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How to Argue for Life Extension

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Getting Better
Part 2: Scarcity or Abundance? Place Your Bets

By Max More, Ph.D.

In the first part of this series of articles, I looked at the beliefs of people around the world about progress. Despite clear data showing improvements in all the trends about which people were surveyed, in every country unwarranted pessimism was rife. I looked at some causes of falsely pessimistic beliefs.

In this article, I'm going to look at past predictions and forecasts that turned out to be excessively pessimistic. I'll especially pick on butterfly ecologist Paul Ehrlich since he has been so influential, so wrong, and so persistent in his errors. We will look at a famous bet between Ehrlich and economist Julian Simon and extract some lessons from it. Finally, I'll examine the Simon Abundance Index – an excellent measure of the improving state of the world.

Faulty Forecasts

Pessimism has been with us for a long, long time. Some of it is understandable given the context of the time. In the early Industrial Revolution, England was rapidly burning its way through forests for fuel. It must have seemed inevitable that wood supplies would be exhausted. An apparently safe prediction would be to foresee the end of the iron industry as England was mostly stripped of forestland in the first half of the eighteenth century. Wood for charcoal fuel was running up against the need for wood for shipbuilding. But along came coal. And the steam engine. And so on.

Pessimism can easily co-exist with recent major progress. Consider Northern Europe and North America in 1830. Enjoying the longest period of peace in a generation, they benefited from a flow of inventions, discoveries, and technologies. Matt Ridley notes that the term "technology" was coined in that year. [Ridley, 2010, 283] He points out some of those innovations: steamboats, cotton looms, suspension bridges, portland cement, the Erie Canal, the electric motor, the first photograph, Fourier analysis. Surely, a time for optimism!

And yet, around 1830, opponents of the Liverpool to Manchester railway "forecast that passing trains would cause horses to abort their foals. Others mocked its pretensions to speed: 'What can be more palpably absurd and ridiculous than the prospect held out of locomotives travelling as fast as stagecoaches!' cried the *Quarterly Review*. 'We trust that Parliament will, in all railways it may sanction, limit the speed to eight or nine miles an hour.'"

Remarkable progress was experienced from 1875 to 1925 in Europe including an unprecedented rise in living standards. This time saw the spread of electricity, cars, typewriters, universities, movies, vaccines, and indoor plumbing. Despite this, many intellectuals obsessively worried themselves and others with thoughts of imminent decline, degeneration, and disaster.

The Great Horse Manure Crisis of 1894

A 125-year-old example may seem amusing today, but it was taken extremely seriously in the day. It is also notable because the logic behind the fear is the same as that behind many more recent supposed crises. Around the time that the nineteenth century turned into the twentieth, the streets of London were trafficked by over 11,000 hansom cabs, plus several thousand horse-drawn buses, each using 12 horses per day. Altogether, the city was traversed by over 50,000 horses daily. That doesn't even count the other horse-drawn conveyances delivering goods. An average horse would produce 15 to 35 pounds of manure daily along with 2 pints of urine. (New York could boast of 100,000 horses and about 2.5 million pounds of manure a day.)

The manure drew in vast numbers of flies which spread typhoid fever and other pathogens. As if large quantities of poop and pee weren't enough, working horses live only about three years. Dead horses were hard to move so it was common to let them rot until they could more easily be sawn into handy-size pieces to carry away. In 1894, *The Times* newspaper predicted: "In 50 years, every street in London will be buried under nine feet of manure." This became known as the 'Great Horse Manure Crisis of 1894'. Now, I haven't checked the volume calculations, but have no reason to doubt that prediction given its simplistic straight-line projection.

The situation seemed so dire that it was debated at the world's first international urban planning conference in New York. No solution was offered. Urban life was surely doomed. As we all know, "peak poop" was soon reached, and nobody was buried in it over their head. Henry Ford figured out how to build cars (automobiles) affordably and electric trams and motorized buses

replaced horse-drawn buses. Worldwide, horses ceased to be enslaved to our transport needs and motorized engines took over with far less noisome emissions. Unlike horses, motor vehicles have become vastly less polluting over the subsequent years.

Keep shoveling the manure

More recently, we have seen plenty of remarkably intelligent people make predictions that turned out to be hilariously (or soberingly) off the mark. In 1950, Albert Einstein warned that "only the creation of a world government can prevent the impending self-destruction of mankind."

English novelist and chemist, C.P. Snow, wrote in 1961 that "within, at most, 10 years, some of those [nuclear] bombs are going off. I am saying this as responsibly as I can. That is the certainty."

Joseph Weizenbaum, an MIT computer scientist, stated in 1976 that "I am completely certain … that by the year 2000, you [students] will all be dead."

Hans Morgenthau, an influential international relations theorist, declared in 1979 that "the world is moving ineluctably towards a third world war—a strategic nuclear war. I do not believe that anything can be done to prevent it." I have to admit that in 1979 I feared the same thing. However, I was only 15 at the time and the Cold War was warm.

According to the Bulletin of Atomic Scientists and their Doomsday Clock, humanity has been at a few minutes to midnight for 75 years! We've been *this* close to extinction every year, year after year after year. When I checked the clock in 2021, I found that the clock had been set at 100 seconds to midnight – the closest ever. It will all be over, any time now. I should note that the editor at the Bulletin does acknowledge that there is basically no method behind this alarmist madness. It began as a reflection of one person's subjective feeling and remained that way.

