CRYONICS

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Cryonics 101

An overview for the general public

By Yuri Deigin

Since this is a 101, let's start with the basics. What is cryonics? From a consumer's point of view, cryonics is just *life insurance*. Not the usual euphemism for a payout to one's loved ones after his death, but a method to maximize one's own survival. Or a way to hedge against catastrophic depreciation of your most valuable asset—your life.

From a technological point of view, cryonics is a method of putting an organism on pause – into a state of *suspended animation* – in order for it to be restored back to life in the future. To achieve this pause, cryonics employs cooling of the organism to very low temperatures. Note that cryonics is not the only possible method, just one of them. Maybe in the future science will discover ways of inducing long-term suspended animation without the need to cool the body. But it hasn't yet, and cryonics is presently the only viable and commercially available method.

Why do we need cryonics? The answer is simple. Because our bodies have one unpleasant feature. They die. Nobody likes it, but most people prefer to gloss over the unpleasantness by coming up with various excuses why they need to accept it. A brave few, however, refuse to do so. Instead, they acknowledge the problem and attempt to use science and technology to eradicate it or at least mitigate it. Cryonics is one of the tools such brave people have invented for the benefit of humanity. Other tools you may be more familiar with—defibrillators, heart-lung machines, pacemakers, organ transplants, vaccines and antibiotics. They all stem from the same motivation—increase every human's odds of survival.

Of course, at the present level of scientific and technological advancement, there is no guarantee that anyone cryopreserved today will be restored back to life (or *reanimated*, as per cryonics parlance) in the future. To claim that cryonics guarantees anything would be intellectually dishonest. But what cryonics does provide, unlike any other technology, is a chance of revival. It might be very slim, but a nonzero chance is still better than zero, especially when it applies to an infinitely valuable asset – one's life.

By the way, cryonics can be viewed not only as life insurance, but also as an "ambulance to the future". That characterization might not be of relevance for most of us today, as we are still in decent health, but for some people the question of life and death is a much more urgent issue—people who only have weeks or months to live. They already know that modern medical technology will not be able to save them, so their only hope for survival is medicine of the far future, and cryonics is their only chance to benefit from it.

But enough purple prose, let's dive deeper into the science behind cryonics. What evidence is out there that cryonics can work? Broadly, it can be subdivided into two categories: what we see in nature, and what we see in experiments.

Nature

A great number of our planet's inhabitants can survive subzero temperatures for months. The most numerous are, of course plants, most of which can safely tolerate temperatures from -4°C to -12°C.

Many animals too have evolved the ability to periodically endure exposure to subzero temperatures. I won't list them all, just mention a few survival champions. The most notable is the Siberian salamander (*Salamandrella keyserlingii*) which regularly encounters temperatures as low as -50°C and some claim it is even able to be revived after spending 90 years in the permafrost[1]. Here he is:

SOME PHOTOS HAVE BEEN REMOVED FROM THIS ARTICLE DUE TO COPYRIGHT ISSUES

The second place in the Colder Games goes to another frost-resistant amphibian, the wood frog (*Rana Sylvatica*), which can spend many months in a half-frozen state. Another remarkable animal capable of surviving for months at -20°C as pupae is the cecropia moth

(*Hyalophora cecropia*). It is a large insect, with a wingspan of up to 16 cm. To achieve this feat, Cecropia has developed its own mixture of cryoprotectants, namely a combination of glycerol and sorbitol[2].

Of course, let's not forget about our much closer warm-blooded mammal relative, the arctic squirrel (*Spermophilus parryii*), which can spend weeks in torpor while its body temperature fluctuates between -2 to 5°C. It was shown that it completely shuts off[3] its electric brainwave activity (as do humans who are cooled below 18°C). By the way, this supports the hypothesis that long-term memory, which is the basis of our identity, is encoded in the structure of the brain—neurons, synapses, etc., rather than in its electrical activity.

Humans, by the way, although lacking in cold-resistance ability when compared to the above champion cryonauts, can also successfully survive deep hypothermia. Here are a few well-known examples:

1. Two-year-old Michelle Funk spent more than an hour under ice-cold water. When rescuers found her, her body temperature was 19°C and she showed no signs of life. However, doctors were able to quickly revive her, and were surprised to find that her brain did not show any signs of damage.[4]

2. 1-year-old Erika Nordby spent several hours in the snow at a temperature of -24°C. Her body temperature dropped to 16°C. After 6 weeks in the hospital, she fully recovered and was discharged.[5]

3. American Justin Smith spent 12 hours in the snow at a temperature of -5°C. Paramedics who found him declared him dead, but the ER doctor did not agree and began to carry out resuscitation. After half an hour, Jusin's heart resumed beating. Doctors believed that Smith's brain was severely damaged, but that proved not to be the case, as Justin fully recovered and returned to normal life.[6]

4. Canadian Tayab Jafar spent several hours at a temperature of -11°C. His body temperature fell to 21°C. After 10 weeks in the hospital, he was discharged in good health.[7]

5. Swedish skier Anna Bagenholm spent half an hour under the ice, cooled to a record 13.7°C. After several weeks in the hospital, Anna fully recovered.[8]

6. Jean Hiliard was found in the snow at a temperature of -30°C, where she spent more than 6 hours. After several weeks in the hospital, she fully recovered.[9]

7. Russian tractor driver Vladimir Kharin was successfully revived in 1960 after being found frozen in the steppe where he had spent several hours in subzero temperatures.[10]

8. Japanese ice cream truck driver Masaru Saito got locked inside his refrigerator and was found frozen several hours later. He fully recovered.[11]

9. One of the earliest described cases in the medical literature occurred in 1951, when a 23-year-old American from Chicago spent 12 hours at temperatures from -18°C to -24°C. At the same time her body temperature dropped to 16°C. Although doctors had to amputate her fingers and legs below the knees, the rest of her organs were not injured.[12]

10. The earliest documented case of recovery after deep hypothermia occurred with a Swedish farmer in 1756 and has been described in the publication of the Swedish Academy of Sciences in 1757.[13]

11. There are 6 cases of successful survival after several hours of being in the cargo hold of the aircraft at temperatures below -40°C.[14]

12. Probably the most famous, although not the most applicable example is that of Beck Weathers, who in 1996 fell asleep on top of Mount Everest, and then woke up and came down to base camp on his own.[15]

As we see above, nature has many examples of organisms which are able to withstand deep subzero temperatures. Therefore, it is only reasonable to try to unravel the biological mechanisms that enable them to do so, and to try to adapt them to humans with the goal of pausing our biological processes.

Experiments

First, let's very briefly go through the main detrimental issues associated with deep cooling of living organisms. The main problem is certainly the formation of ice crystals that can damage cells, as crystals (a) are prickly and (b) take up more space than the original water. But this is not as scary as some opponents of cryonics make it out to be, painting pictures of exploding cells and other nonsense.

First, as tissue cools, water from cells exits into the extracellular space, so the cooling cells actually shrink rather than explode. Secondly, ice has only 9% more volume[16] than water, and cells have a much greater margin of elasticity, due to which they can

safely tolerate the increase or decrease in volume, as well as the presence of a certain amount of ice in the intracellular space. Thirdly, cryobiology has learned to saturate cells, tissues, and whole bodies with *cryoprotectants*—substances that minimize the formation of ice crystals during freezing. Coupled with optimal protocols of controlled temperature reduction, this enabled scientists many decades ago to successfully master the technology of freezing (or *vitrifying*, to be precise) and thawing back embryos and whole organs.

Here is a table of organs or tissues that as far back as 1980 scientists already knew how to freeze to -79°C and then thaw back to viability[17]:

TABLE I
Mammalian Organs and Organized Tissues Successfully Preserved by Slow Freezing to −79°C[a]

Adrenal cortex	(47)	Prostate gland (pieces)	(47)
Bone marrow	(26)	Renal tissue	(21,45,51)
Cornea	(26)	Seminal vesicles	(47)
Embryos	(15)	Skin	(26,32)
Epididymus	(47)	Spleens	(4)
Fallopian tube	(47)	Superior cervical ganglion	(41)
Hearts (fetal)	(10)	Testicular tissue	(11,47)
Hypophysis	(47)	Thymus glands	(42)
Intestine	(23,26)	Thyroid tissue	(40)
Ovarian tissue	(39)	Ureters	(3)
Pancreases (fetal)	(31)	Uteri	(6,47)
Parathyroid glands	(46)	Vasculature[b]	(2,4,22)

[a] References given in parentheses.
[b] Partial success.

Among other cooling problems I should also point out denaturation (unfolding) of proteins, but, fortunately, denaturation from lowered temperature is often reversible. This stands in contrast to denaturation from increased temperatures—a boiled egg cannot be unboiled. Also, since as temperature lowers, all chemical reactions (and hence biological processes) are slowed down and ultimately (for all practical purposes) stop, damage from such denaturation for quickly frozen organisms is minimal.

Finally, among problems arising from deep low temperatures, I should mention thermal macro-cracks, in particular those that happen below -140°C. Just how dangerous they are remains an open question, but there are opinions that their danger is low to moderate. Also there might be some new technology on the horizon that could help minimize those cracks, for example, by not allowing the temperature of the patient to fall below -140°C.[18]

Let us now transition from theory to practice and look at the experimental data—when scientists were trying to freeze organisms that do not normally like being frozen – humans, for example. But first, let's take a look at animals.

A variety of insects were successfully being frozen and thawed as far back as 100 years ago, so insects no longer surprise anybody. Therefore, I will mention only one insect example (plus the insect-like tardigrade).

Many have heard about the indestructibility of tardigrades (*Tardigrada*)—they were sent into space, and frozen to -196°C without any cryoprotectants. And -196°C was no problem for these guys, as they were thawed and lived on.

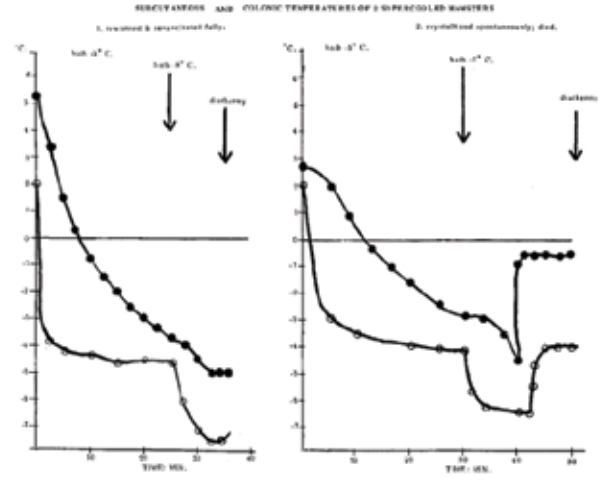
Nematode worms are a favorite model organism of biologists. They were used to perfect vitrification technology, achieving a 100% survival rate. Moreover, it was also shown that their long-term memory is retained[19] after many days of being frozen at -80°C. That was a very important result providing evidence that cryogenic freezing is able to preserve the personality of the patients.

> In other experiments, the Alaskan beetle (*Upis ceramboides*) was successfully thawed after cooling to -75°C, and this is a much larger creature than nematodes or tardigrades.

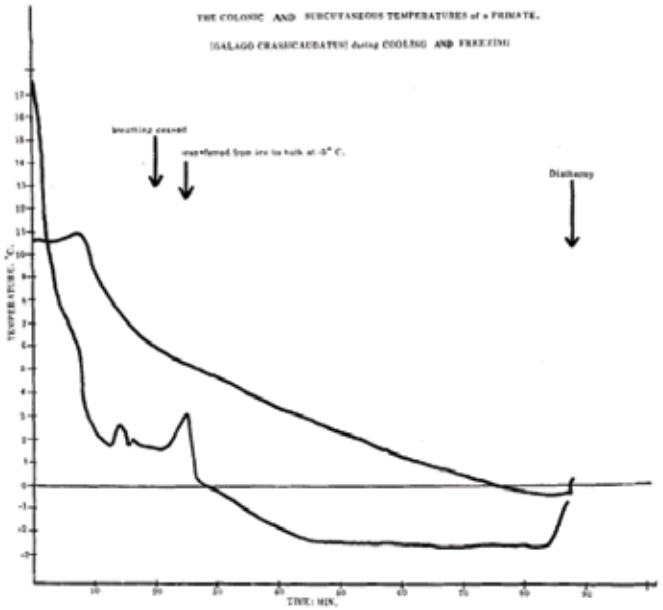
Some of the first but highly important experiments on freezing mammals were carried out as early as 1951 (the very first was performed in 1912 by Porphyry Bakhmetyev when he induced anabiosis in a bat, which he described in his1912 (!) article[20]). In these studies, rats were cooled without any cryoprotectants, and it was found that even as the temperature is lowered to 0°C (but not below), it is possible to achieve almost 100% survival. Moreover, some rats were frozen and thawed repeatedly—some as many as 10 times (poor bastards). The researchers also found that during rapid freezing (*supercooling*), when the water has no time to turn into ice, some rats can survive even being cooled to -3°C.[21]

Also in the 1950s, other researchers froze hamsters, cooling them to a temperature of -1°C, and varied freeze time to establish how much ice formation their bodies can tolerate. In these experiments, it was shown that as much as 60% of water in the brain can be transformed into ice with no visible effects on animal behavior after thawing.[22]

Moreover, in some 1954-6 studies the hamsters survived even after cooling below -3°C. Some of them were cooled to body temperature between -3°C and -5.5°C, at which they were held for 16 to 38 minutes, and then rapidly heated back up and revived, after which those hamsters lived for many months without any apparent health issues:



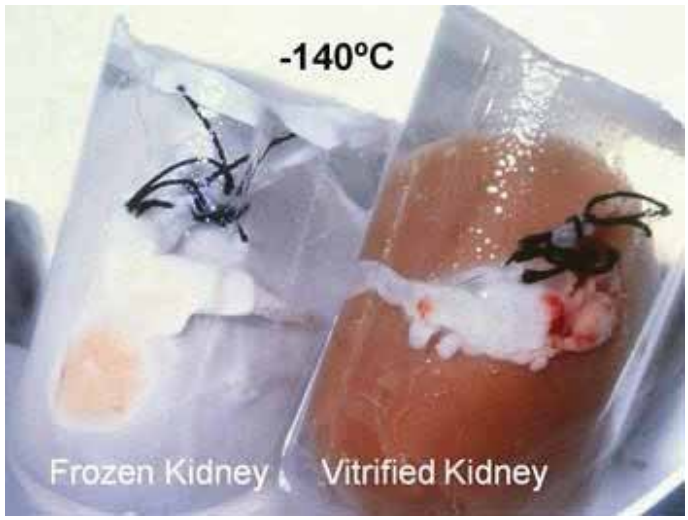
Experiments on primates[23] (*Galago crassicaudatus*) in the same 1950 studies were less successful. After freezing below 0°C (without cryoprotectants!) the primates initially recovered, but none survived for more than a day, dying either from pulmonary edema, or from intraperitoneal bleeding (seemingly caused by the gastric juice that diffused during freezing from the biliary glands or stomach into abdominal tissues). But their cooling graphs are still quite impressive:



The twenty-first century, too, has something to boast about. For a long time cryopreserving a kidney remained an unattainable goal—upon defrosting, both its structural integrity and function were critically impaired. But in the early 2000s, Gregory Fahy was able to finally achieve it. By the way, it is quite symbolic that this was done under the auspices of a company called *21st Century Medicine*.

In his experiments, Fahy removed a kidney from a rabbit, vitrified it and cooled to a certain temperature, then thawed it and transplanted back to the donor, while simultaneously removing the second healthy kidney. In 2003, Fahy was able to find a successful combination of cryoprotectants and a rather complex vitrification protocol, which allowed him to successfully cool the kidney to -22°C or -45°C,[24] and for two rabbits, he was able to achieve cooling to as low as -130°C.[25] Notably, while 30 rabbits survived various cooling protocols to between -22°C or -45°C, only 2 rabbits had their kidneys cooled to -130°C. Of those one died 9 days after return transplantation, but the second lived for 48 days after which it was sacrificed for histological analysis.

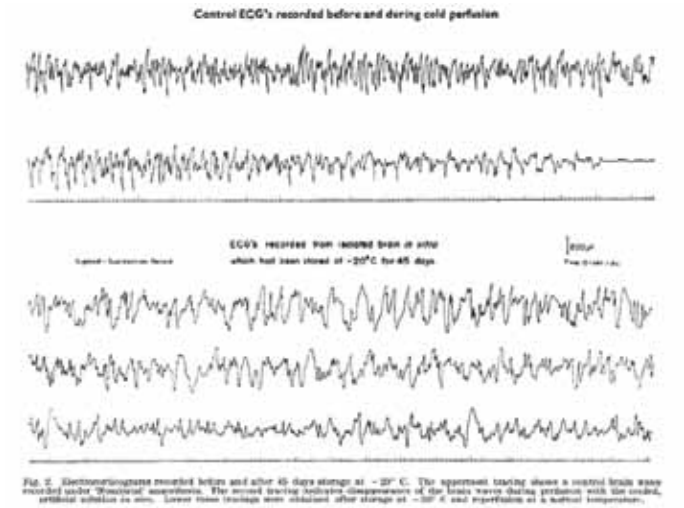
By the way, this famous photo that demonstrates a striking difference between a frozen and vitrified kidney originates from a 1984 work[26] by Fahy et al.:



In 2008, a group of Israeli scientists reported successful preservation of murine and porcine livers,[27] as well as rat hearts,[28] but their method of verifying viability was quite limited and did not include transplantation back into living animals to verify actual organ function.

Compared to the kidney, the brain is considered by cryobiologists to be more tolerant of cryopreservation. Many studied showed its full or partial freezing or vitrificaton without subsequent structural damage. Moreover, several studies have even demonstrated preservation of some of its functions.

The most intriguing of such studies were done by a Japanese cryobiologist Isamu Suda. In 1966, Suda published a paper in which he claimed that he was able to detect electrical activity in cat brains after they have been frozen at -20°C for several months.[29] Here is an excerpt of EEG graphs from his work:



And here is his perfusion apparatus:

involved certain irreversible tissue processing (or *fixation*) with aldehyde, rendering impossible any biological brain function upon thawing, but this does not negate the importance of this achievement for cryobiology.

In 1974, Suda published another, more detailed paper.[30] In it, he claimed that even after 7 years of being frozen at -20°C cat brains exhibited synchronized electrical activity for a few hours after thawing, although of lower quality than that of control brains not subjected to freezing. He also compared EEGs of "fresh" brains and brains after 5 days of storage at -20°C; their results were virtually identical.

Here I must mention that to date no one has managed to reproduce Suda's results. At the same time, no one has really attempted an identical step-by-step reproduction. Before his retirement, Suda sent a copy of all his experimental notes and data to Gregory Fahy who looked over them and did not observe any signs of falsification.

Fahy, too, has done a lot of research in pursuit of an optimal protocol for cryopreservation of the brain. In 2016, along with Robert McIntyre and other colleagues from 21st Century Medicine, he was awarded the Small Mammal Brain Preservation Prize[31] for technology that enabled perfect preservation of a rabbit brain's histological structure. Moreover, in 2018 McIntyre and Fahy also received the Large Mammal Brain Preservation Prize[32] for their success in preserving the structure of a pig brain. It should be noted that the particular technology used by them

Long before that, in 2006, Fahy along with Yuri Pichugin et al. demonstrated that with a certain combination of cryoprotectant and vitrification protocol, slices of rat brains could be perfectly preserved even after cooling to -130°C: more than 90% of their samples retained their structure and even the potential for electrical activity (as measured by the proportion of sodium and potassium ions as compared to the control).[33]

Moreover, in 2007, 21st Century Medicine announced[34] that it was able to directly confirm the preservation of basic electrical "learning ability" (long-term potentiation, LTP) in rabbit brain slices after vitrification, and later elaborated on those results in a 2012 book chapter *Cryopreservation of Precision Cut Tissue Slices*.

Fahy and Pichugin's research helped establish an optimal cryoprotectant composition and perfusion protocol for cryonics patients. Today, anyone can look at the perfused brains of some of these cryonics patients thanks to the miracles of computer tomography and YouTube.[35]

In the video frame on the next page, we see that the patient's brain contains almost no ice (blue), and is well-saturated with cryoprotectant (green, purple and orange).

As a curious aside rather than for serious consideration, I should mention that in 2016, Suda's cat brain experiments got upstaged by a strange paper in which several Canadian scientists from

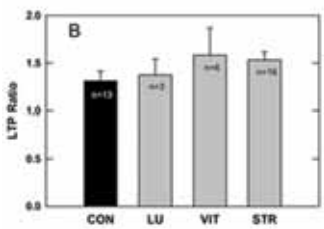
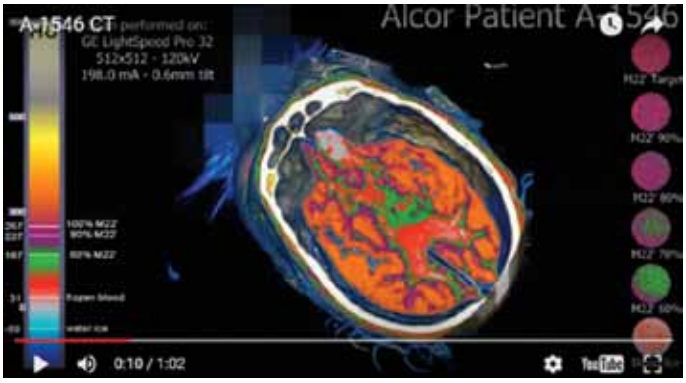


Figure 6B. Lack of effect of vitrification on the long term potentiation (LTP) response, a form of neurophysiological "memory" which consists of a permanent increase in the magnitude of the response to a given CA3 cell stimulation (recorded in this case as the amplitude of the excitatory post-synaptic field potentials at the Schaffer collateral-CA1 dendrite junction) as a result of prior "training" (intensive stimulation) of the involved synapses. Control brain slices increased their field EPSP response to about 30% above the baseline response amplitude (LTP ratio of about 1.3) in response to prior "training". The same basic result was also seen after loading and unloading of VM3 (LU); after loading of VM3, vitrification, rewarming, and unloading of VM3 (VIT); and after storage of vitrified slices for days to months below the glass transition temperature (STR; storage time had no effect on the results obtained). n values record the number of independent experiments for each bar. Previously unpublished data of 21st Century Medicine.



Sudbury published some highly odd results. They claimed that they were able to detect electrical activity in human brains that have been stored in formalin for over 20 years.[36]

Formalin is a well-known tissue fixative that is widely used in the storage of various biological samples precisely because it irreversibly arrests chemical and electrical activity at the cellular level. Roughly speaking, it "glues" cells shut, turning them into jelly. Thus, no one expected aldehyde-fixed tissues to maintain any biological function—if only because fixation perforates cell membranes making them unable to pump protons, which is a prerequisite for transmission of electrical impulses. That is why virtually everyone is highly skeptical of the Canadians' claims.

