quarterly in January, April, July, and October. A CryoFeast is held once a year. For information on Northern California meetings,call Mark Galeck at (408) 245-4928 or email Mark_galeck@pacbell.net.

FLORIDA

Central Florida Life Extension group meets once a month in the Tampa Bay area (Tampa and St. Petersburg) for discussion and socializing. The group has been active since 2007. Email arcturus12453@yahoo.com for more information.

NEW ENGLAND

Cambridge:

The New England regional group strives to meet monthly in Cambridge, MA – for information or to be added to the Alcor NE mailing list,please contact Bret Kulakovich at 617-824-8982, alcor@bonfireproductions.com, or on FACEBOOK via the Cryonics Special Interest Group.

PACIFIC NORTHWEST

Cryonics Northwest holds regular meetings for members of all cryonics organizations living in the Pacific Northwest.

For information about upcoming meetings and events go to: http://www.cryonicsnw.org/ and http://www.facebook.com/cryonics.northwest

A Yahoo mailing list is also maintained for cryonicists in the Pacific Northwest at http://tech.groups.yahoo.com/group/CryonicsNW/.

British Columbia (Canada):

The contact person for meetings in the Vancouver area is Keegan Macintosh: keegan.macintosh@me.com

Oregon:

The contact person for meetings in the Portland area is Chana de Wolf: chana.de.wolf@gmail.com

ALCOR PORTUGAL

Alcor Portugal is working to have good stabilization and transport capabilities. The group meets every Saturday for two hours. For information about meetings, contact Nuno Martins at n-martins@n-martins.com. The Alcor Portugal website is: www.alcorportugal.com.

TEXAS

Dallas:

North Texas Cryonauts, please sign up for our announcements list for meetings (http://groups.yahoo.com/group/cryonauts-announce) or contact David Wallace Croft at (214) 636-3790 for details of upcoming meetings.

Austin/Central Texas:

We meet at least quarterly for training, transport kit updates,and discussion. For information: Steve Jackson, 512-447-7866, sj@sjgames.com.

UNITED KINGDOM

There is an Alcor chapter in England. For information about meetings, contact Alan Sinclair at cryoservices@yahoo.co.uk. See the web site at www.alcor-uk.org.

If you are interested in hosting regular meetings in your area, contact Alcor at 877-462-5267, ext. 113. Meetings are a great way to learn about cryonics, meet others with similar interests, and introduce your friends and family to Alcor members!

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 a cryopreservation is easy!

Step 1: Fill out an application and submit it with your $150 application fee.
Step 2: You will then be sent a set of contracts to review and sign.
Step 3: Fund your cryopreservation. While most people use life insurance to fund their cryopreservation, other forms of prepayment are also accepted. Alcor's Membership Coordinator can provide you with a list of insurance agents familiar with satisfying Alcor's current funding requirements.
Finally: After enrolling, you will wear emergency alert tags or carry a special card in your wallet. This is your confirmation that Alcor will respond immediately to an emergency call on your behalf.

Call toll-free today to start your application:

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