Eco-pessimist Lester Brown has a consistently poor record. In 1974 he predicted that a turning point had been reached and "farmers can no longer keep up with demand". They did. In 1981, he said "global food insecurity is increasing", but it was not. 1984: "the slim margin between food production and population growth continues to narrow". Still wrong. 1989: "Population growth is exceeding farmers' ability to keep up." Nope. 1994: He declared that a turning point had been reached and food production per person would plummet. Right after that assertion, the price of wheat fell to record lows, and stayed there for a decade. [Ridley, 2010, p.300]

In their 1967 book, *Famine, 1975!*, William and Paul Paddock claimed that mass starvation was inevitable and we should leave hopeless cases such as India and Egypt to starve. When those countries instead improved, they argued in 1975 for a ban on research into increasing food production in high population growth countries. Apparently, they *badly* wanted their prediction to come true and would help it along if they could.

As the chart below shows, food production in India, as well as China and the world, has continued to increase. Checking the food news in India, I find this: "India is expected to produce a record 305.4 million tonnes of grain in 2020-21, an increase of 8 million tonnes from last year's record harvest, according to a report from the Foreign Agricultural Service of the US Department of Agriculture (USDA)… Government wheat stocks have ballooned on back-to-back record harvest, the USDA said. Stocks are estimated at 60.3 million tonnes as of June 1." [Reidy, 2021; 117-118]

At the time of the first Earth Day in 1970, ecologist Kenneth Watt declared, "By the year 2000, if present trends continue, we will be using up crude oil at such a rate… that there won't be any more crude oil. You'll drive up to the pump and say, `Fill 'er up, buddy,' and he'll say, 'I am very sorry, there isn't any.'"

Watt echoed other voices going back decades. In 1919, the U.S. Geological Survey warned that world oil production would peak in 1928. In 2005, Princeton University geologist Ken Deffeyes predicted peak global oil in 2005. Instead, global production has risen steadily from about 32 million barrels per day in 1965 to 95 million in 2018. In 1980, global proven reserves were estimated at 684 billion barrels – about 30 years' supply at that year's rate of extraction. We have since extracted 983 billion barrels, but proven reserves have *nearly tripled* to 1.7 trillion barrels – enough for 50 years at the current rate. [Bailey, 2020]

What's wrong with excessive pessimism?

Of course, there are bad optimistic forecasts. But these seem to be vastly outnumbered by bad pessimistic forecasts. Most of them seem to be apocryphal and taken from science fiction. While optimistic forecasts usually don't cause much trouble (except for overly-bold companies and their own money), overly pessimistic forecasts can spur desperate actions with numerous unintended consequences. If one worrying trend is exaggerated, it will distract attention and resources from more urgent and important trends. Also, getting things repeatedly wrong undermines the credibility of institutions and experts.

When the bad things in the world are overdramatized, people fall into a constant, heightened sense of crisis and stress. Those who declare tipping points and demand action "now or never" elicit feelings that lead to stress or apathy. The call to urgent action leads you to think less critically. This in turn means supporting costly and counterproductive policies. For instance, they may, as some writers have urged, deny help to the poor due to fear of overpopulation. They may block nuclear power and GMOs even though they can help with climate and hunger and the environment.

When overly dramatic and implausible scenarios are baked into models, those models become used by business and government to make decisions. This leads to actions being proposed which are costly, ineffective, and drain our ability to tackle more realistic problems.

We should remember something emphasized both by Julian Simon and Hans Rosling: Things can be bad *and* getting better. By failing to look at the long-term trends showing improvements, we over-focus on what's bad and distressing, imagine it's worse than it is, and assume that it's getting worse still.

Let's look at a famous bet, this being between an optimist and a pessimist, the former with a good understanding of the economy and the latter… not.

The Simon-Ehrlich Bet Re-Examined

Any useful thinking about the trajectory of human wellbeing will have to consider the availability of resources. Dystopian visions of the future typically involve a world of starvation, poverty, and energy shortage. More hopeful visions see a world in which there are plentiful resources to provide for the needs and wants of everyone. When considering the future, the former view has been promulgated over many years by Stanford biologist Paul Ehrlich, his most famous book being *The Population Bomb*. The hopeful view has been given foundation by economist Julian L. Simon, author of the classic *The Ultimate Resource*.

Simon and Ehrlich disagreed over the nature of the relationship between abundance of resources and population growth. As a neo-Malthusian, Ehrlich argued that population growth would lead to scarcer resources and far higher prices. Simon argued that the opposite was true: As population increased, the price of resources would decline in the long run. Short-term price spikes would spur four responses among people: they would consume less, search for new supplies, invent and discover substitutes, and recycle. These four actions would result in long-run prices that were even lower than before the spike.

Ehrlich had published a claim that "If I were a gambler, I would take even money that England will not exist in the year 2000". When this scenario did not occur, he responded that "When you predict the future, you get things wrong. How wrong is another question. I would have lost if I had taken the bet. However, if you look closely at England, what can I tell you? They're having all kinds of problems, just like everybody else."