What is the importance of experiments demonstrating the brain's ability to restore its function after an interruption in its functioning (even a short one, and even without freezing)? Because they show that cryonics can work: after all, almost all neuroscientists agree that long-term memory, and therefore our personality, is encoded in physical structures of the brain, and not in its electrical activity. Moreover, electrical activity of the brain naturally ceases below +18°C, but with proper recovery this cessation does not have any long-term negative consequences, as evidenced by humans undergoing profound hypothermia or brain surgery,[37] as well as in experimental animals—from nematodes and hamsters to primates.

In fact, various medical procedures that involve stopping brain activity with subsequent full recovery have been repeatedly validated in dozens of experiments on animals, and are even presently undergoing clinical trials in humans in the United States—see the EPR CAT trial of suspended animation, which is evaluating cooling gunshot victims to 10°C.[38]

Prior to use in humans, the above suspended animation technology has been tested in our close evolutionary relatives—pigs. Just as in human EPR CAT patients, those pigs had all their blood drained and replaced by a cooling saline solution while bringing their body temperature to 10°C. In total, more than 200 pigs have undergone this procedure with successful recovery,[39] and before pigs, a similar protocol was tested in dogs.[40]

Moreover, Mike Darwin (former Alcor CEO) and colleagues were even able to prolong the duration of bloodless anabiosis to 5 hours.[41] That means a dog spent 5 hours completely without blood, and then was fully restored, including its long-term memory—recognizing familiar people and responding to commands. And it was not an isolated experiment. Together with Jerry Leaf, Mike Darwin performed a whole series of "total body washouts."[42]

Finally, I want to give honorable mention to a cat that in the 1980s managed to recover after an hour of heart stoppage—and that was without any cooling.[43]

All these data allow us to hypothesize that, even with a delay of several hours between the onset of clinical death and the beginning of perfusion of the cryonics patient, the latter still retains reasonable chances of future restoration of brain function. First, because even without cooling, irreversible brain changes begin to occur[44] only after 1–2 hours, and neuronal necrosis begins only after 4–6. And secondly, because the brain is a highly plastic organ that is able to recover from serious injuries.

Let me mention just a couple of cases of such recovery.

Probably the highest-profile case is that of US Senator Gabrielle Giffords,[45] who in 2011 was shot right through the brain, and six months later returned to work in the Senate. The left photo

is of her in the hospital, and on the right one she is skydiving a few years later.

There is also another case of a successful recovery from a bullet wound to the brain, Rachel Barezinski.[46] The bullet passed through but Rachel survived and recovered:

Moreover, some people undergo removal of an entire hemisphere,[47] and others survive even worse brain injuries:

And even if all other body parts of a cryonics patient will not be suitable for recovery, as long as the brain remains viable, there will be a chance to restore the patient's identity. After all, several head transplantation experiments have been successfully performed by the fathers of transplantology, Vladimir Demikhov and Sergei Bryukhonenko, as far back as the 1930s. The photo below shows a living dog's head separated from its body:

There is even archive video footage[48] of several two-headed dogs, some from Demikhov, others from Bryukhonenko:

By the way, it was Demikhov's pioneering work that paved the way to successful human kidney and heart transplants, as was confirmed by Christiaan Barnard himself—the first surgeon to successfully transplant the human heart in 1967. Demikhov also inspired Robert J. White to perform his head transplant research that culminated in a successful monkey head transplant. In his research, White also found that the brain is not rejected by the recipient,[49] unlike other organs.

In my view, all of the above data support the idea that the main task of cryonics is to ensure maximum viability of the brain for future revival.

About that revival

Proponents of cryonics like to joke that there already are thousands of revived cryonics patients among us. The only caveat is that they were frozen and revived while they were still embryos. Still, that is quite a successful achievement of cryobiology. Especially considering that some of these cryonauts were frozen for decades.[50]

Revived embryos are certainly impressive, but they are only 4 or 8 cells large. However, there are even more impressive achievements. For example, some women with cancer undergo removal of their ovaries, to protect them from chemotherapy, have them frozen and then transplanted back. And these ovaries resume their function: women who have undergone such procedures have given birth to more than 70 children.[51]

Unfortunately, cryobiology cannot yet boast of something more significant—for example, of recovering a mammal after cooling it to temperatures below 0°C. There are rumors that some researchers were trying to do this with pigs, but public confirmation of this has yet to surface. Let's hope that in the near future we will see such – or even more impressive – experiments.■

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Scholar Profile: João Pedro de Magalhães

By Nicole Weinstock

It's not every day that the aspirations of your eight-year-old self stick around into adulthood, much less when they are as ambitious or pioneering as finding a cure to aging. But that's Dr. João Pedro de Magalhães for you.

Pedro presents at Basel Life, an annual life sciences conference in Switzerland. Photo courtesy of Susanne Seiler.

An accomplished biogerontologist and Reader (Associate Professor) at the University of Liverpool, Dr. de Magalhães is cutting the edge of aging research in the 21st century. His findings—including the genomic sequencing of the long-lived and cancer-resistant bowhead whale and naked mole rat—have been published in prestigious academic journals, such as *Nature* and *Cell*, and garnered the attention of major news outlets worldwide, from CNN to the Washington Post to the Times of India. His heavily-cited Human Aging Genomic Resources (HAGR) is the most comprehensive collection of online genomic databases and tools to date. It is the ultimate reference for scientists and researchers worldwide looking to study the genetics of human aging using modern approaches like functional genomics, network and evolutionary analyses, and systems biology. De Magalhães has presented for TEDx in Ghent (Belgium), Aveiro (Portugal) and Imperial College (England), and published an animated YouTube video, "Why do animals have such different lifespans?" with more than 2.3 million views.

Though his reputation precedes him, de Magalhães is a life extensionist with a decidedly human touch. He is a devoted father and amateur comedian with a weakness for hot chocolate and animation—just check out his animated short, "What is Aging?" on YouTube. Pedro is also a lifelong soccer player and musician. He started composing and recording under the artist name of *Senescence* (formerly *Dark Angœl*) at 16, and even released his own twelve-track album, *Legend of Hrothgar*, in 1999.

While de Magalhães himself does not have cryonics arrangements, the ramifications of his aging research for cryonicists worldwide is tremendous. We are privileged to dive deeper into his world of science, sequencing, and senescence for this special first edition of *Cryonics* magazine in 2019.

Pedro was born and raised in northwest Portugal, in the coastal "Second City" of Porto. Famed for its role in the long-time production and export of port wine as well as its historic center, designated a UNESCO World Heritage Site in 1996, Porto is an irresistibly suggestive backdrop for a blossoming aging expert. But for de Magalhães and many other youngsters who grow up in well-known metropoles, it simply symbolized home. "I don't think I was much influenced in terms of my work or my vision by [Porto]...I was influenced when I started noticing that people die."

The weight of inevitable aging and death, coupled with the sensation of needless limitation in human lifespan prompted an ever-growing list of questions, concerns, and fears starting in Pedro's elementary school years. "This was before the Internet," he notes, "so nobody knew you could even study aging. So I thought, "'Well, I'll start studying aging.'"

One of the most significant experiences in his emerging commitment to this field was a childhood bout of pneumonia. "My great-grandfather died of pneumonia, so my grandparents were worried about me. But obviously we had penicillin, so I just had some penicillin shots and I was perfectly fine. I reasoned, 'Okay, so in the same way that we can cure a disease that we couldn't 50 years ago, maybe it's possible that 50 years from now we'll be able to cure aging.'"

Confident, bold, and independent, de Magalhães's character reflects many of the unsung virtues of only children, not to mention a refreshing style of child-rearing in the age of overbearing parents. He comes from a secular, STEM-inclined (Science, Technology, Engineering, Math) family unit, his mother a former mathematics school teacher, and his father, an

De Magalhães hard at work in his office at the University of Liverpool.

IT professional. "My parents always encouraged me to think for myself and develop my own ideas," he says, a philosophy he embraces with his own two children today.

Pedro was, unsurprisingly, an accomplished student, with more than satisfactory grades—including those in his mother's favored subject—so adolescence left him ample room for exploration. He was a committed soccer player who offset his caloric burn with a more sedentary interest in computers. These early autodidactic programming experiences would later form the building blocks for the many genomic research databases he would assemble.

Though de Magalhães's interest in the study of aging became apparent in primary school, his ultimate goal within the field materialized in high school. "I remember telling my parents I wanted to cure aging, that this was what I wanted to do, and I'm not sure they said it was impossible. But they definitely said that it wasn't going to be an easy thing to do."

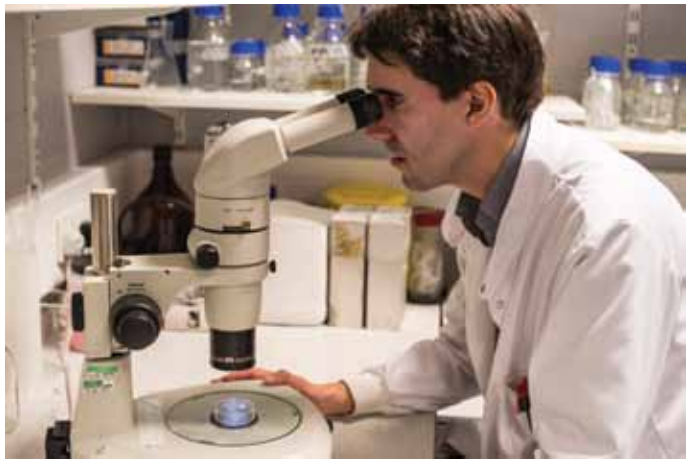
Balancing ambition with this healthy dose of cautionary wisdom, Pedro carefully considered the various academic pathways that could jumpstart his career aspirations. Medicine was a lengthy course of study that was too heavily focused on patient work for his purposes. Biology tended too strongly towards plant studies. His decision came down to the subjects of biochemistry or microbiology, of which Pedro elected the latter given its emphasis on lab work over theory. His careful deliberation was rewarded. "I developed quite a lot of laboratory skills working in the microbiology course," he reflects, "so that was a very good choice in hindsight."

Not ready to take the plunge to study abroad, de Magalhães elected to study at the Escola Superior de Biotechnologia at the Universidade Católica Portuguesa in Porto. Before graduating in 1999, he was fortunate to intern at the UnIGENe Research Group, where he focused on Machado-Joseph disease. A rare neurogenerative disease often mistaken for Parkinson's due to crossover symptoms, MJD is a dominantly inherited form of ataxia (lack of muscle control and coordination) that typically results in paralysis.

As thorough in his application process as in his lab work, de Magalhães explored a number of programs for his doctoral studies, coming into contact with senescence experts like Aubrey de Grey of the SENS Research Foundation and Bernard Strehler, the then-director of USC's Andrus Gerontology Center, in the process. He eventually decided on the University of Namur in Belgium where he studied from 1999 to 2004 under the late Olivier Toussaint in the Ageing and Stress Group. Toussaint was a visionary and pioneer in Stress Induced Premature Senescence (SIPS) and a well-known coordinator of aging-related research networks who Pedro humbly credits for his earlier development in the field.

Post-doctoral studies brought de Magalhães overseas, where he worked alongside prominent geneticist George Church at his Harvard lab. "George is not just a great scientist, he's also a very nice person," Pedro remarks. In addition to enjoying the company of a smart and amicable boss, these Boston years also formed part of a meaningful legacy. "[Aging] is not the main focus of this lab," says Pedro, "but he does some work on aging even now. I think I can take some credit for that."

"You know, we can change a gene in worms and make them live 10 times longer." That is one of the mind-boggling factoids that



Pedro takes a closer look at worms under the microscope. Photo courtesy of Alan Bannister.

de Magalhães shares with his students during an annual series of lectures on the biology of aging. Now a full-time professor at the University of Liverpool, he teaches hundreds of students each year while heading up research for the Integrative Genomics of Aging Group. This group studies the genetic, cellular, and molecular mechanisms of aging, while focusing on experimental and computational methods that shed light on the relationship between genotype and phenotype, as well as that of the human genome and aging/longevity.

Pedro and his lab have earned international recognition for their work in genomic sequencing and analysis, particularly that of long-lived and cancer-resistant animals. Their efforts to unravel the aging mechanisms at play in the East African naked mole rat, for example, provide a valuable comparative model for the long-time (but short-lived) rodent research standard: the mouse. While the naked mole rat's hairless, wrinkled body and claw-like front teeth support limited sales of its stuffed animal incarnations, this eusocial mammal is capable of living more than 30 years, making it is the longest living rodent on record. It has several extreme physical traits that are believed to contribute to its lifespan, including low metabolic and respiratory rates—it can survive without oxygen for 18 minutes—and an imperviousness to pain.

Jumping from pet-sized land mammals to marine behemoths, de Magalhães's lab is also working on the analysis of the bowhead whale genome following the completion of its sequencing in 2014. With an estimated lifespan of more than 200 years, this massive baleen whale became the first whale of its size, and the largest animal on record, to undergo genomic sequencing. While the naked mole rat spends its life in oxygen-deprived tunnels underground, the bowhead withstands similarly extreme environs in Arctic and sub-Arctic waters. Armed with the largest mouth and thickest layer of blubber in the animal kingdom, it does not annually migrate to warm waters like many of its marine brethren.

In addition to the naked mole rat and the bowhead whale, the Integrative Genomics of Aging Group is also analyzing the capuchin monkey's genome. Frequently seen on the silver screen as an exotic pet, and recently, as a support animal to quadriplegics, this particular primate can live more than 54 years. Given its closer relation to humans than the rodent or whale, the capuchin monkey is a uniquely valuable model for long-lived mammals under analyses.

It's hard to admit to a favorite child, but de Magalhães concedes his number one. "I think the bowhead is the most interesting to me. But in an ideal world I would sequence every single species on earth, and I would then compare all the genomes and try to figure out exactly what makes us live longer than chimpanzees, and what makes bowheads live longer than other whales, and so on. That's what I'd do in an ideal world."

Long-lived and cancer-resistant mammals under analysis by the Integrative Genomics of Aging Group

Naked Mole Rat

Lifespan: 30+ years
Habitat: Underground burrows in East Africa

One of the most famously unattractive mammals, the naked mole rat is impervious to pain, and can survive up to 18 minutes without oxygen. It is the first mammal known to exhibit eusociality; only one female reproduces per colony. Photo courtesy of Roman Klementschitz, Wien from Wikimedia Commons

Capuchin Monkey

Lifespan: 54+ years
Habitat: South and Central American tropical rainforests, dry forests, and mangroves

A Hollywood favorite, the capuchin monkey is named after an order of friars from the 16th century. They are recognized as one of the most intelligent of New World monkeys, and have been trained as service animals in recent years. Photo courtesy of David M. Jensen (Storkk) from Wikimedia Commons.

Bowhead Whale

Lifespan: 200+ years
Habitat: Arctic and sub-Arctic waters

Named for its bow-shaped skull, this massive baleen whale measures 35 to 45 feet at maturity. It has the thickest layer of blubber in the animal kingdom, and can break through 8 inches—possibly more—of sea ice, allowing it to survive in extremely cold waters. Photo courtesy of Bering Land Bridge National Preserve via Wikimedia Commons.

The polar opposite of the capuchin, the marmoset lives for just five to sixteen years. Its genome has now been sequenced, adding another extreme to the "bestiary of aging."

A seasoned public speaker at schools, retirement communities, and larger venues like TEDx, Pedro is attuned to some of the social objections that pave the road between here and the idyllic. "We do have a lot of people who don't think we should be tinkering with aging…That's why a lot of us, myself included, in the field tend to focus more on health span, not lifespan, nowadays. Because you can question whether people should live longer, but nobody questions that people should be healthy."

Technological advances have steadily reduced the time and cost of genomic sequencing, but researchers still have to be selective in choosing their research models for other reasons. "A lot of times the bottleneck is getting samples," says de Magalhães. The samples used to sequence the bowhead DNA for example, came from a collaborative effort in Greenland, where native tribes are allowed to hunt a very limited number of the whales each year. Acquiring samples from something like a blue whale—another giant whale on Pedro's genomic sequencing wish list—would present similar, if not severer challenges.

Aging research is also unique in that technological advances and diminishing financial constraints do little to assuage an inherent and central limitation. "Sequenc[ing] can be made cheaper, and easier, and quicker," says Pedro, "but a clinical trial, or even a study of aging in mice, it's still going to take several years. There's no way around it. You can try to find biomarkers that will give you readouts earlier. There might be little ways of doing it a bit faster, but not radically faster. And that is a big limitation. That's one of the reasons I don't think we're going to solve aging, or cure aging in my lifetime, or in the foreseeable future."

Despite his estimations, de Magalhães is far from pessimistic about progress in his field. "There are now big consortia to sequence hundreds of species, and I think certainly in the next 10, 20 years we'll have thousands of vertebrates and mammals sequenced." Apart from the blue whale, he hopes to expand what he refers to as the "bestiary of aging" to include very short-lived organisms as well. "I think the extremes, whether they be bowhead whales or supercentenarians, can teach you about healthy aging and successful aging." The marmoset, a squirrel-like anthropoid primate, is another mammal with an extreme lifespan of interest to Pedro; its genome was sequenced by a lab similar to his. The marmoset is vulnerable to age-related diseases common to humans, like cancer and diabetes, and tends to live between five and sixteen years—just a fraction of the lifespan of the capuchin monkey and other primates.

Apart from the professional landscape of aging, personal events have also influenced de Magalhães's vision of the future. In 2016, his wife and the mother of his two daughters, Joana Costa, passed away from breast cancer after several years of battling this disease. "It's only increased my commitment to solve death," says Pedro, "either by developing cures for the major diseases affecting humankind, or by developing procedures that allow human medical biostasis."

As with many life extensionists, cryonics thinking does not lie far afield for de Magalhães. His first exposure to cryonics was in grade school. He recalls a moment around the age of ten where it was referenced in a story that was read in his English class. "I think I was intrigued, but not fully convinced." Though many years have passed since his youth in Porto, and his research and interests have brought him closer to the cryonics community, his views on the subject have endured. "I'm still not persuaded that the current methods for cryonics work, but I'm very interested in advancing the field, and developing better cryopreservation methods."

To that end, Pedro has gone to considerable lengths to do his part. In addition to encouraging a growing amount of support for cryobiology research at his university, he has also teamed up with eleven other researchers to support the UK Cryonics and Cryopreservation Research Network. Established in 2015, this alliance includes other advisors such as Ralph Merkle, Robin Hanson (previously profiled in *Cryonics* magazine), and Aubrey de Grey, among other household names.

De Magalhães has also raised awareness of cryonics in more mainstream forums. In 2017, he gave a TEDx presentation at Imperial College, a public research university in London, titled, "Cryonics: fantasy or a bridge to the future?" What followed was a comprehensive overview of the field, associated technological advances that might develop in partnership with it (ie: nanotechnology), and some of the future ramifications of cryonics, like organ transplantation and space exploration.

"Cryonics and cryopreservation in general strike me as fields with tremendous potential. Developing the technology to cryopreserve human organs is, by itself, a huge breakthrough with important medical implications. I think it's far simpler than other goals in biomedical research, including curing diseases like cancer, Alzheimer's or even curing aging, which is arguably much harder than curing cancer or Alzheimer's. Therefore, I'm convinced that with more research into cryopreservation, but still far lower levels than, say, cancer, we can make important breakthroughs."

De Magalhães at a debate on immortality at the annual Brave New World conference in Leiden, The Netherlands. Photo courtesy of Annick Elzenga.

Interview

What are your lab's more recent projects/findings in the field of cryobiology?

Our main results have focused on studying molecular signatures of cryoprotectant toxicity, which in turn may provide insights on mechanisms and also potential targets for developing drugs to neutralize toxicity. More recently, we have also been developing methods for the cryopreservation of flies, but we are still in the early days of that project.

I should also say that although my lab has done some work in cryobiology, I would like to do much more. Unfortunately, cryobiology is not a priority of my university or of funding bodies in the UK. Moreover, students tend to be more excited about fields like cancer, zoology or aging than cryopreservation. Therefore, cryobiology is an area that is much harder to study than other fields like cancer or even aging. We need more funding and more people in cryobiology!

You have mentioned concerns about cryoprotectant toxicity in previous presentations and interviews. At what point would you deem the toxicity levels acceptable? What would be the markers of this for you?

Ideally I would like to eliminate or neutralize all the toxicity from cryoprotectants. What is acceptable depends on the applications. For cryopreserving cells, we don't need all the cells to survive, so current toxicity levels are acceptable. When looking at organs, however, we require most cells to survive and maintain their function. It is hard to say how much we need to lower toxicity for cryonics, and some people would claim that current levels are acceptable already because they believe nanotechnology will fix everything in the future; but, I would argue that we need to substantially improve toxicity to make cryonics more viable.

As for markers, in our in vitro studies we employ cell mortality, so we look at the percentage of cells dying when exposed to cryoprotectants.

One important premise of cryonics is that the original structure of a biological system can be inferred from its damaged structure. Which technologies do you envision dealing with this aspect of cryonics?

This is somewhat outside of my expertise, but I would guess imaging technologies, coupled with computer models and simulations to infer the original structure, plus nanotechnology for subsequent repair.

Which advances in cryonics would prompt you to make cryonics arrangements yourself?

At this stage of my life I think it would have to be something pretty dramatic, like technical advances that allow cryonics procedures to preserve biological viability of most brain cells. That said, I think it is certainly possible, even likely, that when I'm older (and closer to death) I will make cryonics arrangements.

What is your opinion of aldehyde-stabilized cryopreservation (ASC)?

It is a very impressive technique for structural preservation, but as I commented in *New Scientist* (https://www.newscientist.com/article/2077140-mammal-brain-frozen-and-thawed-out-perfectly-for-first-time/), ASC employs a deadly chemical, which creates huge challenges for future biological revival. In theory, nanotechnology might allow biological revival following ASC, but given what we know now ASC will make things much harder for future revival.

What is the "Cryonics and Cryopreservation Research Network"? What have been its greatest achievements to date?

Our UK Cryonics and Cryopreservation Research Network is a group of UK researchers who, together with international advisors, aim to advance research in cryopreservation and its applications. Although we are a small group, we hope to

promote academic and industrial activity on cryopreservation, and discuss its potential applications, including cryonics. We hope to attract and excite students and other researchers about cryobiology, contribute to knowledge exchange and help attract interest and funding to the field.

We have engaged the UK media (*BBC*, *Sky News*, *ITV*, etc.) and in doing so clarified many misunderstandings concerning cryonics, but clearly we need to do much more to raise awareness and get more people and funding into cryobiology.

Do you still support the establishment of a storage facility in the UK? (Mentioned in your Dresden DGAB Scientific Symposium presentation in 2014)

Absolutely. I think it would be very important to have a storage facility in western Europe, and ideally, multiple storage facilities in different countries. I don't necessarily think that the UK is better than other countries—it has its advantages and disadvantages—but certainly establishing a storage facility in Europe would be a major first step.

The crocodile is assumed to have a remarkably effective immune system. Do you think we can learn something from them to mitigate immunosenescence?