Frustrated with a debate that didn't lead anywhere, Simon challenged Ehrlich to a more realistic wager. He offered "to stake US$10,000 ... on my belief that the cost of non-government-controlled raw materials (including grain and oil) will not rise in the long run". Simon challenged Ehrlich to choose any raw materials he wanted and a date more than a year in the future. If the inflation-adjusted price fell over that period, Simon would win; if they rose, Ehrlich would win. Ehrlich picked copper, chromium, nickel, tin, and tungsten. The bet was agreed on September 29, 1980, with September 29, 1990, as the payoff date.

Between 1980 and 1990, global population grew by more than 800 million – the greatest one-decade increase of all time. This looked like the ideal conditions for an Ehrlich win. But by September 1990, each of the selected metals had fallen in price. Adjusted for inflation, the real price of the basket of metals had fallen by 36%. In October 1990, Paul Ehrlich mailed Julian Simon a check for $576.07, acknowledging Simon's winning of the wager.

Matter settled? Hardly! Losing a clear bet stings. It was not surprising that advocates of neo-Malthusianism wanted to dismiss the outcome. Alas, they had something to go on since Simon agreed to a bet that was improperly advantageous to the Ehrlich side, even though they did lose in this case. Some researchers examined historical prices of those five metals and came to a different conclusion. [Kiel 2009; McClintick, 2005] Kiel et.al. looked at prices in 98 ten-year intervals between 1900 and 2007 – during which time the world population quadrupled. They found that Ehrlich would have won the bet 61.2% of the time with an average return of 10.5%.

So, matter settled *now*? No! Commodity prices over a decade are a poor measure of long-term scarcity or abundance. The prices vary greatly with economic cycles. Simon made a mistake in using real prices (prices adjusted for inflation). In his book, *The Ultimate Resource 2*, Simon points out several alternative measures of the cost of a commodity. You can look at the nominal price or the real price. You can look at the price compared to average wages. Or you can compare it to household income. Even inflation-adjusted real prices are not the best measure because you are looking at the cost of a commodity relative to the cost of money. If real earnings have gone up more than the cost of money, the commodity is more affordable. In discussing copper, he wrote:

> "The most important measure is the price of copper *relative to wages*. This price has declined very sharply." "Every measure leads us to the same conclusion, but these calculations of expenditures for raw materials as a proportion of total family budgets make the point most strongly." [Simon 1998, 31,33]

Pooley & Tupy reviewed data from 1900-2019. Understanding that what matters is the real price of resources compared to real earnings, they used time prices – how many hours of work it takes to pay for a fixed amount of a resource. [Pooley & Tupy, 2020] They found that Simon wins the bet 54.2% of the time with an average return over this 110-year period of 2.22%. Given the war clause in the original bet, the researchers ran the numbers excluding the years for World War I, World War II, the Korean War, the Vietnam War, and the War on Terror. Simon

would win the resulting 73 ten-year bets 69.9% of the time with a return of 18.0%.

During that 119-period, the time price of the five-metal basket of commodities **fell by 87.2%** despite a huge growth in both US (330%) and global population (375%). Put another way: "The time required for a blue-collar U.S. worker to earn enough money to buy one basket in 1900 would get him or her 7.84 baskets in 2019." Although nominal prices of the basket increased by 2,909%, over the same period blue-collar hourly income increased by 23,485%.

Simon and others have found the same result for numerous other resources. On p.167 of *The Ultimate Resource 2*, Simon shows the falling cost of oil, coal, and electricity relative to CPI and to US wages.

While Ehrlich took a static view of resources, Simon understood that resources don't really exist until people find them and put them to use. What happens when the price of a resource rises? Human ingenuity and intelligence driven by the market incentive to control costs lead to a search for new supplies and spur innovations that allow us to substitute or do more with less. In Simon's view, this will lead to prices lower (in real terms) than in the past.

I don't think that has to be true in every case. With real prices, the cost of resources is just measured against the value of money. But what matters to us is whether we have to give up more, the same, or less of other goods. Measuring cost by earnings makes sense. Real prices can be a quick guide to whether something is truly getting cheaper or not – especially when prices are low and stable – but it's *affordability* that matters.

Ehrlich's Failed forecasts

Failed forecasts and predictions from doomsayers are abundant. They are a resource that seems truly endless. Ehrlich has been a remarkably rich source of forecast failure. Here are a few founded on his assumptions of fixed limits and scarcity:

> "What will we do when the [gasoline] pumps run dry?" After that question, gasoline became cheaper than it had in decades.
>
> Ehrlich on DDT: "The US life expectancy will drop to forty-two years by 1980, due to cancer epidemics." But both cancer incidence and the death rate from cancer fell steadily, falling 16% between 1950 and 1997, accelerating after that. US life expectancy at birth went up from 70.5 in 1967 to 74.4 in 1980 to 79.1 today.
>
> 1975: "In the 1970s and 1980s, hundreds of millions of people will starve to death in spite of any crash programs embarked upon now. At this late date nothing can prevent a substantial increase in the world death rate." In 1968, in 34 out of 152 countries the daily food supply was under 2,000 calories per person. In 2017, that was the case in only 2 of 173 countries.
>
> "India couldn't possibly feed two hundred million more people by 1980." [*The Population Bomb*] By 1974, India was a net exporter of wheat.
>
> "Most of the people who are going to die in the greatest cataclysm in the history of man have already been born. By…[1975] some experts feel that food shortages will have escalated the present level of world hunger and starvation into famines of unbelievable proportions. Other experts, more optimistic, think the ultimate food-population collision will not occur until the decade of the 1980s." ["Eco-Catastrophe!" 1969] In reality, between 1950 and 2000, barley, corn, cotton, oats, and wheat became three times cheaper when compared to wages. World food prices fell by half from 1960 to 1995. [Moore, 2000, p.197; Goklany, 2007 p.23]
>
> "Dr. Ehrlich predicted… that the oceans could be as dead as Lake Erie by 1979. Today Lake Erie is palatable, and Dr. Ehrlich is not." (P.J. O'Rourke, *Parliament of Whores*)

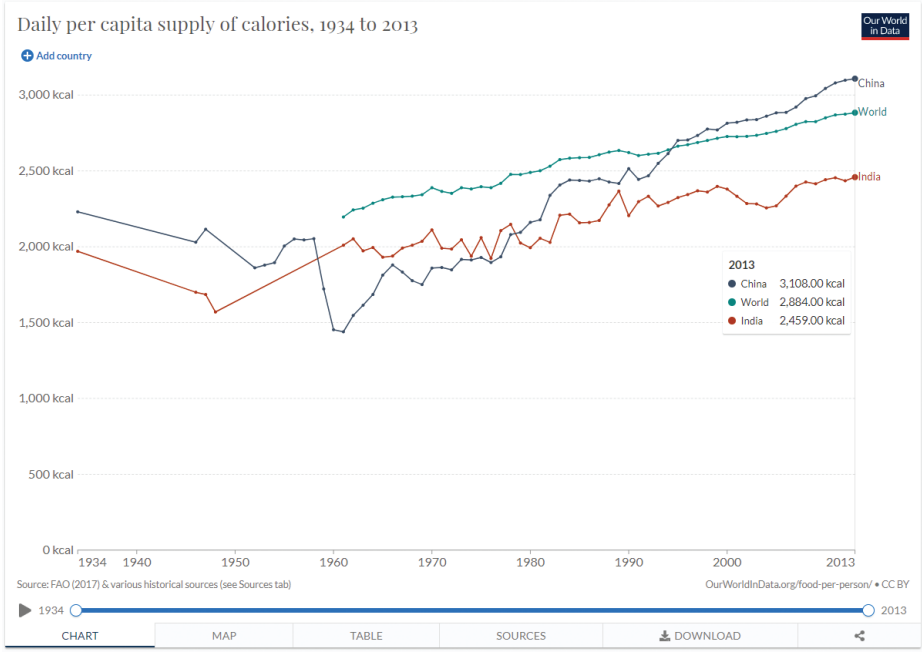

Figure 1: Daily per capita supply of calories, 1934 to 2013

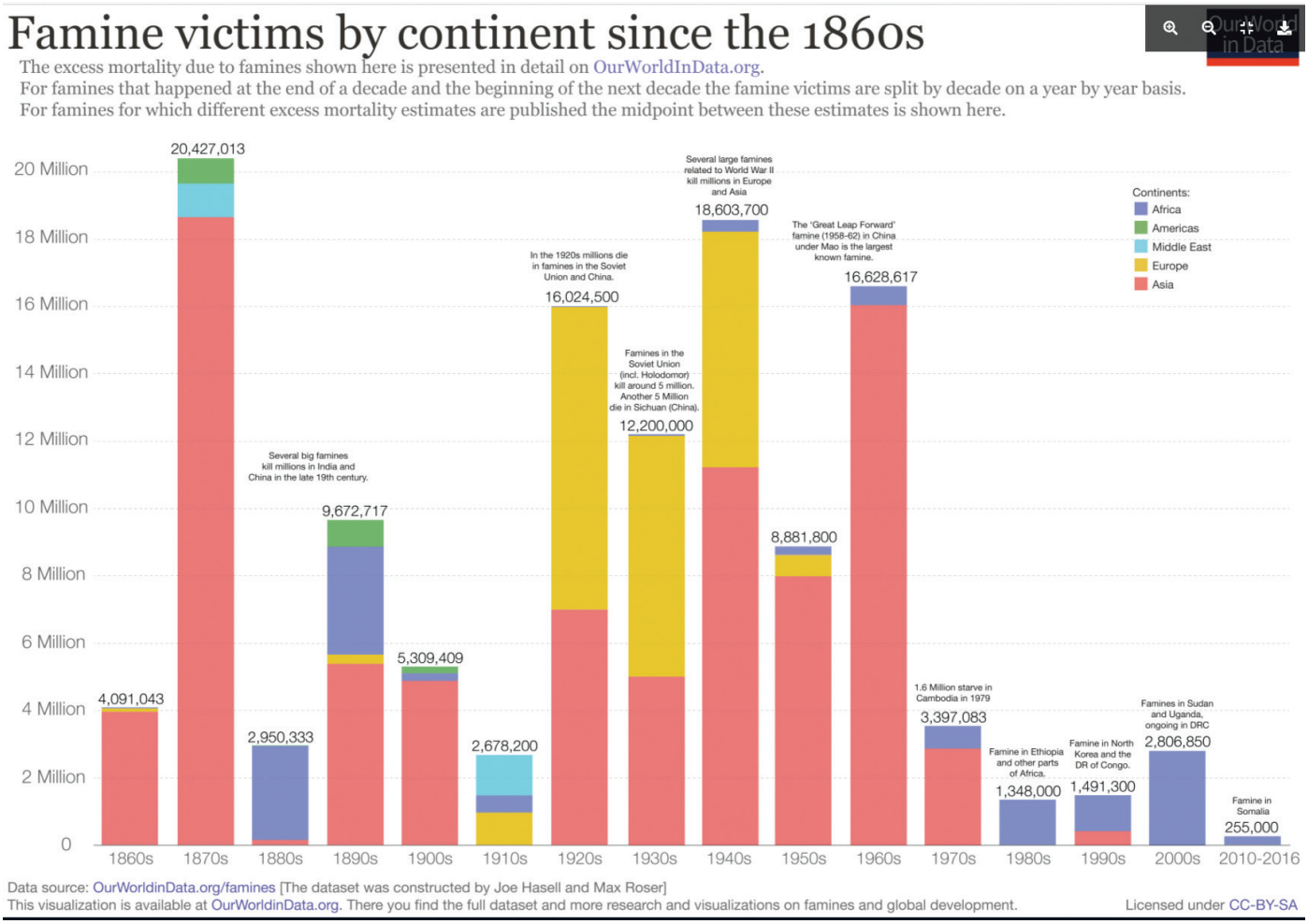

Figure 2. Famine victims by continent since the 1860s [OWID2]

> "Most of the people who are going to die in the greatest cataclysm in the history of man have already been born," [From a 1969 magazine article.] "Sometime in the next 15 years, the end will come. And by 'the end' I mean an utter breakdown of the capacity of the planet to support humanity." [Ehrlich on CBS News in 1970]
>
> "Population will inevitably and completely outstrip whatever small increases in food supplies we make. The death rate will increase until at least 100-200 million people per year will be starving to death during the next ten years." [*Mademoiselle*, April 1970] A claim made in 1970, just before an agricultural revolution that rapidly increased the world's food supply.

Famine since 1970 has been unrelated to food supply. Famine resulted from wars and political problems, including the Cambodia starvation of 1970, African famines in the 1980s and the DR of Congo in the 1990s, and so on. Fewer people die in famines over time.

Famines aside, fewer and fewer people are undernourished. Certainly, there is plenty of room to improve availability and affordability of nutritious foods (and not just calories). Again, things can be bad but getting better. According to the FAO, the percentage of the global population who are undernourished has fallen from just over 50% in 1945 to 20% in 1985 to about 11% in 2015. Here are daily calories per capita over the last several decades:

> China: 1934: 2230. 1961: 1439. 1990: 2515. 2013: 3108.
>
> India: 1950: 1570. 1970: 2111. 2013: 2559.
>
> World: 1961: 2196. 1990: 2621. 2013: 2884.
>
> Sources: [OWID 3; Bailey, 2020, p.16]

Undernourishment, percentage of population

	1969-71	1979-81	1990-2	2000-2	2014-16
Latin America	20	14	15	11	6
Asia	40	30	24	18	12
Africa	34	31	28	25	20
Developing World	37	28	23	18	13
World	29	19	19	15	11

Source: Norberg, 2017, p.20

Ehrlich told readers of the 1970 Earth Day issue of *The Progressive* that between 1980 and 1989, some 4 billion people, including 65 million Americans, would perish in the "Great Die-Off." At that time, he also warned that "[i]n ten years all important animal life in the sea will be extinct. Large areas of coastline will have to be evacuated because of the stench of dead fish."

In a 1971 speech at the British Institute For Biology, he predicted that: "By the year 2000 the United Kingdom will be simply a small group of impoverished islands, inhabited by some 70 million hungry people. If I were a gambler, I would take even money that England will not exist in the year 2000." *New Scientist* magazine approvingly drew attention to his speech in an editorial titled "In Praise of Prophets."

Ehrlich provides an exceptional example of how *not* to behave when thinking and communicating about possible futures. He often attributes some combination of stupidity and scientific ignorance to those with whom he disagrees. Alluding to Simon's book, *The Ultimate Resource*, saying 'The ultimate resource – the one thing we'll never run out of is imbeciles." He often uses words like "ignorant," "crazy," "imbecile," and "moronic."