We can learn a lot from other species, including crocodiles, tortoises, whales and mole rats. I think we have really only scratched the surface as far as understanding the biological innovations and capacities of other species. This is an area of huge potential, including in the context of immunosenescence and even cryopreservation.

An emerging theory about late-onset Alzheimer's Disease is that it is strongly associated with infections and immune system decline. What is your perspective on this?

Alzheimer's Disease has an inflammatory component, and there is some correlative evidence between infections and AD. Likewise, age is the primary risk factor for AD, and the immune system declines with age, so there is a possible link. The problem, however, is that correlation does not imply causation, and more research is needed to investigate the biological links between these processes.

Are there any therapies or products in the "anti-aging" marketplace that you consider credible?

There are products that may have health benefits, or applications in the context of specific diseases, but there is not enough evidence at present to say for sure that any anti-aging therapy can retard the human aging process. Having said that, I am optimistic about the development of longevity drugs in the foreseeable future. There are a number of promising compounds and avenues. ■

To learn more about Dr. de Magalhães, please visit his personal website www.jp.senescence.info and his lab website pcwww.liv.ac.uk/~aging/. To access the Human Aging Genomic Resources (HAGR), go to www.genomics.senescence.info.

Cryobiology. 2015 Dec;71(3):405-12. doi: 10.1016/j.cryobiol.2015.10.142. Epub 2015 Oct 22.

Insights on cryoprotectant toxicity from gene expression profiling of endothelial cells exposed to ethylene glycol.

Cryopreservation consists of preserving living cells or tissues generally at -80 °C or below and has many current applications in cell and tissue banking, and future potential for organ banking. Cryoprotective agents such as ethylene glycol (EG) are required for successful cryopreservation of most living systems, but have toxic side effects whose mechanisms remain largely unknown. In this work, we investigated the mechanisms of toxicity of ethylene glycol in human umbilical vein endothelial cells (HUVECs) as a model of the vascular endothelium in perfused organs. Exposing cells to 60% v/v EG for 2 h at 4 °C resulted in only a slight decrease in subsequent cell growth, suggesting only modest toxicity of EG for this cell type. Gene expression analysis with whole genome microarrays revealed signatures indicative of a generalized stress response at 24 h after EG exposure and a trend toward partial recovery at 72 h. The observed changes involved signaling pathways, glycoproteins, and genes involved in extracellular and transmembrane functions, the latter suggesting potential effects of ethylene glycol on membranes. These results continue to develop a new paradigm for understanding cryoprotectant toxicity and reveal molecular signatures helpful for future experiments in more completely elucidating the toxic effects of ethylene glycol in vascular endothelial cells and other cell types.

To read the full article, go to https://www.sciencedirect.com/science/article/pii/S0011224015003922.

Quality of Patient Care in Cryonics: A Systematic Approach

By Aschwin de Wolf

This article is adapted from the Alcor Human Cryopreservation Procedures Manual.

Introduction

The term "patient care" requires little explanation in mainstream medicine. When a patient is admitted to a hospital for a routine medical procedure there is usually an obvious expectation of what the desired outcome should be – even to people without a medical background. The hospital employs qualified personnel to ensure that the intended procedure conforms to protocol, and medical practice and internal and external entities make sure that good practices are adhered to.

In cryonics, however, a common belief is that the only meaningful test of efficacy of a cryonics procedure is whether the patient is revived in the future. In the most fundamental sense this is correct, but framing the issue of quality care in cryonics this way obscures the fact that cryonics consists of several specific procedures that are aimed at a specific outcome for which data can be collected to evaluate how well the delivery of this procedure confirmed to its stated objective.

In this document we will propose a general framework to evaluate patient care in cryonics, translate these objectives into distinct objectives for each major procedure, and discuss its physical, logistical, educational, and staffing implications.

Long Term Care

Alcor's mission statement states that maintaining "the current patients in biostasis" is its first and fundamental goal. This objective is so fundamental that it could potentially conflict with placing new patients in biostasis or conducting research to improve cryopreservation procedures. Since this fundamental goal pertains to patients already in biostasis it is no longer possible to improve their (physical) condition relative to the time when they were placed in liquid nitrogen. One recent caveat to this observation concerns Alcor patients that are currently stored at intermediate temperatures (ITS). Poor maintenance and anticipation of future ITS needs could result in additional fracturing if those patients are placed in regular liquid nitrogen dewars.

In a general sense, however, providing good patient care in the case of long term care means maintaining patients at cryogenic temperatures. This objective does not mean a "passive" continuation of existing physical storage arrangements. For example, dewars are expected to have a finite lifespan and money will need to be set aside for future changes. New dewars can be designed to reduce liquid nitrogen boiloff and reduce the cost of long-term patient care (for example, the gradual replacement of the Bigfoot dewars by Alcor's Super dewars). Alternative storage options and emergency procedures will need to be drafted in case manufacturers and suppliers no longer want or can deliver storage vessels to Alcor. Alternative storage locations need to be considered in case there are political or economical reasons for abandoning the current storage facility.

Two important measures to ensure Alcor can deliver on its most fundamental mandate include the creation of a legally and financially separate patient care trust and the creation of a full-time patient caretaker. The care trust ensures that patients will be shielded from the day-to-day organizational and financial challenges of a membership and service delivery organization. The full-time patient caretaker's sole responsibility is to maintain the patients in cryostasis, documentation, and report to the cryonics organization (and its care trust) on potential developments that can reduce the cost and enhance the safety of Alcor patients.

Cryopreservation

The common denominator of all Alcor patients is that they are cryopreserved. But the variable that matters for evaluating the quality of care is how well they have been *cryoprotected*. For a patient the degree of ice formation can range from a straight freeze (cryopreservation without cryoprotection) to complete vitrification (solidification without ice formation). Elimination of ice formation (or minimization of ice formation in whole body patients) is a minimal requirement of Alcor's cryopreservation protocols but it by no means exhausts its mandate.

It is important to distinguish here between Alcor's long-term research objective and what is possible with current technologies. Alcor's long-term objective is to develop (or implement) reversible cryopreservation, or human suspended animation. Reversible cryopreservation would allow a critically

ill patient to be placed in biostasis without causing any further damage that was not reversible by contemporary means. Alcor's research goal is to conduct or collaborate on research to narrow the gap between human suspended animation and its current cryopreservation capabilities.

What we should require from a cryopreservation protocol evolves and is based on reasonable extrapolations from contemporary cryobiology research. At the time of writing we should expect cryoprotection of the patient with a vitrification solution that can (a) eliminate ice formation at realistic cooling rates, (b) preserve the fine structure of the brain, and (c) recover some viability in cryopreserved isolated brain slices as a marker of minimal biochemical disturbance.

Elimination of ice formation can be assessed by subjecting (neuro) patients to CT scans. Preservation of the fine structure of the brain can be assessed by obtaining microliter samples of the patient's brain for electron microscopy. These brain samples can also be subjected to viability assays such as the K/Na ratio assay. It is important to recognize here that our current understanding is that elimination of ice formation and preservation of the fine structure of the brain is possible but that obtaining high viability readings from brain samples of patients is not yet within our reach. Our current belief is that in very good cases viability of the brain is lost during the early to mid-stages of cryoprotective perfusion because of cryoprotectant toxicity and CPA-induced dehydration of the brain. This means that for a typical cryonics case conducted under good conditions we should collect evidence that we achieved the first two objectives (vitrification and ultrastructural preservation) and support research and development aimed at maintaining viability throughout the whole cryoprotection procedure by further reducing cryoprotectant toxicity, eliminating CPA-induced brain shrinking, and optimization of cryoprotection protocols. At this point each case report should contain CT scans and electron micrographs to document the degree of vitrification and ultrastructural preservation achieved in a (neuro) patient, if applicable.

Stabilization

As the word "stabilization" suggests, the aim of this set of cryonics procedures is to stabilize the condition of the patient from the moment of pronouncement of legal death. That means that, ideally, there will be no further deterioration to the patient's physiological functioning and condition of the brain. Since cryonics procedures can only start after pronouncement of legal death, the initial (pre-mortem) state of the patient is usually beyond the cryonics organization's control. It is important to recognize this because proper evaluation of casework should describe this initial state as its benchmark.

In a good cryonics case, where the patient has not been diagnosed as brain death, and where response can be begun promptly, the objective of stabilization procedures is to keep the brain viable by *contemporary* medical criteria. One helpful way to describe this mandate is that upon completion of stabilization procedures it should be possible to *reverse* those procedures and recover brain function.

Keeping the brain viable by contemporary medical criteria is something that cannot be measured in a straightforward manner because at the completion of stabilization procedures the temperature of the brain is not able to support meaningful whole brain function. What can be done is to take microliter brain biopsies and subject these tissue samples to viability measurements. These measurements in turn can be compared to brain biopsies obtained after the completion of cryoprotective perfusion to understand how cryoprotection affects viability. The sample can subsequently be processed for electron microscopy to obtain information about the ultrastructure of the patient's brain.

Another means to ensure that stabilization procedures are successful in keeping the patient viable is to collect blood samples (pH, electrolytes etc.) and end tidal CO2 readings throughout the procedure. Collecting temperature data during all parts of cryonics procedures is essential because the temperature profile of a patient is a reasonably good indirect measure of brain injury (or lack thereof). Each patient case report should include a presentation of monitoring data and discuss the reason for not being able collect some of this information if this occurred.

Readiness and Deployment

Since its inception it has been routine in cryonics to document stabilization and cryopreservation procedures. When it comes to readiness and deployment, however, policies have often changed from administration to administration – if documented policies existed at all. Since a cryonics organization's state of readiness and deployment policies have profound effects on its ability to timely respond to a patient and the quality of care a patient will receive, a credible quality control – and assurance program should be extended to readiness and deployment as well.

Some of the questions that need to be addressed include: Who is responsible for local and non-local cases? What are the conditions for deploying a local or remote team? What is the composition of a deployment committee and should all parties have equal say in deployment decision (such as for-profit independent contractors)? What is the minimum number of team members required to do the full stabilization protocol? What is the likelihood of having multiple deployments and cases at the same time? What is the role of local (volunteer) teams? Should complete sets of standby kits be deployed to local groups with a lot of members? What makes a region eligible for respectively a cryonics first aid kit or a full set of kits? Which procedures should only be done by medical professionals and which procedures can be done by all trained individuals?

When a cryonics organization answers these questions and incorporates them in a set of policies and protocols, then a formal quality control program will have a framework to evaluate the state of readiness at a cryonics organization, and thus the ability to respond to cases in a consistent and reliable manner.

Training

Like readiness and deployment policies, the training of volunteers and medical professionals can greatly benefit from a set of formal policies, eligibility criteria, and written teaching materials. A review of the history of cryonics training at Alcor reveals a plethora of different approaches ranging from the teaching of members and volunteers to do the most advanced procedures (i.e. surgery, whole body blood washout) to not providing any training at all to non-professionals. A detailed review of cryonics training options and curricula is beyond the scope of this manual, but we want to make a few observations.

The transition from a volunteer-driven standby to employing a team made up of medical professionals does not eliminate the need for providing cryonics training. While medical professionals may be certified and competent to do a specific cryonics procedure (surgery, extracorporeal perfusion, IV placement) they may not be familiar with other aspects of our procedures, or how specific procedures work together to produce a specific outcome. It is therefore important for Alcor (or its contractors) to organize periodical cryonics training courses and provide relevant reading materials and updates.

A second reason why the use of professionals in cryonics does not exempt a cryonics organization from conducting training is that there will still be cases in which the professional standby organizations will not or cannot deploy a standby a team in time. Such a situation does not necessarily indicate poor readiness at the standby organization but can also reflect a rapid decline of the patient or challenges to get to the patient in time due to weather or logistical obstacles. In these circumstances local members and volunteers may have do the initial or all parts of a cryonics stabilization. Teaching local members basic cryonics "first aid" protocols and how to assist a professional standby team is essential for a cryonics organization that covers a country as large as the United States, not to speak of other countries.

It is increasingly recognized in cryonics that using members/volunteers and medical professionals is not mutually exclusive and the nature of cryonics today necessitates a model in which local volunteers cooperate, complement, or sometimes even replace a professional standby team. This "hybrid" model of standby implies that a cryonics organization creates different levels of protocols and training curricula. A proper quality control- and assurance program in cryonics needs to address both the local / volunteer part of cryonics as well as overseeing the use of medical professionals.

Staffing

The staffing of a cryonics organization is a complex topic and we confine ourselves here to making some observations pertaining to the quality of case work and quality control. Currently, Alcor's financial situation allows for the deployment of staff with a medical or scientific background. It is important that the core of Alcor's (local) standby team is made up of at least two individuals with a strong EMS, nursing, or scientific background. When these individuals are a part of Alcor's staff, case work is always a priority and complex coordination of volunteers and contractors is reduced. These staff members should take a leading role in standby equipment maintenance, team composition and deployment, training, standbys and the collection and gathering of case data. In a cryonics organization with a high case load it is important that these individuals are not distracted from these responsibilities by other responsibilities such as extensive writing tasks like case reports.

When generous funding is available in cryonics it is tempting to "recruit" competent staff members to work for (for-profit) cryonics-associated companies so they can focus full-time on research. When this happens, it is important that the cryonics organization creates a structure to interact with, and benefit from, the work of such individuals and that an open line of communication is retained between these organizations and Alcor.

If funding permits, a growing cryonics organization should employ a full-time quality control officer whose sole responsibility it is to maintain a constant level of care, improve procedures, and write or delegate the production of high quality case reports. Ideally, participation of this officer in cases is limited to ensure impartiality. If the cryonics organization contracts with other organizations for standby or other services it should require that this officer has the right to observe all cases and receive all data.

Meta-Analysis

An important reason for writing case reports is that the data that has been collected and analyzed in case reports (and patient files) can form the basis of a comprehensive meta-analysis to discover patterns, trends, and opportunities for protocol improvements. As of writing, there have been several attempts to look at the quality of care by reviewing selected case reports, data, and video footage but so far, no attempt has been made to look at all Alcor's case data with the aim of understanding the evolution of care, problematic areas, and opportunities for protocol and policy changes. In principle, it is possible to extend the idea of meta-analysis to cover areas such as protocols, state of readiness, and training. An important reason for doing a comprehensive meta-analysis, followed by periodical updates is that it allows the cryonics organization to develop a series of benchmarks that can be used to manage today's expectations and future directions.

One useful tool for present and future case reporting is to develop a single outcome measure that can be quickly consulted to understand the quality of the case. Some rigorous attempts have been made to create such a measure to estimate the total amount of ischemic exposure in a patient. Such a measure can then be entered as one element in a compound measure that includes other relevant data such as the degree of ice formation and fracturing events. It is important to note here that such a compound measure does not distinguish between events that were within and beyond a cryonics organization's control. For example, a case in which a family member hid the death of a patient for a week would render a very low score, but this poor outcome cannot not be attributed to the cryonics organization. Overall case measures are important, but context is important, too.

Quality Control Table

The following table lists specific items that need to be addressed / evaluated in any proper cryonics quality assurance / quality control program. This list is not exhaustive and other items could be added to guide quality control management and case reporting. ■

Readiness	**Stabilization**	**Cryoprotection**	**Cryopreservation**
Personnel	Cooling rate	Weight gain/loss	Ice formation (CT)
Protocols	End-Tidal CO2	Brain dehydration (CT)	Fracturing
Documentation	Blood gases	Pressure	Temp. Maintenance
Training	CPS data	Refractive Index	
Kit Maintenance		Viability (K/Na)	
Local groups		Ultrastructure (EM)	

Writing Case Reports

By Aschwin de Wolf

This article is adapted from the Alcor Human Cryopreservation Procedures Manual.

Introduction

The most important reasons for writing case reports are:

1. *To provide a transparent and detailed description of procedures and techniques for members of the cryonics organization and the general public.* Writing case reports "forces" a cryonics organizations repeatedly to document its procedures and protocols in detail. A cryonics organization that never writes anything about its cases and procedures should be treated with more caution than an organization that does.

2. *To validate current protocol and procedures in general, and actual implementation in particular.* A case report should not only record what happened but should be used for guidance as to what should happen in the future. A detailed case report, especially when a variety of physiological data has been collected, contains a wealth of information that can be analyzed for the team members' and patients' benefit. Cryonics cases are relatively rare compared with other medical procedures, so we should try to learn as much as we can from the cases we perform. A series of case reports can be used for meta-analysis.

3. *To serve as a medical record to assist with future attempts to revive the patient.* Although advanced future medical technologies may make it possible to determine the physiological condition of the patient down to the molecular level, it is important to provide as much medical information as possible to help in efforts to revive patients. Having a detailed record of the patient's condition prior to pronouncement, subsequent stabilization, and cryoprotection, may also help the organization in establishing the desired sequence of revival attempts.

4. *To gain more scientific credibility.* If we want scientists and physicians to take us seriously, we need to convince them that we are attempting to cryopreserve our patients in a scientific manner. Professional case reports can provide this kind of credibility.

This article will mainly concern itself with the general question of how a case report can help a cryonics organization in improving protocol, techniques, and skills.

Protocol

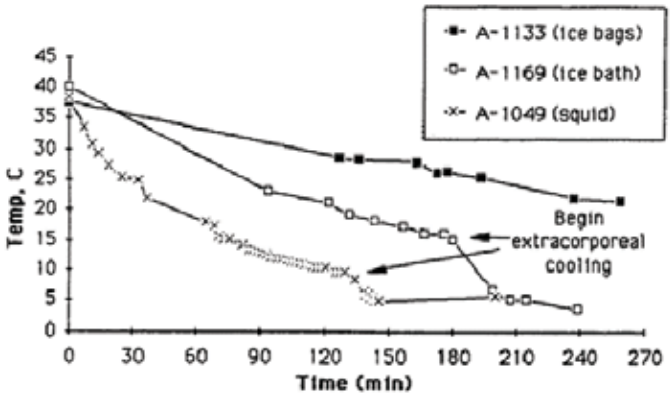
To be able to assess the quality of patient care in a cryonics case, it is important to recognize what the intended protocol was prior to writing about the case. Only if we know what the organization was *supposed* to do will we be able to assess how successful the case was. For example, if there is no mention of collecting (and analyzing) blood gases during a case this may have been because it is currently not a part of the organization's protocol, but it may also be the result of a shortage of skilled personnel, defective equipment, or other problems and deficiencies. Unless the writer of the report specifies what should have happened, it is difficult to assess the quality of preparation and performance. If preparation for the case was limited and there was no (functional) extracorporeal perfusion equipment available, the case report should not simply state that the organization did a case without substituting the blood with an organ preservation solution, but also identify and review the logistical factors or errors that were made that prevented a washout in the field. Since Alcor has a written protocol for all its major procedures, a case report can also refer to this instead of completely articulating it in the report. At a minimum, the case report writer(s) should check the performed procedures against the documented protocol (if available) and discuss changes or omissions in the report.

In practice there will be many deviations between the organization's protocol and what happens during a case. Human cryopreservation cases are not controlled laboratory experiments, and, as many people who have extensive experience doing cases know, unique situations present themselves, including frustrating events that are beyond the control of even the most skilled medical professional. Nevertheless, the inherent unpredictability and uniqueness of cryonics cases is sometimes used as a reason for failing to follow established protocol, or for errors and omissions in patient care. Recognition of the intended protocol will help us to gain a more systematic understanding of what is possible (or essential) and within our control, versus what is not.

Detail

The importance of writing detailed descriptions of the procedures and techniques employed during a case cannot be overestimated. This not only enables the reader to gain a comprehensive understanding of the techniques used, it also allows detailed analysis of the difficulties that were encountered during a case that would not have been noticed if there is only a brief mention of it. For example, instead of simply noting that medications were administered, providing comprehensive details and timelines is essential.

Case reports should be prepared with the possibility in mind that what may seem mysterious, or inexplicable, to the writer may be crystal clear to an expert or perceptive reader when provided with sufficient detail. Providing as much detail as possible also serves to allow for replication of the techniques used by others. This is a critical component of the scientific method. Other investigators or practitioners must be able to duplicate the procedures and obtain the same outcome. Yet another consideration is that factors currently not considered to be important may become so in the future. There are many examples of this in the history of cryonics that have proved essential to improving patient care. For example, in the early days of cryonics bags of ice were used to facilitate external cooling. It was not until comprehensive and consistent core cooling data were collected that it became apparent that this technique required 6-8 hours to cool a patient to approximately +20°C (room temperature) with the patient cooling at a rate of 0.064°C/min. Documentation of these very slow cooling rates provided powerful incentive to develop stirred water ice baths which increased cooling rates to between 0.15°C/min and 0.33°C /min, allowing cooling to about 15°C within 90 minutes to 2 hours after the start of cardiopulmonary support (CPS) (see graph below).



Comparison of Cooling Methods: Above are actual cooling curves for three adult human cryopreservation patients on Thumper support, using ice bags, the Portable Ice Bath (PIB), and the PIB augmented by SCCD (squid) cooling. Patient A-1133 weighed 56.8 kg, patient A-1169 weighed 57.3 kg, and patient A-1049 weighed 36.4 kg. As this data indicates, PIB cooling is approximately twice as efficient as ice bag cooling. The SCCD appears to increase the rate of cooling by an additional 50% over that of the PIB (roughly adjusting for the difference in the patients' body masses). Source: Case Report Arlene Fried (A-1049).

This example is even more instructive because continued diligent and comprehensive monitoring of cooling in multiple patients made clear other factors that were critically important to good outcome or, conversely, prohibited it. A large-framed obese male with heavy fat cover and a large amount of thermal inertia will not cool at anywhere near the rate that an emaciated, petite woman will. Evaluating the patient for fat cover and body mass index before circulatory arrest allows reasonably accurate prediction of the cooling rate and may suggest the need for the addition of other cooling modalities such as "liquid ventilation" or peritoneal lavage with chilled fluid. Favorable results from application of peritoneal cooling in turn will suggest that even greater rates of cooling are possible for all patients and lead to the addition of the modality as a standard part of the protocol.

Failure to gather and promptly analyze data as basic as cooling rate precludes realization that problems exist as well as any possibility of solving them.

It is important to note that an incomplete case report doesn't necessarily indicate failure on the part of a cryonics organization. In a case where the number of team members is limited, all resources may have to be devoted to *doing* the case, instead of collecting data, or assigning an essential person to the job of taking notes. In the case of limited personnel, it is better to do a good case without documentation than to document a bad case. To some degree this conflict between tasks can be avoided by having some of the team members (the team leader, paramedic, etc.) use a voice recorder with a clip-on microphone. But if the number of team members is insufficient, and data collection is not possible, this should be reported in the case report and recommendations should be made and implemented to prevent this situation from occurring again in the future. After all, deployment of insufficient team members is itself a breach of an organization's deployment protocol. Good data acquisition and scribe work are essential for a good case report and, if feasible, should be a full-time job during a case.