Ehrlich has been evasive in acknowledging errors he made, while being intellectually dishonest in taking credit for things he claims he got "right". Despite being demonstrably and repeatedly wrong, somehow people continue to quote him approvingly and his books sell in large numbers. When confronted with his failure to revise his predictions, in 2009 Ehrlich actually responded: "perhaps the most serious flaw in *The Bomb* was that it was much too optimistic about the future." Even someone as green-friendly as Bill Gates recognizes the errancy of Ehrlich's judgment. [Gates, 2013]

The Simon Abundance Index

Inspired by Julian Simon's work, The Simon Project has developed a thorough and highly informative framework for measuring progress. Is progress too subjective or culturally relative to measure? Steven Pinker argues that it's not:

> Most people agree that life is better than death. Health is better than sickness. Sustenance is better than hunger. Wealth is better than poverty. Peace is better than war. Safety is better than danger. Freedom is better than tyranny. Equal rights are better than bigotry and discrimination. Literacy is better than illiteracy. Knowledge is better than ignorance. Intelligence is better than dull-wittedness. Happiness is better than misery. Opportunities to enjoy family, friends, culture, and nature are better than drudgery and monotony. All these things can be measured. If they have increased over time, that is progress. [Pinker, 2018]

The Simon Project looks deeper into the relationship between population growth and resource availability using the new concept of the Simon Abundance Framework. This framework deploys three core concepts: Time Price, Price Elasticity of Population, and the Simon Abundance Index.

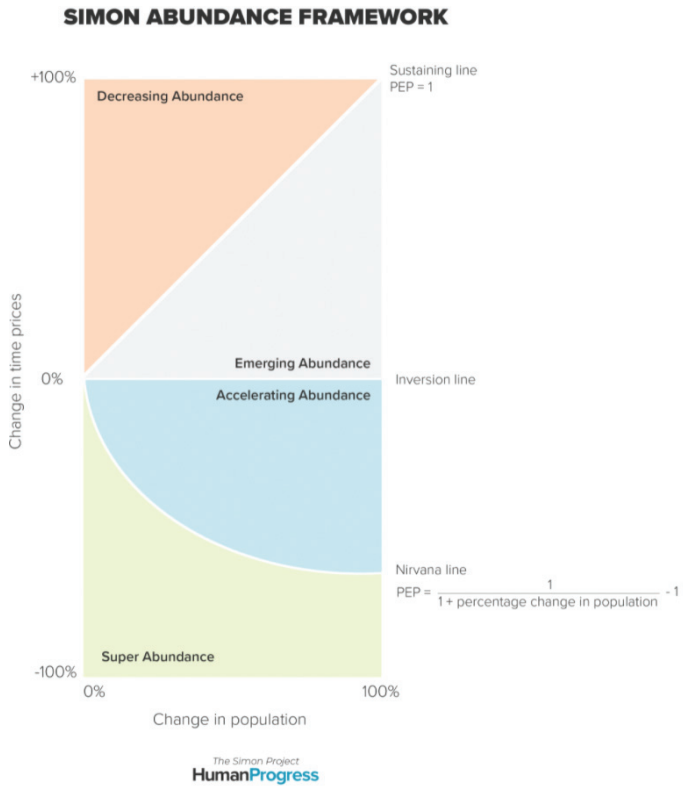

Figure 3: The Simon Abundance Framework

Time price: As we have seen, the time price denotes the amount of time that an average person has to work in order to earn enough money to buy a commodity. The main page of the Simon Project features a chart showing the percentage changes in the time price of 50 basic commodities between 1980 and 2018. It's too big to reproduce here but take a look; it shows the increase in affordability for 50 commodities.

Things can become more affordable in two ways: Through a reduction in the money price, and through an increase in hourly income. The time price captures both the price fluctuations and

the value of labor. The most recent update "found that the average time price of 50 commodities fell by 72.34 percent between 1980 and 2018. Commodities that took 60 minutes of work to buy in 1980 took only 16.6 minutes of work to buy in 2018." Put the other way around, you could buy 3.62 times as much of that basket in 2018 compared to 1980. "The compounded growth rate of abundance came to 3.44 percent per annum. That means that the affordability of our basket of commodities doubled every 20.49 years."

Price Elasticity of Population (PEP): This is a measure of whether population growth increases the availability of resources. This was Simon's view; Ehrlich could never grasp how it could be possible. Elasticity in economics is a measure of a variable's sensitivity to a change in another variable, the variable most commonly being price or cost. The researchers derive a PEP value of -1.016. This indicates that the time price of their basket of 50 commodities declined by 1.016 percent for every 1 percent increase in population. "Over the past 38 years, every additional human being born on our planet appears to have made resources proportionately more plentiful for the rest of us."

Simon Abundance Index: The Simon Abundance Index (SAI) measures the change in abundance of resources over a period of time. The SAI is the (multiplicative) ratio of the change in population over the (again, multiplicative) change in the time price, times 100. The base year is 1980 and the base value is 100. The latest calculations (2019) find the value of the SAI is 618. Seen another way, the Earth was 6.18 times as plentiful in 2018 as it was when Ehrlich and Simon commenced their wager.

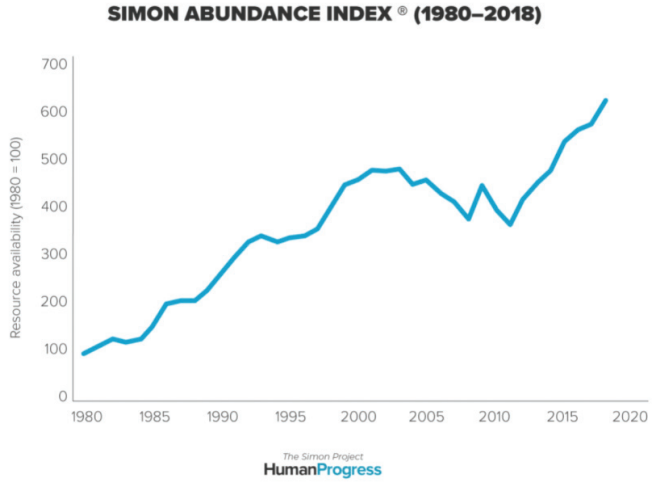

Figure 4: The Simon Abundance Index (1980-2020)

In terms of the Abundance Framework, we are experiencing superabundance – "a condition where abundance is increasing at a faster rate than the population is growing". We have seen compound annual growth rate in resource abundance of around 5% and doubling of global resource abundance every 14 years or so.

Continued improvements in abundance and well-being at the recent rate are not inevitable. As population growth slows and reverses, we may slip out of the super-abundance zone into accelerating abundance or a lower zone. If fear of the future leads the world increasingly to regulate energy and production, and to artificially restrict supply and innovation, the trend could reverse. I will discuss the conditions for continued progress in a later installment of this series.

In part 3, I plan to zero in on perhaps the most influential doomster work, the 1972 report from the Club of Rome: *Limits to Growth*, and its 2021 update. I'll look at why gloomy projections went badly wrong and consider some of the economic forces that give us a basis for more optimistic or "possibilist" projections. ■

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https://ourworldindata.org/

OWID2: https://ourworldindata.org/why-do-far-fewer-people-die-in-famines-today

OWID3: https://ourworldindata.org/grapher/daily-per-capita-supply-of-calories?country=CHN+IND+OWID_WRL

https://www.theatlantic.com/magazine/archive/2019/06/how-to-predict-the-future/588040/

Alcor Longevity Circle of Distinguished Donors

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

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

These benefits are, of course, overshadowed by the immense gratitude members' and patients' families will always have for these especially generous individuals. New levels of membership (higher and lower levels of participation) may also be announced in the future. ■

Support Alcor's **RAPID** Research

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

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

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

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

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

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

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

Alcor Case Metrics 1967-1999

By Michael Benjamin and Aschwin de Wolf

Introduction

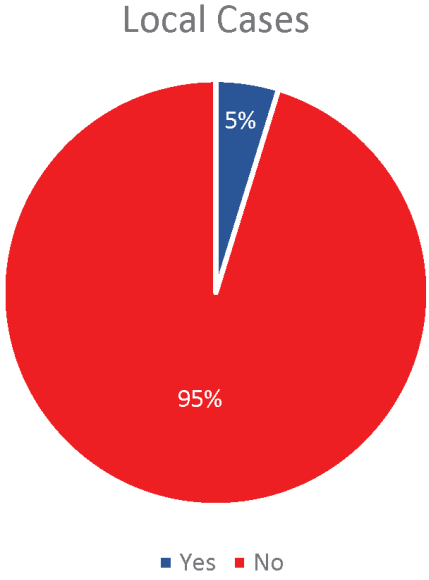
The Alcor Meta-Analysis Project has three distinct objectives: (1) To organize and enter all case data in a comprehensive database; (2) to visually present and publish the data in a format that allows the reader to see trends and patterns; and (3) to identify correlations between specific elements of a case and outcomes.

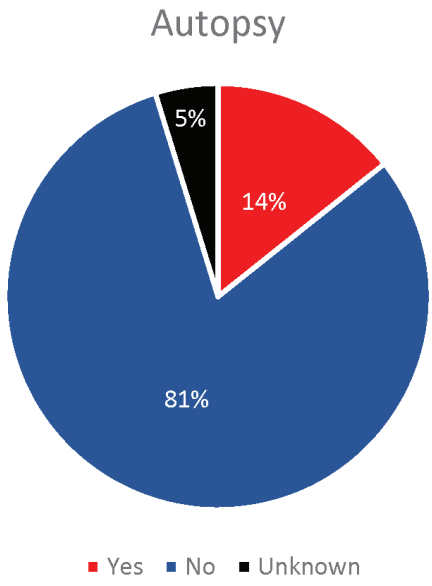
We present here a selection of case data for the years of 1967-1999. Alcor did not exist yet in 1967 but this year marks the cryopreservation of Dr. James Bedford, who is now in Alcor's care. This series ends in 1999, which roughly corresponds to the end of the "pre-vitrification" high concentration glycerol era. There are no CT scans available for this period yet. Detailed case data for James Bedford were not available. As a consequence, some metrics cannot be known (like the S-MIX).[1]

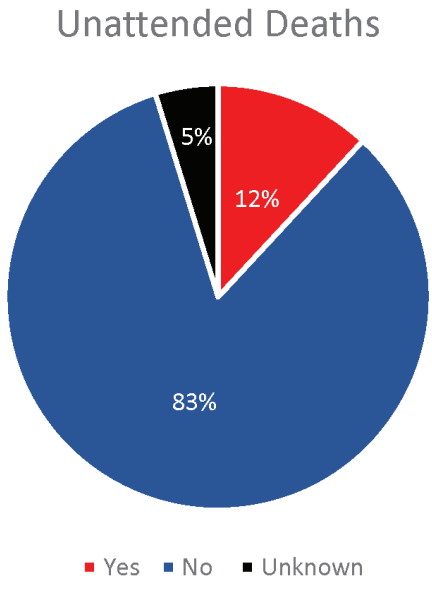
At this stage in the meta-analysis project, we still confine ourselves to presenting factual data and calculated (or estimated) measures. After completing this project for all Alcor cases, we will move to the next step of identifying trends and correlations.