Analysis

Specifying the protocol and describing the case in detail is necessary but not sufficient. A critical review of the information and data culminating in a list of desired changes and specific plans to address them should complement this. Ideally every discrepancy between protocol and reality that has been observed during the case should be discussed. Even in a case where stabilization started promptly after pronouncement, and the protocol was followed to the letter, there is still a lot of (physiological) data that, once analyzed, may require a change in the protocol in future cases.

To assess skills, identify critical failures, formulate solutions, and compare cases in a meaningful and valid way, a consistent and systematic format of reporting cases is essential. A typical case report should be divided into sections describing protocol, patient assessment, preparation and deployment of standby assets, the details of the case (divided in sections such as airway management, cardiopulmonary support, external and other cooling methods, blood washout, cryoprotective perfusion, and cooling to storage temperature), analysis, recommendations, and a variety of (public or non-public) appendices. Such appendices should include time-lines and graphic presentation of data, medications, cryoprotectants, and statistical analysis and comparisons to other cases.

Each case report should not only present solutions, or suggest tests and experiments to identify solutions, but provide a plan of action as to how these things can be accomplished. One approach to ensure that research and tests to validate solutions are implemented, and appropriate remedial action is taken, is to appoint an officer in the organization who is responsible for quality assurance and quality control. This individual's job will be to ensure that case reports are written in a manner consistent with the guidelines as outlined by the organization, as well as to ensure implementation of required changes. It is important to ensure that any issues identified in a case are implemented in the next case (if feasible) and the following case report can then document the implementation of these measures.

Another critical role of case reports is to educate the organization's staff as well as consultants and, where appropriate, the patients' physicians and other health care providers about protocol, procedures and techniques. Although case reports are not and should not be a substitute for comprehensive written protocols, standard operating procedures (SOPs), and thorough training of personnel, sometimes solutions to problems can only be found in case reports where a team member was presented with an unusual problem. Consistent and systematic organization of case reports will greatly enhance the utility of case reports for this purpose. For example, if a reader wants to know about surgical techniques, and problems encountered in gaining access to the circulatory system for blood washout, consulting a case report will be far easier if they're organized in a consistent and predictable manner.

Answering Objections

One objection to writing up a case report is that it is not a controlled experiment and at best provides only anecdotal evidence. This is not the case for the following reasons.

Not all the mistakes and issues identified are of a hypothesis testing nature. For example, if a patient presents team members with a problem that could not be managed with the equipment at hand, the cryonics organization doesn't necessarily need a larger number of cases to decide to make a change to their equipment and can start teaching employees the use of the new equipment right away.

Similarly, what may be perceived as anecdotal evidence for the cryonics organization may be a consistent finding in nearly identical settings in mainstream medicine. For example, some issues during a human cryopreservation case may be well known in hemodynamic management of potential organ donors in hospitals, or, for example, a medication in the protocol that is undergoing trial as a stroke therapy may demonstrate the same adverse effects observed during transport of a cryonics patient.

Of course, such lessons are impossible to learn without broad and deep knowledge of medicine and the relevant research literature. Considering the ever-growing number of publications and hyper-specialization, case reports may increasingly become collaborations between numbers of people with expertise in diverse areas. The individuals with the most valuable input do not necessarily have to be the ones who did the case. A physician dealing with similar issues in a neuro-intensive care unit may identify problems and propose solutions not obvious to those delivering cryonics care to the patient. While the input of team members is necessary for a good report, it does not mean that they will be the most obvious writers of the report.

Monitoring

We don't know for sure how our patient is going to fare in the future but we can know a lot about how our patient fared up to the point of long term care if we monitor his condition continuously. This starts from collecting detailed pre-mortem medical data to monitoring fracturing events during cooldown and doing CT scans.

It is tempting to say that a case went very well if all the steps of the protocol were followed in a timely manner. This is not unreasonable because one would expect a strong correlation between an evidence-based protocol and optimal care. But it is important to keep in mind that the goal of stabilization and cryopreservation is to treat the patient and not the book (as a saying in emergency medicine goes).

Without comprehensive monitoring of the patient through all parts of the procedures a case report will only document a predictable series of mechanical steps and some crude visual indicators of (relative) success at best. The things we are really interested in, like (quantitative) end-tidal CO2 measurements, cardiac output, pH, and cerebral oxygenation, cannot be observed without sophisticated equipment.

Not only do we want to know how the patient is doing after the fact, we would also like to be able to intervene *during* a case if we observe a trend that suggests (alternative) treatment. Only in-depth reporting and analysis combined with a sound understanding of the physiopathology and available treatments will enable us to do so.

Presentation

A comprehensive list of dos and don'ts in writing case reports is not something that can be explored in this article, but some things are worth mentioning. Stylistically, a human cryopreservation report should resemble a medical or research report rather than a sensationalized adventure for the patient or the standby team. This should apply to the organization of the material as well as the choosing of words. As a rule, mainstream medical terminology should be used instead of cryonics jargon or abbreviations that are only known and used within a particular facility.

Editorializing should be limited, and if perceived necessary, be moved to the proper section of the report. For example, jumping from a technical description of procedures to quarrelling among relatives or complaining about government regulation doesn't look very professional. Adverse actions of individuals or organizations that must be reported because the actions materially impacted the case should be described objectively and dispassionately without speculation about motive.

Protocol, procedures, and techniques should be the subject of the report, not people. Cryonics preparation and procedures are very demanding and exhausting for all people involved and mistakes are made and will be made. Errors should be presented as dispassionately as possible to avoid a culture of blame and personal conflict. Experience also teaches that (potential) participants are more open to transparent reporting if a case report will not single out individuals by name in describing procedures. Issues that involve performance of specific people should be dealt with internally during case debriefings, not formal case reports.

No matter how competent the writer of the report is, each report should be proofread by most or all individuals who were involved in the case and, if possible, a variety of outsiders with appropriate technical and medical knowledge, before it is released to the public.

Confidentiality

If the patient of the case report selected in their membership paperwork to remain private after cryopreservation, then the public version of the case report must be stripped of all information that could be used to identify the patient. Pseudonyms may be used as appropriate, and identified as such. At least two people should independently confirm the public or private status of the patient by examining the most recent set of signup documents on file.

No non-staff members involved in the case, whether contract team members, volunteers, family members, medical personnel, funeral directors, or government officials should be identified by name in a public case report without permission of the individual. Similarly, company names, such as funeral homes, hospices, or airlines should not be identified in public case reports without permission. Doing so might jeopardize cooperation in the future.

Public case reports should also exclude any medical history or case details that compromise the dignity or privacy of the cryopreserved person, whether the person is identified or not. Examples of such details include history of cosmetic surgery, substance abuse, sexual history, and mental health unless mental health was central to the cause of legal death. Writers and reviewers of case reports should edit the public version of case reports as though the report was describing their own cryopreservation. If there is doubt about whether a case detail is too personal, it should be excluded from the public report.

Patient Care

Writing case reports as presented in this article may be more demanding and time-consuming than generally has been done in human cryopreservation, but the results may improve patient care to a degree not previously seen. Ultimately, the most ambitious use of case reports will be one in which the case reports are analyzed as a series, measurements are compared, and patterns are established. Reading (and evaluating) a series of case reports in a systematic manner will even enable us to answer some very fundamental questions as to whether, or the degree to which, protocol, procedures, and techniques have improved over the years. A meta-analysis can also reveal what the typical expectations (cooling rate, duration of CPA, cryoprotective perfusion time, edema etc.) for a cryonics case should be, given a certain protocol.

Providing the best patient care possible for current and future patients is the reason why cryonics organizations exist, and considering how powerful a tool a good case report can be, a responsible cryonics organization should devote considerable resources and time to writing them.

As our members and resources increase, and human cryopreservation gradually becomes a part of mainstream medicine, the successful transition from basic algorithmic, volunteer-driven care to evidence-based cryonics will be an important mandate.

Case reports and increasing caseload

One of the biggest challenges facing a growing cryonics organization is that it will also have more cases per year. This challenge is further amplified if all these cases need to be documented. Consequently, a cryonics organization will find itself allocating an increasing amount of time to writing case reports and falling behind publication schedule. One of the most unfortunate responses to such a development would be to try to keep writing case reports in the expected style but to lower standards and take shortcuts.

An alternative approach is to develop a new format for case reports that allows for a shorter report but still captures the essential objectives of case reporting. One approach is to eliminate all the narrative that is not essential for following the mechanics of the case and evaluating the quality of care. In the past there have been several case reports with excessive narrative but little technical reporting or analysis. For a cryonics organization with a growing caseload the opposite approach should be followed. Another approach is to eliminate detail about procedures that were performed without deviations from past protocol and expectations, provided that this is made explicit in the report. As a result, case reports will increasingly read as a description and commentary on events that diverged from protocol or new observations about existing procedures.

To establish a template for such case reports the following approach can be followed. First, it is established what kind of information is essential for doing a meta-analysis of all cryonics cases. Then these parameters are reverse-engineered to create a template for writing case reports that reconcile the need for economy of expression and documenting all the relevant aspects of a case. One important advantage of producing such case reports is they permit easier consultation of the technical details of the case and still meet the fundamental objectives of writing case reports.

Another attractive approach for writing case reports in an era of many cases is to identify one or more important issues or achievements in a case and build the report around this. This approach is consistent with the medical literature where case reports are often produced for patients with unusual outcomes, extraordinary interventions, or new medical developments. For example, a case could be published as "A-20xx: Extraordinary Cooling Rates Achieved During Stabilization" or "A-12xx: Patient with Fracture-Free Storage at Intermediate Temperatures". It should not be hard to find one or two important themes in the case data to justify such an approach. Writing case reports in this manner can be more rewarding for the writer and more engaging to read for the average reader.

The history of case report writing in cryonics shows an erratic potpourri of approaches and styles. One of the most unfortunate casualties has been the objective of using case reports to improve the practice of human cryopreservation and to formulate meaningful research questions for the sciences that inform cryonics. But if systematic thought is given to the objectives of case reporting outlined in this document, steps can be taken to leave this unsatisfactory situation behind while meeting the needs of a growing cryonics organization.

Who should write the case reports?

Historically, the tradition at Alcor was that a team member with the best writing skills and technical acumen wrote the case reports. As Alcor's caseload increased, this responsibility increasingly has shifted to the team leader and/or paramedic that was employed at Alcor. On the surface this does not appear to be an unreasonable choice but there can be complications. First, EMS personnel are not necessarily skilled writers or have the technical acumen to write scientific evaluations of a case. Another problem is that there is a potential quality control conflict of interest issue when the person responsible for leading the case is also the writer. A possible solution is to recruit a quality control officer who is also responsible for writing the case report. This approach permits a more dispassionate analysis of the case and prevents skilled medical professionals being taken away from further education, training, and readiness responsibilities. A disadvantage of case reports prepared by persons not present is lack of direct knowledge of what transpired during the case. If different individuals write reports (which can happen when an organization tries to clear a long log of reports) it is still important to use a consistent template and style. Meta-analysis of large numbers of case reports becomes a lot more complicated when each case report is structured in a different manner.

A common flaw in case reports is high variability in procedure detail and data in a single report. Often this issue can be attributed to the practice of merging materials from various individuals and organizations without checking for (stylistic) consistency. A typical example of such a report is one with a detailed stabilization report from the standby contract organization, an almost non-existent cryopreservation narrative from Alcor, followed by extensive unedited timelines.

Common flaws in case reports

Recurring issues which need to be avoided in professional cryonics case reporting are listed below. In case of doubt, use mainstream medical case reports as a benchmark.

Inconsistent organization of the text from report to report

Improper use of team member names or cooperating people and institutions

Irrelevant anecdotical or biographical information

No reference to the protocol that should have been followed

Unedited, or excessively detailed, timelines

Detailed information about one procedure and little information about another

Imprecise nomenclature (such as the use of "suspension" or naming a section "perfusion" without specifying the type of perfusion)

No discussion of issues, recommendations, or follow-up actions

Notable Case Reports

1984

A-1056, A-1057 and unidentified patient

For all three patients fluid samples were obtained from the body of the patients after neuro conversion. The report specifies cryoprotectant osmolalities for all three patients in fluids obtained from different parts of the body. The author suggests that the low and variable distribution of cryoprotectant can be attributed to low volumes of the cryoprotectant and ischemia-induced perfusion impairment.

1985

A-1068

This case report contains an extensive discussion of blood, washout perfusate, and cryoprotectant perfusate samples.

1987

A-1133

This case report has an extensive appendix with graphs of blood gases, electrolytes, and enzymes data during cryoprotective perfusion.

1990

A-1049

One of the most comprehensive studies of a cryopreservation case ever written. This case also stands out for conducting a renal viability evaluation, which was possible because the patient was a neuro patient. The patient's kidney was subjected to renal slice intracellular/extracellular potassium/sodium ratio tests in a cryobiology lab and the average ratio of 3.5 corresponds to the expected value for such slices after a hypothermic storage time of approximately 2.5 days.

1995

A-1871

Detailed technical case report of the first cryopreservation by *CryoCare*, which was transferred to Alcor in 2001. Multiple external and internal cooling modalities are employed in this case.

2002

A-1876

Three boluses of perfluorocarbon, totaling more than 2 liters, were infused into the lungs of this Alcor patient to accelerate cooling, the first and only time basic "liquid ventilation" technologies have been used in cryonics.

2004

ACS 2004-1

Whole body field glycerol cryoprotection case by *Suspended Animation.*

2006

A-1097

The most extensive Alcor case report since the introduction of vitrification. This report also includes the document "Advances in Cryonics Protocols, 1990-2006." Lowest first fracturing temperature recorded in an Alcor case (-134C)

2010

A-1712

Extensive documentation and discussion of Alcor's response to an autopsy case. ■

Contrastive Underdetermination Resolution, with Application to Cryonics Revival and Other Possibilities for Life after Clinical Death

By R. Michael Perry, Ph.D.

The "copy problem" has been debated in cryonics for many years: Would "you" survive in a future construct very like you but not containing original material? Here an approach to this problem is offered that starts from the position that the problem is scientifically unresolvable, a condition known as contrastive underdetermination. It is argued that a rational choice between alternatives is still possible, the best being that one should accept the notion of survival through a copy. Some deep implications of this viewpoint are considered, including a possibility of restoring long-deceased individuals to life in a distant future.

1. Introduction

Contrastive Underdetermination – when two or more theories or interpretations of things have the same empirical consequences and cannot be distinguished on the basis of observations[1] – poses a problem in a field like cryonics, where mortality is confronted and issues of personal survival are important. In cryonics persons are cryopreserved after clinical death in hopes that future technology can revive and restore them to healthy consciousness. To date no one has been revived from cryopreservation, and clinical death in most people's minds is simply "death," from which there is no likely reprieve, unless mystical or metempirical beliefs are invoked. Cryonics advocates are more optimistic, resting their hopes in future technology to restore those who, they hope, will not have suffered too much deterioration in the aftermath of their clinical dying and subsequent preservation at low temperature. Still, even among these optimists (I include myself) there is much speculation and uncertainty about how it might happen and what issues might be important. Some issues can be confidently assumed to be important, however, even in our present state of ignorance. We would want to know, in particular, if the "same" person would be revived under various assumptions, such as replacement of some or all of the body parts with similar or similarly functioning components. Or instead, would we only have someone who is similar to the original but still an entirely different (or partially different) individual? Opinions vary, and there is no known empirical method for determining the answer. I think this difficulty, whether a person could survive in a copy under various assumptions, is fundamental, in the sense that future science will never simply "find the answer." One must choose one's answer based on different criteria than whether one's choice can be said to "fit the facts," since more than one, significantly different theory or interpretation of the relevant issues will do that. Here I propose a method of contrastive underdetermination resolution (CUR) which allows a choice between competing viewpoints under a wide variety of conditions.

The method endeavors to select, among the empirically equivalent candidates, a theory with "optimal" consequences. We must determine what we mean by "optimal" but at least we have reduced the one philosophical problem to another one, hopefully an easier one to deal with. Once again, there is more than one possible choice of an answer. Some, for example, may want to be as sure as possible that it will be they who are revived and not someone else. On this basis they may elect whole body preservation, accepting the extra cost of the procedure over, say, the neuro option in which only the head with the brain is preserved. Others may feel that there is no metaphysical advantage in being revived as an "original" rather than a copy, and may even make the choice to be revived as a software bot or "uploaded" in a future computational device – supposing this is possible – to escape biological limitations altogether. (The brain should be sufficient for this, so the would-be uploader may be satisfied with head-only or brain-only preservation. Furthermore, assuming a successful upload, the physical remains, including the brain, having now become superfluous, may be discarded or stored indefinitely as a historical relic.) Here I try to give due consideration to the different perspectives on this problem, including the "restrictive" position (RCUR, suggested pronunciation, "are-cure") that the original body may be needed to preserve the original person, so that one should choose the most complete preservation possible. My sympathies however, are with the "expansive" outlook (ECUR, suggested pronunciation, "e-cure") that asserts that one survives if no reasonable empirical test can show otherwise. On this basis, then, a copy of you, which would be similar to you in all important psychological respects, is you. More than one, divergent copy would signify that one individual had split into two or more, and (certainly!) not that the one, original person had died.

The copy problem is essentially a philosophical problem, rather than a physical or scientific one. Contrastive Underdetermination

applies to scientific problems too, however. One case in point is with interpretations of quantum mechanics, or more generally, whether parallel universes or other unseen large domains exist, with deep consequences if they do. Again, there are empirically equivalent theories which affirm and which deny the multiple worlds. There is evidence that can be seen as favoring at least some versions of multiple worlds, such as the success had already with quantum computing and the apparent progress to come. Invoking the expansive ECUR, I affirm their existence. It will be seen that this has interesting and optimistic consequences relating to revival after clinical death – and not merely the clinical variety. An argument is offered which applies to the resurrection of deceased individuals whose information has perished and cannot be recovered, that is to say, who have suffered information theoretic death. Though the information has been lost, the resurrection, which speculatively extends over parallel, multiple worlds or domains in a multiverse, *can happen in essentially only one way*, and thus can be considered authentic.

In what follows, first there is brief note on "perspectives" which touches on underdetermination in science and philosophy, with reference to the problem of mortality. The copy problem which will arguably be important in cryonics revival is then considered. Afterward is a treatment of the resurrection problem in a setting of parallel worlds, and a brief concluding section that notes some reasons to choose cryonics over alternatives even if a general resurrection is eventually going to happen. Much of this latter material is adapted from two articles by the author which appeared in volumes edited by Charles Tandy (2013, 2014), whose support in this project is gratefully acknowledged.

2. Perspectives

In addition to the contrastive underdetermination we are considering here, I note in passing there is also holistic underdetermination, in which a theory fails to match all the observations and one is left wondering what portion of it is amiss and how.[2] (As an example, Newton's theory of gravitation, while highly successful for a long time, was finally found discrepant with certain astronomical observations and was supplanted by the more accurate relativity theory of Einstein. In point of fact, however, Newton's simpler theory still has great usefulness in many settings, where its discrepancies are insignificant.) For contrastive underdetermination, where fitting the observations is not the problem, we can have different "strengths," that is to say, *absolute* or *relative* underdetermination. The absolute or "strong" variety is irremediable, that is, no advances in science or knowledge will ever tell us that one version is right and all the others are wrong, at least insofar as the different theories can be tested experimentally. The relative or "weak" variety, on the other hand, will eventually yield to greater scientific understanding. (There is, of course, the difficulty that one would have to foretell the future to determine this level of strength. Still, some versions of underdetermination considered here do seem of the strong variety, as noted, mainly when the issues involved are philosophical rather than scientific.)

It is easy to see how contrastive underdetermination is unavoidable in any attempt to explain or account for whatever is observed. For example, we, our whole visible universe, might be in a computer simulation, governed by an advanced Sysop, who might at any moment cause things to happen very differently from all that we have observed so far. To combat such distracting speculations and reduce the extent of underdetermination we can invoke Ockham's razor or the principle of parsimony, named after the 14th-century philosopher and theologian William of Ockham, which seeks the simplest possible explanation that is consistent with observations.[3] Although this has proved overall to be a good rule of thumb, sometimes it is unclear what explanation is really "simplest."

For example, should we think, like the modern astronomer, that the stars are suns like our own but at a vastly greater distance, to account for their faintness compared to the solar brilliance? Or are they much fainter lights than the sun to begin with, and not so far away? Another such conundrum concerns the shape of the earth. Is it flat or round but with a curvature so gentle it is not perceived? In the case of the stars, based on Ockham's razor alone, and lacking the telescope or minutely detailed observational knowledge, we might go either way. For the shape of the earth, the flat earth theory is clearly simpler if both theories will fit, since otherwise we would have to contend with just how much of the putative curvature the earth has. Both questions were, of course, settled long ago (for most people at least) by better scientific data, including observations from space. The contrastive underdetermination was only relative – removable with better observations – not irremediable in principle or absolute.

Round Earth seen from lunar orbit (NASA, 1968), sunlit side facing upward. Photo Credit: NASA, 1968, https://www.nasa.gov/multimedia/imagegallery/image_feature_1249.html, accessed 31 Oct. 2018.

In philosophy, however, concepts such as truth, beauty, love, justice, and goodness have a myriad of associated theories and opinions, with no clear idea as to which might be "the one right answer." It seems plausible, in some of these cases

at least (take beauty for instance), that there may never be this one "right" answer – the answer instead may be said to be "a matter of taste." But such a conclusion sometimes is especially discomfiting and frustrating, for example, when it comes to life and death issues. Would persons, ourselves in particular, survive or not under certain conditions, as with the copy problem? The answer will depend in a sensitive way on how we define the relevant concepts and very different answers will be given by approaches that are empirically indistinguishable. We do not wish to feel that the answer is just a matter of taste, though, as I have speculated, the underdetermination in the case of the copy problem seems absolute. Hopefully the approach taken here with ECUR will not seem whimsical or just "a matter of taste" but can be taken more seriously.

The problem of death has been with humankind as long, we may conjecture, as our brainpower allowed us to perceive our mortality and its apparent inevitability and finality. At heart we are opposed to death, our own and that of others – natural selection has made us that way. If it occurs we seek a remedy. In ancient times various beliefs grew up about an afterlife and what one should do in this life to assure that one would be happy and well provided for in a world to come. Those of more scientific bent, particularly in more recent times, often belittled these beliefs and instead called for acceptance of death which, they confidently asserted, could not be significantly forestalled or remedied. More recently some have challenged these latter views, again on scientific ground. The cryonics movement started in the 1960s as one form of challenge to the prevailing attitudes about death. After cardiac arrest there is a time window when the patient is not considered "alive" by today's criteria, but deterioration still is limited. If you treat the body and cool it to cryogenic temperatures, there seems a real chance, at least in the minds of advocates, that future advanced techniques could restore the patient to a healthy state.

Cryonics offers hope for those able to take advantage of it, but there are many others who perished or are perishing today without it. Is there any hope for them, if we exclude putative supernatural or other metempirical powers or forces? Most today would say no, probably including those in cryonics, yet a small residue of the thinking community has seriously proposed otherwise. We shall consider this thinking tradition briefly later, in our introduction to the problem of resurrection involving parallel worlds. For now we return to cryonics and the copy problem.

3. The Copy Problem in Cryonics

"Will it work?" people ask of cryonics. In the early days such a question was likely to evoke a simple scenario. A deep-frozen body – the patient – stays dormant for a short or long time, then – if cryonics "works" – the patient is restored to functioning by some form of advanced future technology. The same body, with its structural integrity more-or-less intact, stays in place from the time of preservation to the time of revival. Success – restoration to healthy consciousness and full functionality – means that not only is someone *like* the original patient restored, it *is* the original patient, vigorous and active once more. (Even here there are dissenting voices, concerned about the repairs that might be necessary, and so on; here I am ignoring these difficulties as secondary to the main issues.)

Will it work? James Bedford is cryopreserved as a whole body, January 12, 1967, the first human cryopreservation under controlled conditions with revival as a goal. Photo courtesy of Robert Nelson. Further reference on the Bedford case: R. Michael Perry, "Notes on the Cryopreservation of James Bedford," Cryonics 35(2) (Feb. 2014) 10-15, https://www.alcor.org/cryonics/Cryonics2014-2.pdf, accessed 31 Oct. 2018.

In other cryonics scenarios, though, questions are raised. In the case of neuropreservation (head only) we imagine it should be possible to recreate a close approximation of the original body using information in DNA so the patient will have full functionality and may have a healthier and better functioning body than before. Some though raise the issue of whether this replacement of all but the head would result in the "same" individual. The patient may look and feel healthy and be fully functional, and have similar appearance and memories, and even believe they are the same, but still not be the same person as before.

A more drastic scenario of replacement would follow if, using advanced future technology, we created a complete duplicate cryopreserved individual and revived them. (This should be possible if we had a general-purpose molecular assembler able to make atomically exact copies of stable molecular structures and could operate at low temperature. The laws of physics appear to allow such a possibility.) Would this copy be the "same" person as the original? (Without this worry, the replacement might be an advisable procedure; an elderly patient, for example, could be restored to full youthful vigor by rebuilding from the ground up.) Going still further, suppose we imagine that a person is, essentially, a kind of computation that is running on "hardware" consisting of their body, mainly the brain. An equivalent sort of program could be started up on an advanced computational device of the future, and the person could continue their life in that way. (This is the "uploading" scenario, also essentially what is called whole brain emulation or WBE, leaving behind aging and all other biological ailments with the body, which after the procedure may be discarded.)

Overall, we have the "copy problem" when the whole body is not just straightforwardly preserved and eventually revived. Can "you" – the "real" you – survive in a copy (or partial copy)? Opinions in cryonics as we have noted vary from the restrictive – denying that a copy is you, to the expansive position that accepts that one could survive in a copy. In the latter case, in the form supported here, the survival occurs even if the entire original is replaced, and even if the person, their mental processing, thinking, and so on, is expressed or "run" in a different physical substrate, as with uploading.

It is no trivial matter, at least to many of us, whether it *is* you who will survive. We want to come back in the future, for it to be really us not just someone who is similar but still a different person. (I am not contesting that that person too would then have a right to exist. But I think most would agree that we do not have a moral obligation to die so that some other person can be created and "occupy our place" in the world, even if they could play the role very well and also be glad *they* were alive.)

So we apparently have a serious problem, with no obvious answer or way to resolve it, in the scientific manner we would like to think possible. We may hope, perhaps, that "science will find the answer," much as we hope that revival from cryopreservation (say the straightforward, philosophically uncomplicated whole-body variety) will be possible someday, when more research is done and technology is more advanced. On the other hand, though, I think there is much reason to be skeptical that an answer to the copy problem will be found this way, even though I am hopeful that cryonics revivals *will* happen this way, that is, due to future scientific and technological advances. The two problems really are quite different. Revival is basically an engineering problem while the copy problem is philosophical. As the philosophical problem that it is, the copy problem is susceptible of more than one answer, each of which will "fit the facts," that is, be indistinguishable from its rivals empirically. It appears to be a case of absolute contrastive underdetermination. One should not be despairing, however; I think the problem has a reasonable resolution, which is to simply invoke ECUR and declare that one would indeed survive in a copy, if such could be made. Before making this firm commitment, it is worthwhile to consider some additional issues. Sometimes, in fact, the copy scenario (better thought of as replacement in these cases) seems fairly unproblematic, and many would not be troubled by it.

4. Surviving as a Copy[4]

Imagine the following thought experiment. In the future, artificial brain cells have been developed. One of these could replace a cell in your brain and perform the same neurological functions as the natural cell. (Perhaps, as an added bonus, the artificial cell would be more durable and less prone to damage or degradation over time, maybe impervious to strokes and other present ailments.) So suppose now that gradually, over a period of time, your natural brain cells are all replaced with the artificial ones. This could happen when you are fully conscious. Onboard, say, are advanced nanorobots who each day, during an 8-hour period when you are fully awake, replace one cc of your brain, less than 0.1% of the total, so the whole process takes about four years. At each stage in the replacement, outside observers see that you continue to function and have no complaints about what is happening, nor do you feel anything unusual. So finally, the whole brain is replaced, and "you" have become a copy. The copy, though, according to many people, would still be "you" – not some other person, and the fact of the replacement of your natural gray matter with an artificial equivalent would not weigh against that conclusion, precisely because the replacement was gradual. (This might hold even if the replacement were accompanied by replacement of body parts with artificial similarly functioning components, so your "housing" finally ended up 100% artificial, or effectively you had been uploaded.)

Objections are raised, however, against the idea of a sudden replacement. Suppose you are anesthetized, a copy is made with advanced technology, the original while still unconscious is destroyed, and the copy awakened. Some (not all) would say that a different individual was produced and the original had died.

Other objections also persist. One concerns the "multiple duplicates" problem. Suppose, in the preceding scenario, the original was *not* destroyed but also awakened, so that both individuals began to have differing experiences and live separate lives. Some would say that, not only are there separate persons now, but neither is the original who was anesthetized; that person instead is now dead and can never be restored. I would not go so far, but consider that the one person has now fissioned and become two. A similar rationale would apply

if more than two copies resulted; it would be fissioning, not death.

Each of the copies, then, is not best regarded as being identical in all respects to the original, but as being a *continuer* of the original. If this seems alienating and counterintuitive, the same situation clearly applies in everyday life also. Your "self" of today is hardly identical in all respects to your past selves, but has enough affinity with them, normally, that it can reasonably be said to be a continuer of these past selves. But your self of today would not be the only possible or conceivable continuer of the past selves. Suppose this afternoon you watched a football game on TV, passing up the chance to take a stroll in the park. If instead you had taken that stroll, that version of you would still be a continuer of your past selves prior to your decision to choose the one activity over the other. So, in the case of multiple duplicates we are considering, each is reasonably a continuer of the original, even including the case that the "original" is awakened along with the rest. There is no special significance attaching to this one copy, regardless of its provenance, provided the other copies are faithful. The original one person (the *real* original) can reasonably be said to have fissioned into more than one. The above scenario assumes that the duplicates, after their creation, will have gone on, for a short time or long, to live separate lives – have separate, distinct thoughts, perceptions and experiences. If somehow this did not happen, but their perceptions and thoughts all matched in lockstep, a different assessment would be called for, where instead we would have one individual with multiple instantiations – more about this later.

For now, that you could survive as a copy means that, for instance, a cryonics revival that replaced parts of your body – other than the brain, which is restored intact – would be valid. The whole brain could be replaced also, but would require copying from the original, preserved organ or at any rate, accurate inference. Similarly, "you" would survive if your identity-critical information is extracted from your remains by some future method and uploaded to a computational device which "runs" an accurate version of you, that is, carries out WBE. In short, "you" would authentically return to functioning so long as a process sufficiently similar to you is restarted, regardless of substrate materials that were used.

Recognizing that not all objections can be met, I here invoke ECUR and accept the position that you would survive in a copy, even if the copy were produced while you were completely unconscious. (I hope the advantages of this position, in terms of the possibilities to be discussed, will tempt some of those opposed to it to reconsider.) The copy could be produced by copying information from a source such as preserved remains (as anticipated in cryonics). But I will take the more general view, again invoking ECUR, that a copy from whatever source, even if not actually "copied" at all but created from scratch, constitutes a basis for survival.

5. The Self as a Pattern not a Token[5]

Persons in short are patterns or *types* not material objects or *tokens*. More specifically we are evolving, finite patterns that alter and develop over time but also are subject to duplication and recreation. We have already considered the seeming difficulty if one self is replaced by several – it really is not a problem. As for recreation, it provides that a pattern that previously existed but might have been destroyed can continue the person's existence even after the destructive event occurred. It is not necessary that anything remain of the pattern between its destruction and its recreation, only that the pattern on second appearance be like or similar enough to the original. Thus we are overlooking considerations of individual, like occurrences of the same pattern, that is to say, identical tokens, having separate identities.

More specifically, the self, as viewed here, is essentially a computational process, analogous to a computer program running on a machine (the "body").[6] Combined with patternism, we can be seen as software in operation rather than hardware. This model gains credibility from the fact that all processes in nature are, at basis, algorithmic, based on quantum theory. Everything is, in effect, a quantum computation. And quantum graininess assures us that all important changes occur in sudden jumps like state changes in a digital device such as a human-made computer. Persons then are delineated by finite descriptions or "programs." Although a computer might run a program which never is altered in the course of execution, we also have interactive programs that respond to changes in input (stimuli from the outside), to the extent that the computer code itself may be modified, with new instructions or changes or deletions in existing instructions in the code. Such may happen with what we are calling a person as well, though clearly there must be limits on the allowable changes to ensure that we still in some reasonable sense have the "same" person. In any case the person-program at all times remains finite. This includes each person at each stage of his/her subjective existence or "state of computation," that is to say, each *person-stage*.[7] The set of all these possible person-stages, expressed in an appropriate formal language, is denumerable and could in principle be enumerated by a computer running over infinite time. In this way all possible person-stages of all persons who ever lived or will live could be created, furnishing a multiple basis for resurrecting those persons who are deceased.

The body-machine or "hardware" which "runs" the person-program – and thus the person – is not essential to the person being "run" but might be changed by the program being transferred to another device. Moreover, the self is really not "in" the body exclusively; in principle one could imagine multiple instantiations of the self-computation so the self must be regarded as being distributed over the (likely very) many constructs in reality as a whole which are engaged in equivalent computations. Elsewhere I have called this principle

– that one's self is distributed over multiple instantiations – *Interchangeability*: one copy of you running is as good as another, where both are running, equivalently, in lockstep, even if at different times and/or speeds.[8] This scenario in particular would gain credibility if we imagine that there are alternate universes or other large domains in which similar processes sometimes occur. The existence of such alternate worlds is controversial but has some able defenders.[9]

Overall, then, reality as a whole appears to have ongoing processes that cover everything that, under the laws of physics, has a nonzero probability of happening. This means that, in particular, all possible, finite histories must be happening somewhere. Somewhere, in a universe like ours, on a planet like our Earth, Napoleon won the Battle of Waterloo, or President Lincoln was not assassinated, or a race of intelligent dinosaurs rather than hominid mammals evolved and developed space travel. This principle I call *Unboundedness*.[10] At present there is no way to prove or disprove it, though it does seem natural (if something is "possible," why should it not happen, somewhere?). Again invoking ECUR, I assume Unboundedness here, along with Interchangeability. The two together comprise the UI assumptions, as I have referred to them elsewhere. Together they will be important in the resurrection scenario to be presented.

It is worth noting that, while both Interchangeability and Unboundedness are unproven assumptions that rest on contrastive underdetermination, they differ in one important respect. Interchangeability is a philosophical position, based on a definition of what would constitute personal survival, and inherently (as far as I can see) beyond the power of science to confirm or disconfirm. Unboundedness, however, makes a claim about reality which may be amenable to empirical testing. (That there could be parallel worlds is suggested, for example by quantum computing, still in its infancy but possibly in the future clearly superior to the classical variety for important problems. In this case the multiple worlds hypothesis, specifically the Everett many-worlds formulation of quantum mechanics, would provide a handy explanation for how the extra computing is being done.[11])

In general, we expect that computations which have been equivalent up to a point will not continue in lockstep very long but quickly diverge leading to fissioning of the person which up to then was only one individual but multiply instantiated. However, there is still a small chance that the lockstep correspondence will continue for a considerable period. So in the whole of (presumably infinite) reality, we could expect to find infinitely many instantiations, say, of one person, Alice, running in lockstep. Let any finite time pass, and but a very small fraction, though still infinitely many of these instantiations, will still be running in lockstep, while the rest will have diverged into multiple Alices. The lockstep and diverging computations both play a vital role.

To restate and summarize: a "person" is expressed, at any given subjective, conscious point in their life, as a set of material constructs or *instantiations* distributed over reality as a whole, generally in different, parallel worlds. (According to Max Tegmark these are very far apart yet definitely exist.[12]) Each instantiation is a material object consisting of a person-machine that is "running" the person in question. Each is supplying the particular features of consciousness that also recur identically in each of the other instantiations. (The "identical" recurrence follows from the computational model in which processes can be exactly replicated in different devices, and is supported as a physics principle by quantum graininess.) *Duplicate consciousness is shared consciousness*, as once again provided through ECUR. (And this seems clearly a philosophical rather than a scientific instance. It would be arguably impossible in principle to disprove; second, it has highly desirable features. So with claimed justification, it is assumed.) The self can then be seen as a persistent entity, able to survive the physical destruction of the body in two possible ways. One is through instantiations whose existence continues while one particular instantiation is destroyed (direct survival in parallel domains including different universes). The other is through the creation of a new instantiation, whether by informed or uninformed (accidental) means.

A little more should be said about the notion of instantiation. We assume that like or equivalent processes that we consider persons are running on different devices. The devices themselves would not have to be similar or clones of each other for their processing to be equivalent. But the processing should be equivalent, at least insofar as what we call consciousness is involved, to insure that there is duplicate and thus shared consciousness. In the above we are assuming that some form of exact or exactly equivalent, high-level duplication in the processing occurs, so that different constructs will be instantiations of the same person and not distinguishable individually as separate persons with different conscious experiences. As noted before, we might expect that devices that had been running equivalently could diverge and express different consciousness at any time, fissioning our one individual into more than one.

6. Preliminaries for a Resurrection

The Russian 19th-century philosopher Nikolai Fedorov developed a theory of resurrection based on a then-current, scientific perspective, and extrapolating to future capabilities yet to be developed. Using these putative methods it should be possible to trace the motions of individual atoms (or small particles) back in time to determine their placement in the bodies of persons now deceased. Using additional yet-to-be developed methods it should then be possible to reposition these same particles and thereby restore the dead to life.[13] Fedorov was devoted to the idea that such a resurrection ought to happen and considered this project a "common task" for a future, advanced human civilization which would unite the living with their

ancestors and others of earlier times so that the highest happiness could be enjoyed by all.

In view of the preceding discussion it should be clear that the resurrection problem reduces to the informational problem of arriving at a sufficiently accurate, finite description of the resurrectee. From this, given reasonable assumptions about future capabilities, a functioning copy of the deceased individual could be created, with appropriate adjustments such as elimination of diseases and disabilities. (To restore the exact atoms of the original in their original places, as might have preoccupied Fedorov, would not be necessary as long as an appropriate replica was made, or more generally, some construct with equivalent functioning to emulate the desired individual.) For Fedorov, the critical recovery of information for positioning the atoms was apparently allowed by Newtonian physics, much as, on a larger scale, planetary motions over centuries could be accurately predicted or retrodicted from astronomical data. But the advent of quantum physics has seen hopes fade for tracing atomic motions into the distant past, at least by any process remotely prototyped today. Some, it is true, have held out hope for such recovery by future, exotic methods grouped under the rubric of *quantum archaeology* (QA).[14] QA, if successful, would be a form of virtual time travel that would tell us, among other things, the minute brain structure of past individuals who died and whose remains were not specially preserved, as with cryonics. That, on the contrary, a straightforward recovery of information now obliterated is impossible seems strongly suggested by certain experiments involving loss of information.[15] I think it likely and assume that the hidden past – what is obscured by loss of information involving chemical decomposition, decay, melting, erosion, burning, and other destructive processes extending over time – cannot be recovered by any archaeological method likely to be developed. Fedorov's ideas of resurrection through some means of deciphering a unique, hidden past must therefore be abandoned.

With this as a starting point, I propose an alternative strategy to QA that I call *parallel recreation* (PR). PR will focus on *recreation* of information not *recovery* in the usual, archaeological sense, though archaeology to its allowable limits is (preferentially) to be employed, supplemented by informed guesswork. In this way the desired information can be obtained so that resurrection of the dead can occur. PR assumes a worldview in which reality as a whole is not confined to the visible universe but consists of a multiverse in which individual universes or equivalent coexist in parallel and give rise to histories, again in parallel and unfolding in all variations allowed by physics, with appropriate probability-weights. Though not strictly necessary to an individual resurrection, PR as envisioned here might advisedly focus, Fedorov-style, on many resurrections as part of one comprehensive effort. Such a project could be initiated at some point, within a few centuries or even sooner, when mature nanotechnology (controlled manipulation of matter at atomic scales) is available. First the historical record including archaeological remains and, more distantly, fossils, would be thoroughly mined so that substantially all surviving information would be recovered. Though this would be inadequate for resurrections the necessary additional information would be filled in by guesswork to produce a *timeline cohort*, a population of individuals representing one timeline of Earth history. (This would not be limited to humans but other sentient life-forms could also be included and arguably should be.) Parallel efforts meanwhile that automatically occur in parallel universes would reconstruct all variations of timeline cohorts corresponding to different timelines that fit our (partially complete) historical record as well as theirs. In this way, all individuals of our past history in all its physically allowable variations would be resurrected. (In addition to this there would be cohort creations in universes with differing historical records to ours, also as a consequence of parallelism.) Each timeline cohort will be authentic to the universe of its creation, though not uniquely so, based on the philosophical premise that irretrievable loss of information makes the past ambiguous, which once again could be justified on grounds of ECUR. In effect the observer must be considered a nonlocal phenomenon, distributed over all those parallel domains in which his/her copies or instantiations reside.

7. The Resurrection Is Unique[16]

Here we show in more detail how a resurrection would happen under PR and, in fact, can only happen in essentially one way. A simple coin toss experiment can illustrate some of the basic features, which can then be extended as needed. A coin is shaken in cupped hands and tossed, generating one bit ("heads" or "tails"). The one bit at this point forms part of the historical record. Next, without looking at the coin or recording its orientation, the experimenter shakes up the coin again, erasing the bit from the record. The coin is tossed again, generating another bit, which this time is recorded. In what sense, we ask, is the recorded bit a recreation of the lost bit? There are three possible philosophical approaches to an answer, the third of which is assumed here.

For the first, "provenance is everything" and "there is a unique historical timeline, even if we do not know what it is." The first, lost bit thus is irretrievably in the past. The second bit may be the same as the first but it does not matter, at best it is "just a copy."

For the second approach there is still the unique historical timeline in which information may not survive. But provenance is not really important, only the end product, in this case the one bit. There is a fifty-fifty chance, then, that the lost bit has actually been found again. It was (possibly) found without any knowledge of the original, without the recovery of a "hidden past" that is promised under QA. Enough bits guessed in this way would suffice for a description of a person suitable for a resurrection. Such an effort, we may imagine, could be

constrained appropriately so that a person-description, in a suitable, predefined language, actually resulted rather than say, a rock-description or, much more likely, just random noise. Nonetheless, the number of bits that must be guessed would still be huge, so the chance of a correct guess would be vanishingly small and no hoped-for resurrection would be remotely likely in time bounded by the age of the known universe.

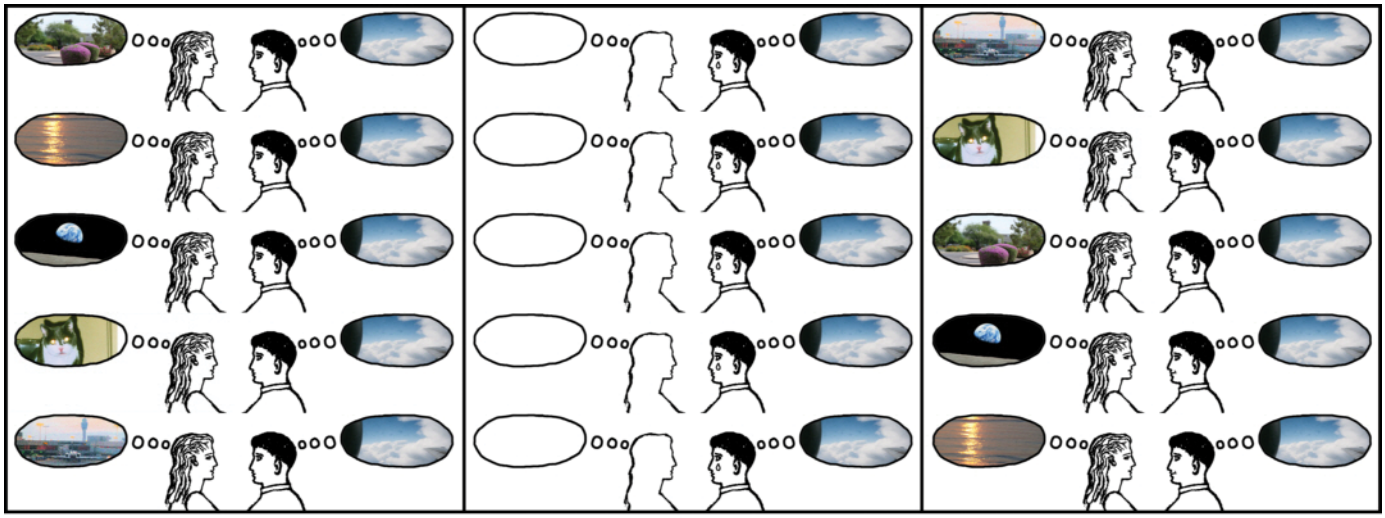
For the third approach and the one assumed here, the multiverse exists and comprises the larger theater that is intended for PR. We no longer have the one experimenter tossing a single coin, but opposite numbers of him are distributed through innumerable parallel worlds also tossing coins, half of which return "heads" and half "tails" on each of the two occasions. (More correctly, the one experimenter is distributed over or instantiated in the many worlds, but remains one not many.) On the second occasion the one bit in its two varieties is generated, so that both versions reappear, accounting for all the (two in this case) versions that originally existed. Provenance is not important, nor is there just one historical timeline. So the lost bit in its two varieties is recreated with one hundred percent probability and fidelity.

Here, *the whole process can happen in only one way*. This will seem counterintuitive if we focus on just the one coin toss in one setting. The second toss, the "resurrection," could come up in one of *two* possible ways. However, we interpret this process not as just one happening in one parallel branch of reality, but include all the other branches as well. In that expanded setting, both alternatives occur regardless of what happens locally, in one setting only. Every local setting where one alternative occurs is matched by one where the other occurs, no matter how an individual case turns out. And "local settings" really have no individuality of their own but one can only note if one is the same or different from another. (If this seems questionable, I again invoke ECUR.) From the standpoint of an imaginary external observer able to see all the parallel branches at once, the toss *always* has the same outcome. Overall, the resurrection, in this case of the one bit, happens in only one way.

A coin toss involves only one bit but these ideas can be extended to happenings with arbitrary, finite spatiotemporal extent and finite descriptions (finitely many bits). Suppose Bob is a friend of Alice. Bob knows some information about Alice, and values their friendship, but there is much about Alice that only she herself knows. Suppose a tragedy happens and Alice is lost. Bob collects all the surviving information about Alice, which still leaves much that is missing. The missing information is filled in by random guesswork, with appropriate probability weighting and other constraints based on what has survived. An Alice emerges that the delighted Bob cannot tell from the one who perished, nor can anyone else. (This would have to follow in view of our assumption that the recreation of Alice is managed so as not to conflict with what was known about her before her demise.) A critic, however, claims that what has been created is only a fantasy version of Alice, or at best, a version that may have existed in some parallel branch of reality, but, with very high probability, not our branch. It is not the same Alice, he asserts. You could not guess all those missing bits exactly the same as they were before.

The answer to the critic follows straightforwardly from the discussion above. Loss of information makes the past ambiguous. There was no one version of Alice, before the tragedy, that was "the one real version" for our parallel world or timeline as opposed to the others. Different versions must be considered equally authentic, or weighted by appropriate probabilities, in view of the information loss. (It should be noted here that there will be highly unlikely versions of Alice which still fit the surviving records; these would have a corresponding low, not zero, probability of being created in the randomized process.) The Alice we have constructed must be considered part of our historical timeline. Said timeline is not really a "line" but branches out to cover all past histories that fit the surviving record, including in this case whatever is known about Alice. Bob, on the other hand, since he has full access to the information about Alice, will extend in identical copies to all those parallel branches where the different versions of her resided, before her loss. After the restoration, the same versions, each one different from the others, are paired up with the same, identical version of Bob. In terms of set theory, we just have the set of all pairs $\{\text{Alice}_n, \text{Bob}\}$ where n indexes all the (finitely many) versions of Alice. The Alices vary but Bob stays the same. The set comes out the same regardless of the outcome of a particular instance of creating a version of Alice at random. (Multiple creations of the same version of Alice will occur too, and are not a problem.) So overall, the resurrection of Alice can be done in only one way, if we remember that we are not just undoing one particular loss somewhere (as might happen with cryonics, when the remains are well preserved) but all possible, similar losses in all the parallel worlds.

Again, the same considerations apply if we expand our scope to the case of an entire timeline cohort of individuals as described above. As with the single individual and the coin toss, again we are dealing with a finite number of bits which have been lost and which we are trying to restore. "Alice" is the whole cohort of all those who perished and "Bob" is the community of future individuals who will resurrect them. Again, the resurrection, in this case we could call it the *general resurrection*, essentially can happen in only one way. On this basis, such a resurrection is authentic, and it happens in the face of irretrievable loss of information. Such a resurrection depends, in fact, on the idea that, while information is lost in individual cases, the knowledge remains of what would be the extent of all possible fill-ins that would fit the surviving record. A randomized process of guesswork, done in the different parallel worlds, will then in fact fill in all these possible versions, to be paired in each case with an identical copy of the community of resurrectors. So in all one obtains a restoration of what existed prior to the loss.



The resurrection of Alice. (a) Before loss of Alice, different versions confront Bob, whose knowledge of Alice is limited, thus all versions of Alice look alike to Bob and all versions of Bob are alike. (In this toy example there are five varieties of Alice; in real life there would be many, many more, yet still a finite number.) (b) Tragedy causes loss of Alice, so versions of what remains of her are now identical in the parallel worlds. (c) Resurrection restores the versions of Alice by random guesswork across the parallel worlds. Though the order of the Alice versions in (c) is apparently different from that in (a), the versions of Bob are all identical so there is really no difference. Photo Credit: artwork by author, photo-montage based on author's personal collection plus NASA image

8. Managing One's Clinical Death: a Case for Cryonics[17]

Cryonics advocates who doubt the likelihood of the general resurrection scenario as presented here and lack mystical beliefs generally view cryonics as the only possible escape from clinical death. If the ideas presented here are accepted, on the other hand, everyone who is dying can have hopes of an eventual return to life, though there are many unknowns. One might concern the time frame necessary to gather historical information for the projected resurrection. A few centuries at most might suffice for information obtainable on Earth or nearby in the solar system, assuming that mature nanotechnology and other technological assistance (advanced artificial intelligence, for example) becomes available. Would that be enough? The possibility must be considered that extraterrestrial civilizations might have recorded significant historical information, through use of telescopes or other instruments. While it may be imagined that much of significance would not be detectable this way, given the astronomical distances involved, there could still be important information saved. A resurrection initiative will have to consider this possibility, and may be delayed many centuries or millennia while matters can be investigated. Or perhaps an accommodation will be developed so that resurrection can occur earlier and minor historical discrepancies detected later could be adjusted for.

A straightforward recovery of the necessary information would be desirable, eliminating the need for PR and probably restoring the decedent to consciousness earlier than would otherwise occur. This is what is aimed for in cryonics, with the recently deceased stored at low temperature. Its advocates (again, self included) feel that it is the best course to follow, technically, to manage impending clinical death. Even though the resurrection possibility, for those who accept it, offers an alternative afterlife hope, arguments can be made that in this case also it would be better to choose preservation leading to straightforward revival, other factors equal. One such argument concerns an anticipation of what one's place in a future society would be and how one might behave to gain rewards. The best sort of rewards arguably would follow from the pursuit of enlightened self-interest. Enlightened self-interest in turn would call for such activities as doing good in the world and benefiting others, in hopes of reciprocal benefits. Resuming one's life sooner, as should happen through cryonics revival, would provide more time and opportunities to do good in the world and thus reap greater rewards. The difference in perceived rewards could be quite considerable if cryonics revival would anticipate the general resurrection by centuries or millennia. One form of doing good could actually be to assist in the general resurrection when it comes, as a labor of love, to help the less fortunate who were not recoverable by more direct means.

In any case, at clinical death one is put at the mercy of others. Hopes must rest on "friends of the future" to scientifically provide for revival and resumption of one's life. Though there are many uncertainties, it is clear that those who will carry out

a revival must have a motive. They would surely value life themselves and very likely will have achieved a very long life through control of what we call aging. Arguably, they will not be indifferent to the personal details of those being revived, but those that seem more attractive to them will in some way "have it better" in the world they return to than others seen as less desirable. (These others too, one hopes, will eventually be helped to overcome any deficiencies and join the rest on an equal footing.) An argument could be advanced that the very choice one makes of cryonics would both be important in furthering the desirable aim of conquering death, as well as signifying a level of sincerity in this cause that those involved in revival, very advanced and godlike by our standards, would view with favor. Roughly, "if you want to gain rewards by fast-track reentry, and in addition be favored by the future gods who will revive you, then choose cryonics."

One problem with the above is that cryonics is expensive; not everyone can afford it. If you are unable to afford it, but still seriously desire it, what do you do? Do you appeal to others for funds? Do you look to lower-cost alternative methods of preservation such as chemical fixation, or storing your genome with a "mindfile" of your personal experiences? Can you justify your pursuit of self-preservation in terms of how much extra good you plan to do if you succeed, when others will not be able to have it for themselves? Coping with death is not easy in this world, even when some methods have shown enough promise to have attracted a circle of devotées. If all goes well, our world of the future will have advanced beyond all that, and death will not be anything like the issue it is today. Everyone should have a stake in this future, so we must continue our efforts today to optimize the outcome, both for ourselves and others. ■

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8 MP1.
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11 See, for example, DD.
12 MT.
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From Brain Preservation to Reconstruction

Summary of the April 2018 Carboncopies *workshop on whole brain emulation*

By Keith Wiley

On April 29th, 2018, Carboncopies hosted its second workshop of the year. This hybrid-format workshop, viewable both online via a live interactive video stream and in person onsite in the San Francisco area, had the theme of considering how a cryopreserved brain might be emulated via whole brain emulation (WBE). This topic was chosen in response to the recent announcement by the Brain Preservation Foundation (BPF) that they had awarded their Large Mammal Prize in March for the successful preservation of a pig's brain (http://www.brainpreservation.org/large-mammal-announcement/). The winning preservation protocol, Aldehyde-Stabilized Cryopreservation (ASC), lends itself directly to WBE and so the BPF announcement was chosen as the inspiration for Carboncopies' second workshop of the year. The workshop addressed topics such as what sort of model parameters should be required of a whole brain emulation (WBE) so that the result may be judged a preservation of a person's mind and identity, what features of a preserved brain should be required so as to provide the necessary information for an eventual scanned and emulated model, and what real-world contemporary examples can we draw from for inspiration or as an illustration of the potential progression of such technologies as our technological capability evolves.

The opening talk, From Brain Preservation To Reconstruction, was by Dr. Randal Koene (founder and CEO of Carboncopies). This talk introduced WBE and investigated the technical aspects of how WBE would be performed on a preserved brain, with attention paid to the open questions, such as determining which information from the brain needs to be captured and utilized in an emulation. What information can be gathered from the brain to understand and recreate memory engrams? At a lower level, Koene asked what neural parameters are the determinant factors of how neurons accumulate and perform memory functions for the retention of information in the brain from past experiences, and with the effect of altering current behavior and subsequent state changes in the brain. What are the circuit architectures and neural or synaptic properties of memory and cognition? What library or reference guide might we build of neuron and synapse types and their varying properties? Koene emphasized the need to better understand large-scale organization, such as brain regions and algorithmic models of regional behavior.

Another question Koene broached was that of determining the success criteria of WBE. How do we know that a WBE has successfully reproduced an individual's mind? Koene proposed the concept of a neural fingerprint, some objective measurement of brain structure or function that distinctly identifies an individual, such that if a WBE exhibited the same fingerprint we could judge it to represent the same person who preceded the preservation. What sort of validation test or data would inform us on such matters? Koene proposed that in addition to neural modeling and neural circuit validation, we might also desire (or require) psychological behavioral validation by comparing the WBE's behavior to similar behavioral tests preceding the preservation process.

Koene also emphasized the importance of acknowledging model imprecision. No model is perfect and while this realization may shut the doors to philosophical acceptance of WBE as identity preservation for some readers, it certainly will not be considered prohibitive by others. For those readers willing to accommodate realistic variations between a model and its source data, what are the tolerable model variances in terms of error or generalized noise and randomness? How precise must one neural fingerprint measurement be to another for them to fall under the same identifying label? What parameters can we utilize in our model variance tolerance function?

Koene finished his introductory presentation with a reminder that WBE can serve multiple purposes. While longevity is an oft-touted goal, another huge source of motivational objectives is the almost limitless possibilities to improve and expand human cognition as the future unfolds.

Following Koene's talk, Dr. Keith Wiley, a board member with Carboncopies, presented Why a Whole Brain Emulation from your Preserved Brain is Probably You. This presentation was purely philosophical. It did not touch on recent or ongoing neurological experiments. The focus of this talk was what Wiley calls the copy problem, the question of whether the best interpretation of WBE of a preserved brain isn't identity preservation, but rather that some sort of metaphysical identity copy emerges in the WBE and that the original identity is left behind in the brain. Wiley's talk was primarily a series of counterarguments to the copy judgment. Wiley tackled multiple concerns that are commonly used to support the copy claim. Such concerns include continuity streams of consciousness or of neurological activity, the question of how identity purportedly spatially relocates from the brain to the WBE computer, and what implications should be taken from the possibility of a nondestructive process in which the person

and/or brain revive despite a WBE having also been created. Wiley urged a philosophical position that personal identity is primarily psychological, instantiated by information patterns of neural configuration. As such, he specifically argued against the alternative of body identity, in which identity is physical instead of abstract and informational. Finally, Wiley proposed a variation of psychological identity called branching identity, which handles most of the paradoxes and conundrums that popularly confound body and simplistic psychological identity.

Dr. Kenneth Hayworth, from Howard Hughes Medical Institute and Janelia Research, then presented the Aldehyde Stabilized Cryopreservation (ASC) technique that won the BPF mammal preservation prizes, and asked whether ASC is sufficient to preserve the information critical to a later WBE. Hayworth's talk focused on the neural underpinnings of memory and how such issues inform the requirements of successful brain preservation. What features of the brain must be preserved to enable whole brain emulation? Hayworth emphasized that the starting position of such considerations is an assumption of physicalism, i.e., that the mind is solely the product of processes, ostensibly computations, occurring in the physical brain, a conclusion supported by a century of experiments.

ASC has been confirmed to enable indefinite storage of the neural features considered by modern neuroscience to be the critical components of neural function, such as connectomic topology (which neurons connects to which), as well as individual connection properties (chemical and morphological traits of synapses and neurons). The assumption is that ASC should enable virtually unlimited technological capability for revival. The only question remaining is whether sufficient information is actually preserved. Hayworth argues that whether an emulation is of sufficient quality is in the eye of the beholder and that if the mind is computational, then there is no further fact, as the saying goes, regarding imperfect copies of neural function or personal identity.

Regarding the issue of continuity of consciousness, Hayworth described how we have a self-model and associated narrative that is continually written into our long-term memory and that our identity (our sense of self) persists across breaks in consciousness, such as anesthesia, only because of our memories. We feel that our identity has survived sleep, fainting or anesthesia exclusively because our memories upon reawakening create the experience of our long-term self continuity; there is no other property at any level of abstraction, physical, psychological, or philosophical, that is relevant to this basic fact. Therefore, the crucial property in question is preservation and continuity of long-term memory, be it declarative, episodic, learned, or innate. These memories are stored in patterns and strengths of synaptic connections.

Hayworth seeks a computational description of these synaptic properties. In other words, not only does he want to understand the topology and transmissive functions of synapses, but he also wants to abstract those brute physical facts to their implied computational properties and implications for memory representation. Hayworth concluded his talk by emphasizing that ASC appears by all counts to preserve the necessary structural and molecular features of memory, and by restating his desire that the professional neuroscience community take up these questions of further validation and investigation in earnest.

Alicia Smallwood presented a concise and inspiring overview of analogous tasks and projects in a talk titled Reverse Engineering Demo: What Integrated Circuit Reverse Engineering Teaches Us About Reverse Engineering the Brain. In this informative presentation, Smallwood walked the audience through a set of videos by Ken Shirriff that demonstrated reverse engineering of integrated circuits (ICs), a problem that is quite similar to reverse engineering the brain. In both cases, a physical substrate comprises thousands to millions of microscopic components organized into a massive, complex, and convoluted signal-transmitting and signal-processing network. The goal is similar: to deduce the underlying functions performed by the physical network. The ICs are sliced apart, layer by layer, and then imaged with a metallurgical microscope. This initial step is very similar to slicing and scanning brain tissue of course. The captured images must be registered (aligned and overlapped) and then analyzed. Once components are identified and labeled, nascent comprehension of parts of the chip begins to emerge. Established abstract models (known basic models of transistor circuits) are then applied to further the image comprehension and reverse engineering of the specific chip under investigation.

Shirriff even extended this work to the next logical step: modeling of the deduced structure and function in a software emulation. This step confirmed the correctness of the deduced model and offered yet additional understanding of the chip's observed behavior, which could have been elusive and confusing without the detailed knowledge provided by the reverse engineering efforts. Specifically, he determined that the reason the chip in question performed more slowly on larger numbers was that it would iteratively accumulate sums, such that summing to a greater total took more iterations to complete. This illumination might have been speculated from external behavior, but could only be solidly confirmed through low-level physical analysis, i.e., reverse engineering.

Smallwood and Shirriff concluded with extensions beyond digital ICs, namely to analog chips such as the 555 timer. This talk gave great insight into the process of reverse engineering a neural and synaptic network to deduce algorithmic functions of the brain. While differences between ICs and brains can easily be listed, the principle is nevertheless similar and the presentation was fascinating.

Jonathan Gornet, from New York University, then presented Dynamical Modeling of Extracted Connectomes. How do we discover and determine the Drosophila (fruit fly) connectome, and then how to simulate it on a computer (a fly WBE). Gornet and others have been slicing and imaging fly brains with electron

microscopy, layer by layer, to reconstruct whole neurons (a process frequently known as neurite tracing). Gornet discussed the task of correlating reconstructed morphology with dynamic measurements taken prior to the sectioning, imaging, and emulation process. Gornet walked through a particular neural circuit model in which a neuron is represented by its branching structure, with each branch represented by an action potential function. A neuron then comprises a branching series of such functions, and we can follow an action potential along some sequence of these functions as it traverses a neuron.

Gornet addressed the concern of validation too. He described a motion selectivity experiment in which light bulbs are illuminated from left to right and the membrane potential of a single neuron is observed and modeled. At this stage he simplified his model, representing whole neurons as single functions instead of individual branches. The model's behavior was confirmed to be virtually unaltered by this simplification while reducing the model running time by a factor of forty. An implication of this result was that synapses are the critical feature of signal transmission and that population structure is more important than individual neuron geometry.

Randal Koene returned with a second presentation titled Model Validation and System (De)composition at Multiple Scales. In Koene's second talk, he asked what information is needed to insure that a WBE works. What information is available from a preserved brain and what additional information (if any) is required beyond that provided by a preservation, such as dynamic recordings made prior to preservation? Koene compared building a WBE with reverse engineering an IC, as had been presented earlier by Alicia Smallwood. He emphasized the shared trait of large nonlinear dynamic models, which is the underlying feature of such models. Koene asked whether there might be a dynamic fingerprint that can be compared with an emulation for the purpose of validation. He prescribed an iterative process of parameter estimation, model validation, corrective modification and model selection, and repeated parameterization and validation, ultimately converging on a successful model. Where does this validation data come from? If it is recorded dynamically prior to preservation, then what spatial and temporal scales are required of such data to capture the necessary information for later model validation?

Prof. Dong Song, from the University of Southern California, presented Towards a Clinical Hippocampal Memory Prosthesis. Song's talk presented research into dementia, the biggest neurological disease in the U.S., and for which there is currently no cure. Techniques that have helped some diseases, such as direct brain stimulation (DBS), applied toward Parkinson's with great success, do not work at all on other maladies, such as hippocampal deficits. In fact, DBS can make the hippocampal function even worse. Song described a biomimetic device that mimics hippocampal function and bypasses the damaged hippocampal brain region, a topic that Ted Berger has presented on in previous Carboncopies workshops.

Song presented a classic variant on animal (rat) lever-pushing experiments. In this case, neural firing patterns were recorded in conjunction with these behavioral experiments and then those patterns were computationally modeled as spatiotemporal action potential firing patterns. This recorded code was then used to restore neural function after the memory had been forgotten. Restoration of the memory proceeded by directly stimulating neurons with the previously recorded firing pattern. The rats successfully reproduced behavior associated with the lost memory, demonstrating the successful recording and later external stimulation of memories as neural circuits and firing patterns.

Song has moved on to human trials with clear applications to dementia. Early experiments with humans attempting to remember abstract visual stimuli (visual patterns) have been encouraging and confirm the approach of applying model-based memory restoration.

The workshop concluded with a panel discussion titled Restoring Jane Doe from her Preserved Brain, hosted by Dr. Diana Deca from the University of Southern California and Dr. Stephen Larson of the OpenWorm project. Deca and Larson led other participants through a discussion of whether an emulation of a preserved brain should be interpreted as a preservation of identity. One outcome of this discussion was the suggestion that we be open to the interpretation of a partial chance of identity preservation instead of insisting on judging the matter in the binary terms of success and failure.

The April Carboncopies workshop asked a specific question. Given the recent BPF announcement that we now have a viable long term brain preservation method, what is the subsequent path forward for developing a WBE method to emulate a preserved brain, and relatedly, to philosophically interpret a WBE as a preservation of personal identity? We will not be able to perform WBE of a human brain for a long time, but the path forward seems relatively clear. By extrapolating and extending current research such as hippocampal prosthesis, and by considering related challenges of reverse engineering complex networks, such as integrated circuits, and by carefully considering which neural and cognitive parameters should be deemed salient and required, we can lay out a roadmap for research and development toward the eventual emulation of a whole human brain from a long term preservation.

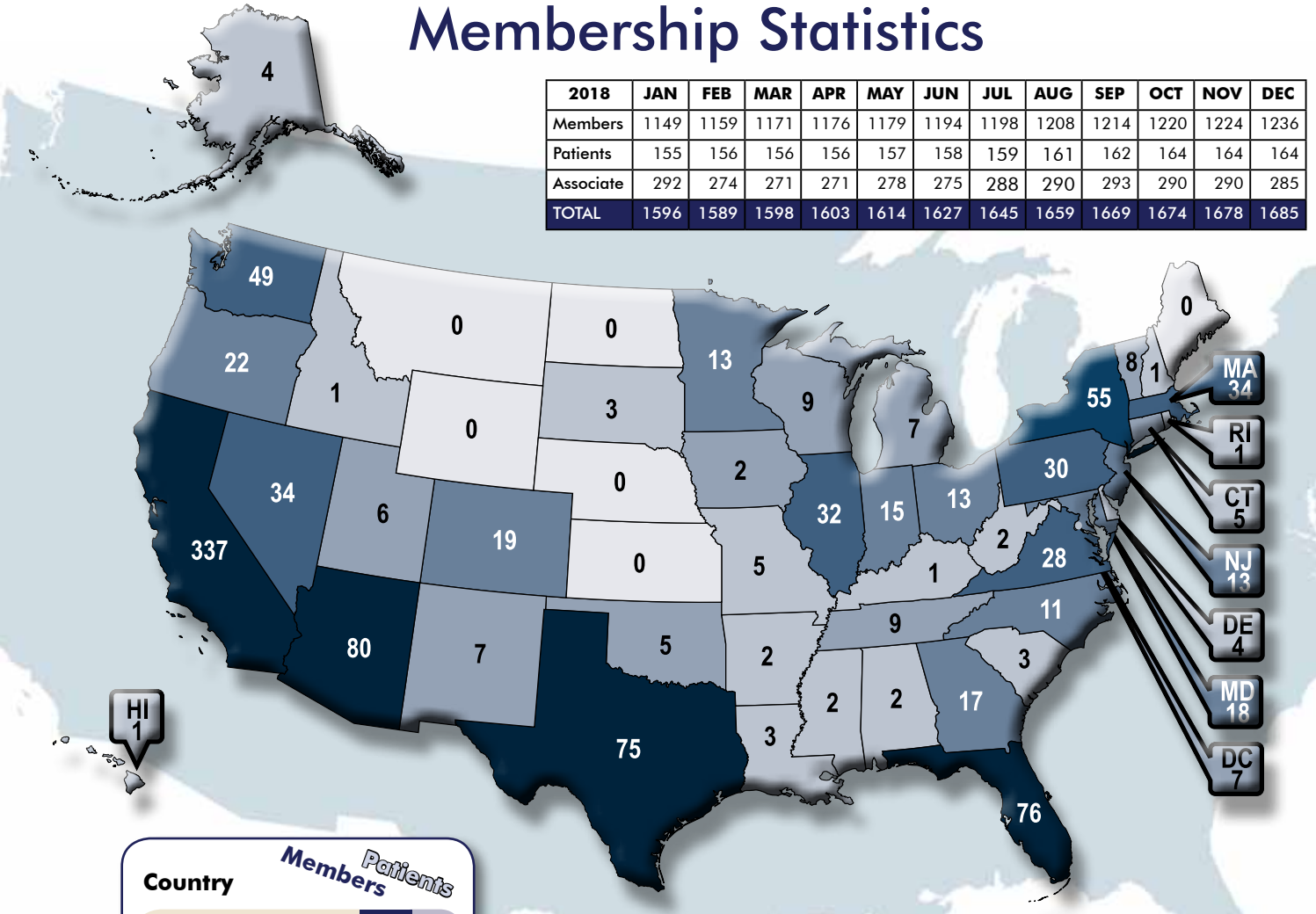
Carboncopies' next workshop is currently scheduled for August 2018 with the topic of delving more deeply into the philosophical questions of consciousness and personal identity. ■

Keith Wiley serves on the board of Carboncopies as director of communications. His book, A Taxonomy and Metaphysics of Mind-Uploading, is available on Amazon.

The workshop's archived URL is https://www.carboncopies.org/workshop-2018-apr and includes links to the videos.

Membership Statistics

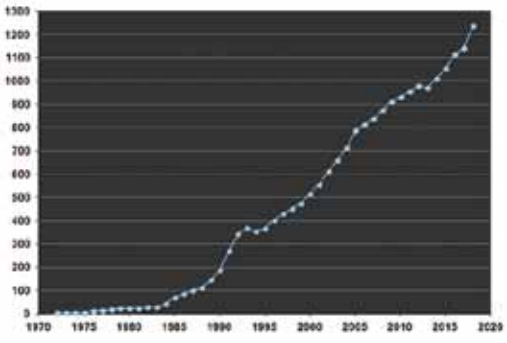
2018	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1149	1159	1171	1176	1179	1194	1198	1208	1214	1220	1224	1236
Patients	155	156	156	156	157	158	159	161	162	164	164	164
Associate	292	274	271	271	278	275	288	290	293	290	290	285
TOTAL	1596	1589	1598	1603	1614	1627	1645	1659	1669	1674	1678	1685



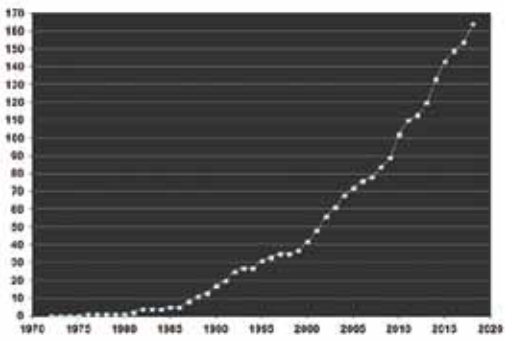
International Members & Patients

Country	Members	Patients
Australia	13	3
Austria	1	0
Brazil	1	0
Canada	57	3
China	0	1
Finland	1	0
France	0	1
Germany	18	0
Hong Kong	2	0
Israel	1	1
Italy	3	0
Japan	5	0
Luxembourg	1	0
Mexico	4	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	1	0
Portugal	4	1
Puerto Rico	1	0
Singapore	1	0
South Korea	1	0
Spain	5	1
Taiwan	1	0
Thailand	5	1
United Kingdom	36	3
TOTAL	165	15

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



Number of Alcor members



Number of Alcor patients

Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

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

To start off this new section in *Cryonics* magazine, we asked *Reason*, the writer of Fight Aging!, a number of questions.

1. Can you tell us about your recent personal involvement in advancing parts of the SENS program?

I founded a company, *Repair Biotechnologies*, with Bill Cherman earlier this year, on the grounds that there are too few entrepreneurs looking at low-hanging fruit in the SENS portfolio, so why not pitch in to help? There is so much that should be done and isn't being done, there is room for another hundred companies to fit themselves in here. We're currently working on one gene therapy to rejuvenate the thymus and another that offers the possibility of reversing atherosclerosis. With success we hope to take on other projects, but of course getting anything done in biotechnology takes much longer than anyone would like. As an industry, it is in the same sort of position that computing hardware and software were thirty or forty years ago: all the promise, things are accelerating, but you still have to build every new product from scratch, and the failure rate for any given experiment or vendor product, even the ones used day in and day out throughout the industry, is high enough to be uncomfortable. We hope to be able to share news of our progress in 2019.

2. You have been a consistent critic of the commercial anti-aging market. Are there any interventions besides caloric restriction and exercise you think are credible now?

Now that human trials have started to show interesting results, it seems that mitochondrially targeted antioxidants and some NAD+ enhancers are worth trying. Modest results, but achieved at low cost for the consumer. These items are still not worth the level of investment in research needed to produce them. That attention could have been far more profitably applied elsewhere, such as on further development of SENS.

I am bullish on senolytics. The publication of results from the first human trials should be very interesting. These are powerfully beneficial treatments, even in their initial, unvarnished form, which get rid of only a fraction of senescent cells. Combination therapies should do much more, attacking these cells through multiple different mechanisms concurrently. It is a terrible thing that it will take a lot of effort to educate people following the trial results, to show them that they can improve the quality of their lives significantly with a low-cost infrequent dose of easily available senolytic compounds. So very many people are suffering unnecessarily right now.

3. In 2016 you announced signing up for cryonics after promoting it for a considerable time. What was the specific reason for this delay?

Procrastination coupled with a willingness to accept the risk of delay. The on-ramp is too hard and signing up requires too much organization to fall into the impulsive category of "I should get this chore off my to-do list today." Cryonics providers could learn from the life insurance providers, who have similar issues, and a whole industry devoted to getting people on board despite the hurdles.

4. What is the biggest obstacle to a wider acceptance of cryonics?

That signing up is not easy. The network effect of incremental growth is muted by the fact that it does require a sustained effort and many discrete tasks to sign up successfully. It is a product that must be sold and hand-held and then maintained over the years, and that makes grassroots persuasion ineffective. No-one likes to take on another burden, and cryonics has that look of a burden when you actually investigate what needs doing. A service that de-burdened the product for a 5%-10% premium over the usual cost would go a long way.

A more extensive recent interview with Reason can be found here: https://www.leafscience.org/an-interview-with-reason-near-term-life-extension-therapies/

Dementia Correlates with a History of Hypertension

Oct, 2018

Hypertension, raised blood pressure, is an important mediating mechanism in aging. It is caused by forms of low-level biochemical damage in and around the cells of blood vessel walls, and produces structural damage to organs and the cardiovascular system, leading to dysfunction and death. Hypertension is sufficiently harmful in and of itself that present methods of reducing blood pressure can reduce risk of mortality and clinical age-related disease, even given significant side-effects, and even given that none of these methods address the root causes of hypertension. They override reactions to damage rather than repairing damage. Repair of that damage, once implemented, should prove far more effective.

One of the ways in which hypertension damages organs is through an increased pace of rupture in capillaries and other forms of small-scale structural damage. This is particularly important in the brain, as it has only a very limited capacity to heal injuries of this nature. Cognitive decline driven by hypertension is in part a progression of tiny, unnoticed strokes, each destroying the function of a minuscule portion of the brain. Over time that adds up, and thus we might expect to observe correlations between hypertension and dementia. Nothing is simple in human data, of course, as even straightforward relationships can be challenging to extract from the very noisy data.

Quote

Hypertension is a highly prevalent condition, occurring in one-third of the world's adults and in two-thirds of adults over 65 years of age. Both hypertension and dementia are age-related comorbidities which may induce considerable disabilities. Some epidemiological studies showed that hypertension is an important risk factor of dementia, which was evident from the positive relationship between blood pressure at midlife and the subsequently higher risk of cognitive impairment or dementia late in life; however, some other studies provided contradictory evidence that low blood pressure was a risk factor for dementia and cognitive decline.

We, therefore, intend to explore the association between blood pressure and cognition. Data were drawn from 3,327 participants at the baseline of Shanghai Aging Study. History of hypertension was inquired and confirmed from participants' medical records. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the early morning. Participants were diagnosed with "cognitive normal," "mild cognitive impairment (MCI)," or "dementia" by neurologists. Multivariate logistic regression was used to evaluate the association between history of hypertension, duration of hypertension, SBP, DBP, or classification of blood pressure and cognitive function.

Our study indicated that history of hypertension, duration of hypertension, and high blood pressure were positively associated with dementia. A significantly higher proportion of hypertension [76.5%] was found in participants with dementia than in those with MCI [59.3%] and cognitive normal [51.1%]. Participants with dementia had significantly higher SBP [157.6 mmHg] than those with MCI [149.0 mmHg] and cognitive normal [143.7 mmHg]. After adjusting for sex, age, education, living alone, body mass index, anxiety, depression, heart disease, diabetes, and stroke, the likelihood of having dementia was positively associated with history of hypertension (odds ratio = 2.10), duration of hypertension (odds ratio = 1.02 per increment year), higher SBP (odds ratio = 1.14 per increment of 10 mmHg), higher DBP (odds ratio = 1.22 per increment of 10 mmHg), moderate hypertension (odds ratio = 2.09), or severe hypertension (odds ratio = 2.45).

Link: https://doi.org/10.3389/fneur.2018.00664

Across Large Populations, Telomere Length Falters as a Biomarker of Aging in the Oldest Cohorts

Oct, 2018

Telomeres are the repeated DNA sequences found at the ends of chromosomes. A little of that length is lost with each cell division, and this serves as a part of the mechanism that limits the number of times a somatic cell can divide. Stem cells employ telomerase to maintain long telomeres through the asymmetric divisions needed to supply tissues with new daughter somatic cells equipped with long telomeres. This split of responsibilities between many restricted cells and a few privileged cells is the primary strategy by which multicellular organisms keep the risk of cancer low enough for evolutionary success.

Given this arrangement, average telomere length in any given tissue is a blurred measure of how fast cells divide and how frequently new cells are delivered by the supporting stem cell population. Over large populations of people, shorter telomere length tends to correlate with greater age, most likely because stem cell activity declines with age. Unfortunately, it is the case that telomere length as presently measured – in leukocytes from a blood sample – is quite dynamic in response to day to day environmental circumstance, and is thus only poorly correlated to aging for any given individual. Telomere measurement services are readily available, but there really isn't all that much that can be deduced from the result. It isn't actionable. If measured again next week or next month, or with a passing infection versus without, then the number will likely be significantly different.

Further, for every study population in which the correlation with aging is affirmed, there is another in which the telomere length data stubbornly refuses to do the expected thing. The study here

produces both of these outcomes, confirming the correlation in younger people, but also finding that the relationship falters for individuals older than 80 years of age. All in all telomere length just isn't a very useful measure of aging. It is not robust enough, and its individual variability means that the numbers are next to useless when it comes to guiding medical decisions.

Telomere Length and All-Cause Mortality: A Meta-analysis

https://doi.org/10.1016/j.arr.2018.09.002

Quote

Telomere attrition has been widely reported to be associated with increased morbidity and mortality of various age-related diseases. In 2003 [it] was reported for the first time that telomere shortening contributed to all-cause mortality based on a study of 143 unrelated Utah residents aged 60-97 years. More recently, other researchers used the largest study so far (n = 64,637) to demonstrate that short telomeres were associated with a higher risk of all-cause mortality. Although several other studies reported an association of telomere length (TL) with all-cause mortality, there is a substantial variability among the findings of these studies due to the different TL measurement techniques and the varying age, sex, and ethnicity of the study participants. To this end, we aimed to perform a meta-analysis of the association of TL with all-cause mortality, taking advantage of both previously published results from cohort studies of the general population and un-published original data from the Swedish Twin Registry (STR).

We found that shorter leukocyte TL was associated with an increased risk of all-cause mortality, although some between-study heterogeneity was observed. The magnitude of the association of TL and all-cause mortality was similar for the youngest groups (younger than 75 years and 75-80 years), but weaker for the oldest old (over 80 years). The results of our STR cohorts were similar in effect sizes compared to several earlier studies, but slightly weaker than those reported by others.

Women have on average longer telomeres and life expectancy compared to men of the same age. Our STR study further confirmed the sex difference in TL. Several plausible biological mechanisms have been proposed to explain the phenomenon. First, estrogen may stimulate the production of telomerase and may be protective against reactive oxygen species damage. In addition, estrogens have been shown to stimulate the phosphointositol 3-kinase/Akt pathway, which contributes to enhanced telomerase activity. Second, the heterogametic sex hypothesis suggests that shorter telomeres in men may arise if the unguarded X chromosome in men contains inferior telomere maintenance alleles. Third, men have a faster rate of telomere attrition than women although there is no difference of TL at birth. The longer telomeres may on the other hand be a reason for the overall lower risk of age-related diseases and consequently longer lifespan of women compared to men.

Enthusiasm for Senolytic Therapies

Oct, 2018

I think it is entirely appropriate to greet the advent of senolytics with enthusiasm. These treatments are the first legitimate rejuvenation therapies to successfully target one of the root causes of aging, the accumulation of lingering senescent cells in old tissues. The first human trial data is approaching publication, but even before it arrives, the evidence to date strongly suggests that meaningful levels of rejuvenation can be achieved in old people at a very low cost. The first senolytic drugs (such as dasatinib and navitoclax) and plant extracts (such as fisetin and piperlongumine) cost very little, and remove only some senescent cells, no more than half in some tissues, and far fewer than that in others. Nonetheless, in mouse studies they reliably reduce chronic inflammation, reverse the progression of numerous conditions ranging from arthritis to Alzheimer's disease, and extend healthy life span even when applied a limited number of times in very late life.

Quote

As we get older, more and more of our the cells in our bodies become dysfunctional and enter into a state known as senescence. These senescent cells no longer divide or support the tissues and organs of which they are part; instead, they secrete a range of harmful inflammatory chemical signals, which are known as the senescence-associated secretory phenotype (SASP). Dr. Judith Campisi from the Buck Institute for Research on Aging, along with her research team, identified that senescent cells secreted the various harmful chemicals that characterize the SASP in 2008, which was when interest in senescent cells really began.

The SASP is a real problem: it increases inflammation, harms tissue repair and function, causes the immune system to malfunction, and raises the risk of developing age-related diseases such as cancer. Even worse, the SASP also encourages nearby healthy cells to become senescent, so even a very small number of senescent cells can cause big problems. Normally, senescent cells destroy themselves by a self-destruct process known as apoptosis or are cleared away by the immune system. Unfortunately, as we age, the immune system becomes weaker, and the senescent cells start to build up in the body. The accumulation of senescent cells is considered to be one of the reasons why we age and develop age-related diseases.

With these experiments, the biotechnology industry had initial proof that targeting one of the aging processes directly could improve health by delaying aging in mice; this began the search to develop therapies that target and destroy these harmful cells. This was the birth of a new class of drugs and therapies that would become known as senolytics. So far, there have

been a number of drugs and naturally occurring compounds with senolytic potential and multiple mouse experiments demonstrating that the clearance of these cells can delay the onset of diseases such as cancer, heart disease, osteoporosis, arthritis, and Alzheimer's.

Interest in senolytics has seen a meteoric rise in the last couple of years, with investment money pouring in as confidence in the approach has reached new heights. There are also a number of companies developing therapies to destroy senescent cells, and it is likely that more will join them in the coming years. Leading the charge is Unity Biotechnology, which was founded in 2011 and has raised over $385 million in funding since then. Other companies are hot on its heels developing ways to seek and destroy these harmful cells. Oisin Biotechnologies, based in Seattle, is one such company. Founded in 2016, it has raised around $4 million to date and is developing a unique lipid nanoparticle-based system to deliver senolytic and cancer therapies. Cleara Biotech, based in the Netherlands, and Spain-based Senolytic Therapeutics are also busy developing senolytic therapies.

Link: https://www.leafscience.org/senolytics-target-aging/

Reviewing the Evidence for HSV1 to Contribute to Alzheimer's Disease

Oct, 2018

Alzheimer's disease starts with a slow rise in levels of amyloid-β present in the brain, an imbalance between dynamic processes of creation and clearance. This produces a state of mild biochemical and cognitive dysfunction that sets the stage for the later, much more destructive phase characterized by chronic inflammation, deposition of altered tau protein, and cell death. The roots of Alzheimer's must lie in the early mechanisms, in the poorly studied initial years of the condition, that cause some people to accumulate amyloid-β at a faster pace. In recent years evidence has emerged for persistent viral infection to play a role. Amyloid-β is coming to be seen as an anti-viral mechanism, and its creation and aggregation is prompted by the presence of viral particles.

Quote

Strong evidence has emerged recently for the concept that herpes simplex virus type 1 (HSV1) is a major risk for Alzheimer's disease (AD). This concept proposes that latent HSV1 in brain[s] of carriers of the type 4 allele of the apolipoprotein E gene (APOE-ε4) is reactivated intermittently by events such as immunosuppression, peripheral infection, and inflammation, the consequent damage accumulating, and culminating eventually in the development of AD.

Population data to investigate this epidemiologically, e.g., to find if subjects treated with antivirals might be protected from developing dementia – are available in Taiwan, from the National Health Insurance Research Database, in which 99.9% of the population has been enrolled. This is being extensively mined for information on microbial infections and disease. Three publications have now appeared describing data on the development of senile dementia (SD), and the treatment of those with marked overt signs of disease caused by varicella zoster virus (VZV), or by HSV. The striking results show that the risk of SD is much greater in those who are HSV-seropositive than in seronegative subjects, and that antiviral treatment causes a dramatic decrease in number of subjects who later develop SD.

It should be stressed that these results apply only to those with severe cases of HSV1 or VZV infection, but when considered with the over 150 publications that strongly support an HSV1 role in AD, they greatly justify usage of antiherpes antivirals to treat AD.

Link: https://doi.org/10.3389/fnagi.2018.00324

Hunter-Gatherer Populations Highlight the Self-Sabotage of Health in Wealthier Societies

Nov, 2018

Modern hunter-gatherer societies are located in the poorer parts of the world, and thus still face challenges in the control of infectious disease. When it comes to age-related disease they can be notably better off than those of us in the typist-shopper societies of wealthier regions, however. This, I would say, has less to do with the components of diet and more to do with overall calorie intake and level of fitness throughout life. There are those who would debate that, and suggest that the specific dietary components shape gut microbe populations, and those populations have just as significant an effect as exercise over the span of a lifetime. Regardless, eating a calorie restricted diet tends to solve both of those problems, making the debate moot in a practical sense, and no-one is arguing against aerobic fitness as a good thing in life.

Quote

From the standpoint of heart health, the Tsimane are a model group. A population indigenous to the Bolivian Amazon, the Tsimane demonstrate next to no heart disease. They have minimal hypertension, low prevalence of obesity, and their cholesterol levels are relatively healthy. And those factors don't seem to change with age. Also minimal is the incidence of type 2 diabetes. Researchers have now conducted the first systematic study that examines what the Tsimane consume on a regular basis and compares it to that of the Moseten, a neighboring population with similar language and ancestry, but whose eating habits and lifeways are more impacted by outside forces.

Using the same measurement strategy employed by the U.S. Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, the researchers interviewed 1,299 Tsimane and 229 Moseten multiple times about everything they had eaten or drunk in the previous 24 hours. Using published and their own nutritional estimates for all items, and a variety of methods to estimate portion size, they provided a detailed breakdown of daily food intake. The high-calorie (2,433-2,738 kcal/day) Tsimane diet was characterized by high carbohydrate and protein intake, and low fat intake (64, 21 and 15 percent of the diet, respectively). In addition, the Tsimane don't eat a wide variety of foods, relative to the average U.S. or Moseten diet. Almost two-thirds of their calories are derived from complex carbohydrates, particularly plantains and rice. Another 16 percent comes from over 40 species of fish, and 6 percent from wild game. Only 8 percent of the diet came from markets.

Despite the low dietary diversity, the researchers found little evidence of micronutrient deficiencies in the Tsimane's daily intake. Calcium and a few vitamins (D, E and K) were in short supply, but the intake of potassium, magnesium, and selenium – often linked to cardiovascular health – far exceeded U.S. levels. Dietary fiber intake was almost double U.S. and Moseten levels. The conclusion: A high-energy diet rich in complex carbohydrates is associated with low cardiovascular disease risk, at least when coupled with a physically active lifestyle (Tsimane adults average 17,000 or so steps per day, compared to Americans' 5,100). Moving away from a diet that is high in fiber and low in fat, salt, and processed sugar represents a serious health risk for transitioning populations.

Link: http://www.news.ucsb.edu/2018/019248/food-thought

MRI Scans Predict Development of Dementia a Few Years in Advance

Nov, 2018

Researchers here demonstrate that MRI scans of white matter in the brain can be used to visualize a form of dysfunction that is strongly associated with the near term development of dementia in patients already showing some degree of cognitive decline. Given that low cost approaches to predicting the declines of neurodegeneration earlier rather than later are still thin on the ground, possibilities such as this one are valuable indeed. The earlier the determination that dementia is ahead, the more opportunities there are to enact preventive strategies.

Quote

Neurologists can get a ballpark estimate of a patient's risk of Alzheimer's dementia using the Mini-Mental State Examination questionnaire, or by testing for the high-risk form of the gene ApoE, which increases a person's risk of Alzheimer's by up to 12-fold. Both tests were about 70 to 80 percent accurate in this study. Other assessments, such as PET scans for plaques of Alzheimer's proteins in the brain, are good at detecting early signs of Alzheimer's disease, but available to few patients. PET scans are expensive and require radioactive materials not found in a typical hospital.

In a small study, researchers have shown that MRI brain scans predict with 89 percent accuracy who would go on to develop dementia within three years. MRI brain scans are widely available and give doctors a glimpse into what's going on inside a person's brain. The researchers used a technique called diffusion tensor imaging to assess the health of the brain's white matter, which encompasses the cables that enable different parts of the brain to talk to one another. Diffusion tensor imaging is a way of measuring the movement of water molecules along white matter tracts. If water molecules are not moving normally it suggests damage to white tracts that can underlie problems with cognition.

Researchers identified 10 people whose cognitive skills declined over a two-year period and matched them by age and sex with 10 people whose thinking skills held steady. The average age of people in both groups was 73. Then, the researchers analyzed diffusion tensor MRI scans taken just before the two-year period for all 20 people. The researchers found that people who went on to experience cognitive decline had significantly more signs of damage to their white matter. The researchers repeated their analysis in a separate sample of 61 people, using a more refined measure of white matter integrity. With this new analysis, they were able to predict cognitive decline with 89 percent accuracy when looking at the whole brain. When the researchers focused on specific parts of the brain most likely to show damage, the accuracy rose to 95 percent.

Link: https://medicine.wustl.edu/news/mri-scans-shows-promise-in-predicting-dementia/

Reviewing GDF11 as a Basis for Regenerative Therapy

Nov, 2018

I think it fair to say that GDF11 was the first concrete target to emerge from the modern reinvention of parabiosis research, in which the circulatory systems of an old mouse and a young mouse are joined. The old mouse rejuvenates a little, and the young mouse is aged a little, most of which seems to emerge from effects on inflammation and stem cell activity. Researchers thereafter started looking for specific signals carried in the bloodstream that might mediate this effect.

There has been no shortage of debate in this part of the field, such as over whether or not it is possible that beneficial factors from young blood can exist, given the evidence. Or whether the early work on GDF11 holds up at all. Work has continued,

however, and matters have progressed to the point at which a well-funded biotech company, Elevian, has been launched. The Elevian researchers claim to have resolved the early conflicting evidence and confusion regarding GDF11, and are now well underway to building a regenerative therapy.

Quote

Cardiac hypertrophy is a prominent pathological feature of age-related heart failure. Using the parabiosis model, it has been demonstrated that age-related cardiac hypertrophy can be reversed via exposure to a young circulatory environment. These experiments revealed that age-related cardiac hypertrophy is at least in part mediated by circulating factors, such as GDF11, which is able to reverse the condition.

The reversal of cardiac hypertrophy in old mice exposed to a young circulation cannot be explained by a reduction in blood pressure in the older mice. An extensive proteomics analysis was performed on the serum and plasma of the animals. GDF11 was reduced in the circulation of aged mice and its levels were restored to those in young animals by parabiosis. A significant decrease was also found in both GDF11 gene expression and GDF11 protein levels in the spleens of old mice. These results suggest exciting therapeutic approaches for the management of age-related cardiac hypertrophy by restoring youthful levels of circulating GDF11.

Recently, the goal of a study in old mice was to reexamine the possibility to restore youthful levels of GDF11 by injecting recombinant GDF11 (rGDF11) and thus reversing cardiac hypertrophy and imparting a young phenotype to the old heart. The conclusions were that recombinant GDF11 (rGDF11) had no effect on cardiac structure and cardiac pump function; these results do not support the concept that GDF11 could be an anti-aging compound.

Muscle satellite cells are responsible for the postnatal growth and major regeneration capacity of adult skeletal muscle. Previous studies demonstrated that impaired regeneration in aged muscle can be reversed by parabiosis, which exposes aged tissues to a youthful systemic environment and restores injury-induced satellite cell activation by the up-regulation of Notch signaling. To determine whether supplementation of GDF11 from the young partner might underlie changes in skeletal muscle in the condition of heterochronic parabiosis, aged mice were treated with daily intraperitoneal injections of rGDF11 to increase systemic GDF11 levels.

After 4 weeks, satellite cell frequency, determined by flow cytometry, and function increased in the muscles of rGDF11-treated mice, whereas other myofiber-associated mononuclear cell populations were unaffected. Aged mice treated with rGDF11 also showed increased numbers of satellite cells with intact DNA. These results indicate that GDF11 is able to regulate muscle aging and may be therapeutically suitable for skeletal muscle dysfunction.

Link: https://dx.doi.org/10.3390/ijms19123998

Without an End to Aging, Every New Technological Advance is Just Another, Greater Monument to the Dead

Nov, 2018

A golden future is ahead of us. Humanity will build wonders upon the Earth, cities on the moon and Mars. There will be arcologies to touch the skies, artificial general intelligences that surpass the minds of humanity, molecular assemblers constructing the necessities of life from soil, resurrected dinosaurs grazing alongside de novo unicorns, and probes departing for the nearest stars. There will be wealth beyond measure, in an age of plenty for all. Hunger and disease will be banished, even as we engineer all of the greatest dreams of past visionaries into reality.

But what does any of this matter without longevity, without radical life extension, without an end to aging? The present, seen from the perspective of futurists two or three centuries past, already appears a golden age of staggering, near-magical machineries. An era of grand wealth and comfort, in which even the poorest of the wealthy nations live the lives of nobility, immune to famine and pestilence. But our cities and our achievements, the towering spires and the internet, the freeways and clinics, are little more than monuments to their originators. The engineers and the creators and the visionaries of this modern world of ours are long dead or even now dying of old age.

It is a noble thing to build a greater technology, to generate the wealth of choice and capability that will aid billions in years to come. To contribute to the construction of the golden future, one step at a time, is right and proper. Yet without biotechnologies to control aging, whatever you or I choose to build will be nothing more than a bigger and better monument to our passing, one increment greater than the monuments of our predecessors, and what difference is that to the dead? It will become one of the countless tombstones of our age, of the all too short span of years in which we and our fellow travelers lived. Then we will be gone, and only the tombstones remain, and then even those will crumble.

We put fences around graveyards. That is a foolish thing, a wished-for separation of concerns that does not and cannot exist. Every city, every building, every road is a marker of the dead. Every last cultivated part of our environment was touched by someone who is now no more, gone to oblivion. When we walk into the doors, or drive over the asphalt, it becomes a marker for us as well. For our generation. This will be the way of it. Whatever we strive to build, no matter how noble, no matter how

useful, it will be nothing more than a tombstone, a monument, a marker destined to be worn down to nothing while we no longer exist. What is the point to this?

The true value of building a better future can only exist when we are all assured of living to participate in that future, in health and vigor, of sound mind and body. A house can only be a house and not a tomb if its architect and resident is alive. Yes, we should build wonders, because we can, because we can dream into existence a far better world. But of greater importance than any other technology, we must build the means to end aging, to enable life to continue for as long as desired. Until we do, we are merely marking time amidst grave sites that will all too soon be our own, and thereafter the grave sites of the next generation, and ever on until we break this cycle. Until we do, all that we achieve is ultimately meaningless. There is no continued story, there is no progression, there is simply death, oblivion, and an end, too soon, over and over again. ■

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

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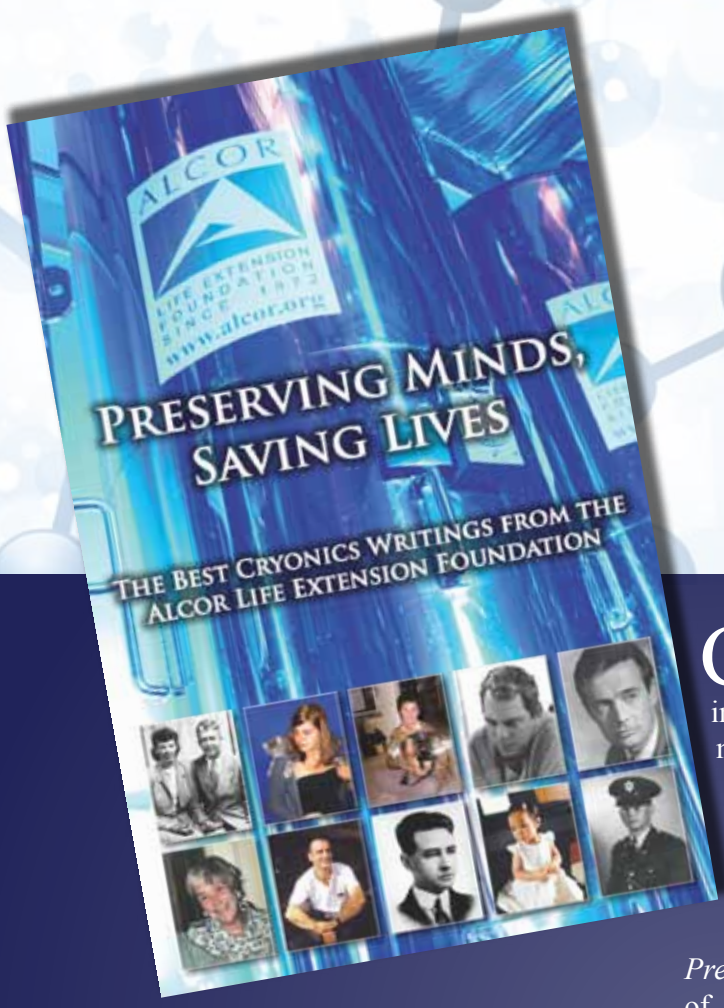

*"*Cryonics *magazine introduced me to Alcor and cryonics at its best back in 1983. The visions and technological breakthroughs that you will read about in this book continue to shape Alcor's mission to preserve life through science."*

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

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

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"Society's failure to take cryonics seriously is a tragedy that is probably costing countless lives. Alcor, notably via its magazine, is leading the fight to change that."

– Aubrey de Grey, Ph.D.
Biomedical Gerontologist and Chief Science Officer of the SENS Research Foundation

"Alcor appears to be the leading organization in the application of cryonics in medicine. I'm proud to be a part of this effort."

– Michael D. West, Ph.D.
Stem Cell Scientist and Chief Executive Officer of BioTime, Inc.

Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry

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

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

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Abstract

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

From the Introduction

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

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

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

Effective Wound Healing Enabled by Discrete Alternative Electric Fields from Wearable Nanogenerators

Yin Long, Hao Wei, Jun Li, Guang Yao, Bo Yu, Dalong, Angela LF Gibson, Xiaoli Lan, Yadong Jiang, Weibo Cai, and Xudong Wang

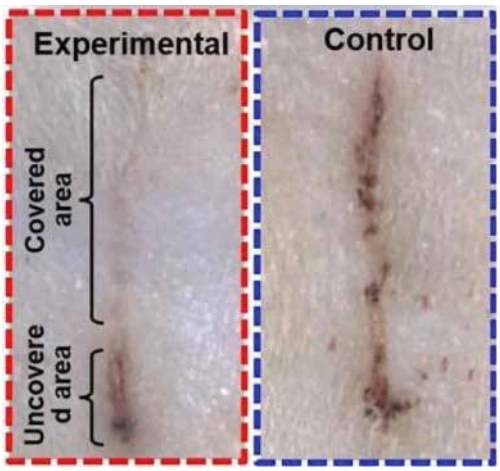
***ACS Nano* 2018, 12, 12, 12533-12540**
DOI: 10.1021/acsnano.8b07038
Publication Date (Web): November 29, 2018

Abstract

Skin wound healing is a major health care issue. While electric stimulations have been known for decades to be effective for facilitating skin wound recovery, practical applications are still largely limited by the clumsy electrical systems. Here, we report an efficient electrical bandage for accelerated skin wound healing. On the bandage, an alternating discrete electric field is generated by a wearable nanogenerator by converting mechanical displacement from skin movements into electricity. Rat studies demonstrated rapid closure of a full-thickness rectangular skin wound within 3 days as compared to 12 days of usual contraction-based healing processes in rodents. From in vitro studies, the accelerated skin wound healing was attributed to electric field-facilitated fibroblast migration, proliferation, and transdifferentiation. This self-powered electric-dressing modality could lead to a facile therapeutic strategy for nonhealing skin wound treatment.

From the Report of *ScienceDaily*:

E-bandage Generates Electricity, Speeds Wound Healing in Rats
Date: December 19, 2018



A wound covered by an electric bandage on a rat's skin (top left) healed faster than a wound under a control bandage (right).
Credit: American Chemical Society

Skin has a remarkable ability to heal itself. But in some cases, wounds heal very slowly or not at all, putting a person at risk for chronic pain, infection and scarring. As early as the 1960s, researchers observed that electrical stimulation could help skin wounds heal. However, the equipment for generating the electric field is often large and may require patient hospitalization. Weibo Cai, Xudong Wang and colleagues wanted to develop a flexible, self-powered bandage that could convert skin movements into a therapeutic electric field. Now, they have developed a self-powered bandage that generates an electric field over an injury, dramatically reducing the healing time for skin wounds in rats.

To power their electric bandage, or e-bandage, the researchers made a wearable nanogenerator by overlapping sheets of polytetrafluoroethylene (PTFE), copper foil and polyethylene terephthalate (PET). The nanogenerator converted skin movements, which occur during normal activity or even breathing, into small electrical pulses. This current flowed to two working electrodes that were placed on either side of the skin wound to produce a weak electric field. The team tested the device by placing it over wounds on rats' backs. Wounds covered by e-bandages closed within 3 days, compared with 12 days for a control bandage with no electric field. The researchers attribute the faster wound healing to enhanced fibroblast migration, proliferation and differentiation induced by the electric field.

Sources: https://pubs.acs.org/doi/10.1021/acsnano.8b07038, https://www.sciencedaily.com/releases/2018/12/181219115519.htm, accessed 30 Dec. 2018.

A Host-Produced Quorum-Sensing Autoinducer Controls a Phage Lysis-Lysogeny Decision

Justin E. Silpe, Bonnie L. Bassler

Published: December 13, 2018DOI:https://doi.org/10.1016/j.cell.2018.10.059

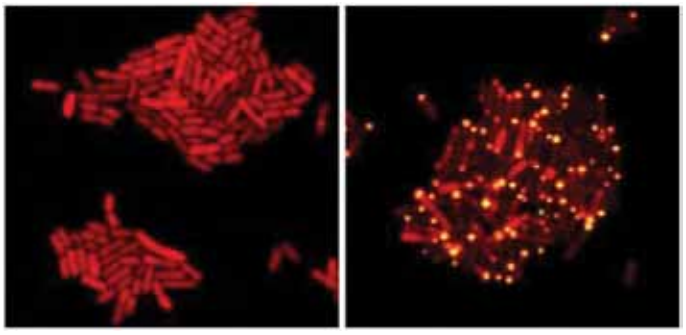
Summary

Vibrio cholerae uses a quorum-sensing (QS) system composed of the autoinducer 3,5-dimethylpyrazin-2-ol (DPO) and receptor VqmA ($VqmA_{Vc}$), which together repress genes for virulence and biofilm formation. *vqmA* genes exist in *Vibrio* and in one vibriophage, VP882. Phage-encoded VqmA ($VqmA_{Phage}$) binds to host-produced DPO, launching the phage lysis program via an antirepressor that inactivates the phage repressor by sequestration. The antirepressor interferes with repressors from related phages. Like phage VP882, these phages encode DNA-binding proteins and partner antirepressors, suggesting that they, too, integrate host-derived information into their lysis-lysogeny decisions. $VqmA_{Phage}$ activates the host $VqmA_{Vc}$ regulon, whereas $VqmA_{Vc}$ cannot induce phage-mediated lysis, suggesting an asymmetry whereby the phage influences host QS while enacting its own lytic-lysogeny program without interference. We reprogram phages to activate lysis in response to user-defined cues. Our work shows that a phage, causing bacterial infections, and V. *cholerae*, causing human infections, rely on the same signal molecule for pathogenesis.

Comments from *Science Daily*:

Biologists turn eavesdropping viruses into bacterial assassins

Princeton molecular biologist Bonnie Bassler and graduate student Justin Silpe have identified a virus, VP882, that can listen in on bacterial conversations – and then, in a twist like something out of a spy novel, they found a way to use that to make it attack bacterial diseases like *E. coli* and cholera.



These E. coli *bacteria harbor proteins from the eavesdropping virus. One of the viral proteins has been tagged with a red marker. When the virus is in the 'stay' mode (left), the bacteria grow and the red protein is spread throughout each cell. When the virus overhears that its hosts have achieved a quorum (right), the kill-stay decision protein is flipped to 'kill' mode. A second viral protein binds the red protein and sends it to the cell poles (yellow dots). All the cells in the right panel will soon die.*
Credit: Images courtesy of Bonnie Bassler and Justin Silpe, Department of Molecular Biology, Princeton University

"The idea that a virus is detecting a molecule that bacteria use for communication – that is brand-new," said Bassler, the Squibb Professor of Molecular Biology. "Justin found this first naturally occurring case, and then he re-engineered that virus so that he can provide any sensory input he chooses, rather than the communication molecule, and then the virus kills on demand." Their paper will appear in the Jan. 10 issue of the journal *Cell*.

A virus can only ever make one decision, Bassler said: Stay in the host or kill the host. That is, either remain under the radar inside its host or activate the kill sequence that creates hundreds or thousands of offspring that burst out, killing the current host and launching themselves toward new hosts.

There's an inherent risk in choosing the kill option: "If there are no other hosts nearby, then the virus and all its kin just died," she said. VP882 has found a way to take the risk out of the decision. It listens for the bacteria to announce that they are in a crowd, upping the chances that when the virus kills, the released viruses immediately encounter new hosts. "It's brilliant and insidious!" said Bassler.

Sources: https://www.cell.com/cell/fulltext/S0092-8674(18)31458-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867418314582%3Fshowall%3Dtrue, https://www.sciencedaily.com/releases/2018/12/181213142206.htm, accessed 29 Dec. 2018.

3D Nanofabrication by Volumetric Deposition and Controlled Shrinkage of Patterned Scaffolds

Daniel Oran, Samuel G. Rodriques, Ruixuan Gao, Shoh Asano, Mark A. Skylar-Scott, Fei Chen, Paul W. Tillberg, Adam H. Marblestone, Edward S. Boyden

***Science* 14 Dec 2018:**
Vol. 362, Issue 6420, pp. 1281-1285
DOI: 10.1126/science.aau5119

Summary: Shrinking Problems in 3D Printing

Although a range of materials can now be fabricated using additive manufacturing techniques, these usually involve assembly of a series of stacked layers, which restricts three-dimensional (3D) geometry. Oran et al. developed a method to print a range of materials, including metals and semiconductors, inside a gel scaffold. When the hydrogels were dehydrated, they shrunk 10-fold, which pushed the feature sizes down to the nanoscale.

Abstract

Lithographic nanofabrication is often limited to successive fabrication of two-dimensional (2D) layers. We present a strategy for the direct assembly of 3D nanomaterials consisting of metals, semiconductors, and biomolecules arranged in virtually any 3D geometry. We used hydrogels as scaffolds for volumetric deposition of materials at defined points in space. We then optically patterned these scaffolds in three dimensions, attached one or more functional materials, and then shrank and dehydrated them in a controlled way to achieve nanoscale feature sizes in a solid substrate. We demonstrate that our process, Implosion Fabrication (ImpFab), can directly write highly conductive, 3D silver nanostructures within an acrylic scaffold via volumetric silver deposition. Using ImpFab, we achieve resolutions in the tens of nanometers and complex, non–self-supporting 3D geometries of interest for optical metamaterials.

Discussion adapted from Anne Trafton, *MIT News***:**

Existing techniques for creating nanostructures are limited in what they can accomplish. Etching patterns onto a surface with light can produce 2-D nanostructures but doesn't work for 3-D structures. It is possible to make 3-D nanostructures by gradually adding layers on top of each other, but this process is slow and challenging. And, while methods exist that can directly 3-D print nanoscale objects, they are restricted to specialized materials like polymers and plastics, which lack the functional properties necessary for many applications. Furthermore, they

can only generate self-supporting structures. (The technique can yield a solid pyramid, for example, but not a linked chain or a hollow sphere.)

To overcome these limitations, Edward S. Boyden and his students decided to adapt a technique that his lab developed a few years ago for high-resolution imaging of brain tissue. This technique, known as expansion microscopy, involves embedding tissue into a hydrogel and then expanding it, allowing for high resolution imaging with a regular microscope. Hundreds of research groups in biology and medicine are now using expansion microscopy, since it enables 3-D visualization of cells and tissues with ordinary hardware.

By reversing this process, the researchers found that they could create large-scale objects embedded in expanded hydrogels and then shrink them to the nanoscale, an approach that they call "implosion fabrication." Currently, the researchers can create objects that are around 1 cubic millimeter, patterned with a resolution of 50 nanometers. (This is comparable to a twentieth of a millimeter resolution over a field of view of 1 meter, or 2,000 pixels.) There is a tradeoff between size and resolution: If the researchers want to make larger objects, about 1 cubic centimeter, they can achieve a resolution of about 500 nanometers. However, that resolution could be improved with further refinement of the process, the researchers say.

Sources: http://science.sciencemag.org/content/362/6420/1281.long, http://news.mit.edu/2018/shrink-any-object-nanoscale-1213, accessed 29 Dec. 2018.

Programmable Design of Orthogonal Protein Heterodimers

Zibo Chen, Scott E. Boyken, Mengxuan Jia, Florian Busch, David Flores-Solis, Matthew J. Bick, Peilong Lu, Zachary L. VanAernum, Aniruddha Sahasrabuddhe, Robert A. Langan, Sherry Bermeo, T. J. Brunette, Vikram Khipple Mulligan, Lauren P. Carter, Frank DiMaio, Nikolaos G. Sgourakis, Vicki H. Wysocki & David Baker

***Nature*, 2018; DOI: 10.1038/s41586-018-0802-y**

Abstract

Specificity of interactions between two DNA strands, or between protein and DNA, is often achieved by varying bases or side chains coming off the DNA or protein backbone—for example, the bases participating in Watson–Crick pairing in the double helix, or the side chains contacting DNA in TALEN–DNA complexes. By contrast, specificity of protein–protein interactions usually involves backbone shape complementarity, which is less modular and hence harder to generalize. Coiled-coil heterodimers are an exception, but the restricted geometry of interactions across the heterodimer interface (primarily at the heptad a and d positions) limits the number of orthogonal pairs that can be created simply by varying side-chain interactions. Here we show that protein–protein interaction specificity can be achieved using extensive and modular side-chain hydrogen-bond networks. We used the Crick generating equations5 to produce millions of four-helix backbones with varying degrees of supercoiling around a central axis, identified those accommodating extensive hydrogen-bond networks, and used Rosetta to connect pairs of helices with short loops and to optimize the remainder of the sequence. Of 97 such designs expressed in Escherichia coli*, 65 formed constitutive heterodimers, and the crystal structures of four designs were in close agreement with the computational models and confirmed the designed hydrogen-bond networks. In cells, six heterodimers were fully orthogonal, and in vitro—following mixing of 32 chains from 16 heterodimer designs, denaturation in 5 M guanidine hydrochloride and reannealing—almost all of the interactions observed by native mass spectrometry were between the designed cognate pairs. The ability to design orthogonal protein heterodimers should enable sophisticated protein-based control logic for synthetic biology, and illustrates that nature has not fully explored the possibilities for programmable biomolecular interaction modalities.*

Comments from *Science Daily*:

Scientists program proteins to pair exactly
Technique paves the way for the creation of protein nanomachines and for engineering of new cell functions

Date: December 19, 2018

Source: University of Washington Health Sciences/UW Medicine

Proteins designed on computer and tested in the lab look a lot like DNA.
Credit: Institute for Protein Design/
University of Washington Health Sciences/UW Medicine

Summary

Proteins designed in the lab can now zip together in much the same way that DNA molecules zip up to form a double helix. The technique could enable the design of protein nanomachines that can potentially help diagnose and treat disease, allow for the more exact engineering of cells and perform a wide variety of other tasks. This technique provides scientists a precise, programmable way to control how protein machines interact.

Sources: https://www.nature.com/articles/s41586-018-0802-y, https://www.sciencedaily.com/releases/2018/12/181219133219.htm, accessed 29 Dec. 2018.

A Roadmap to Revival

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

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

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

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

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

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

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

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

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

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

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

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

What is Cryonics?

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

How do I find out more?

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

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

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

How do I enroll?

Signing up for cryopreservation is easy!

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

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

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

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

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