The magnitude of the project and sheer quantity of data makes it inevitable that some errors can be introduced in the reporting or interpretation of data. In some cases, detailed data is not available and rough estimates need to be made based on the case data that was available and extrapolation of what we know from other cases. We expect this project to increase in comprehensiveness, accuracy, and actionable information.

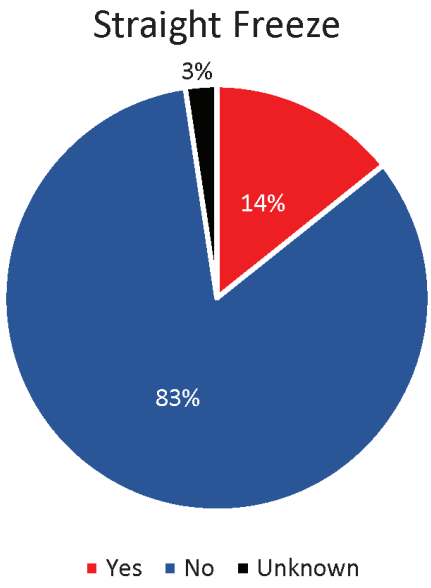
+ Note: The color "blue" represents a "good" outcome and the color "red" a sub-optimal outcome / situation

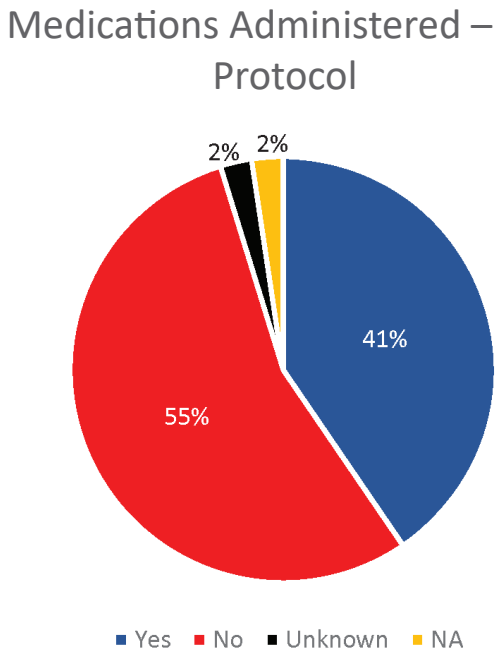


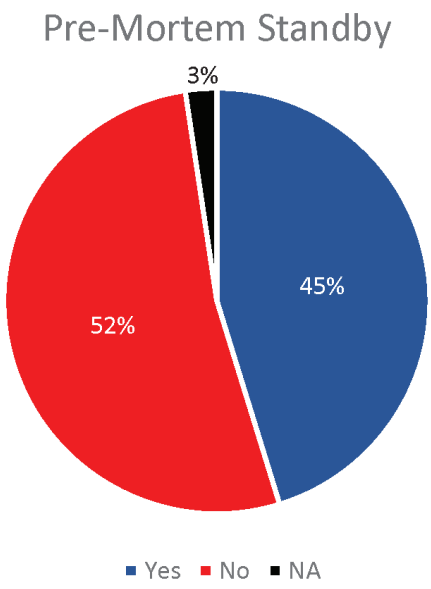


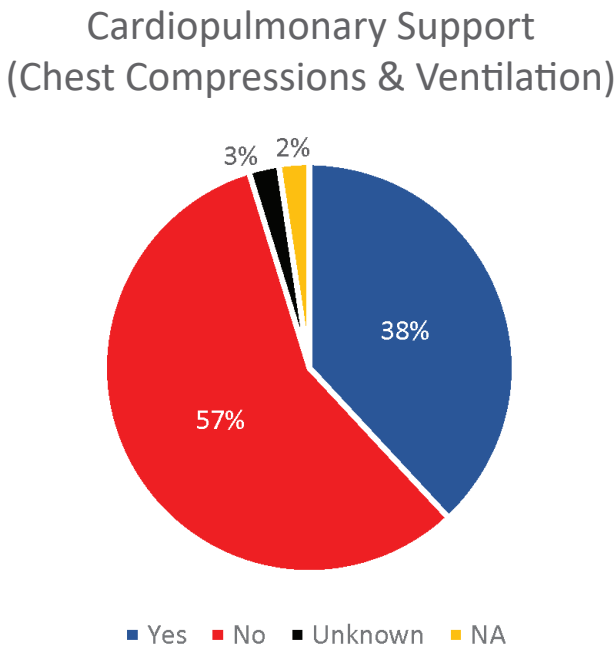


1 For a detailed exposition of the S-MIX metric, see *Cryonics* magazine, 4th quarter 2020, page 12: https://www.alcor.org/docs/measuring-ischemic-exposure.pdf

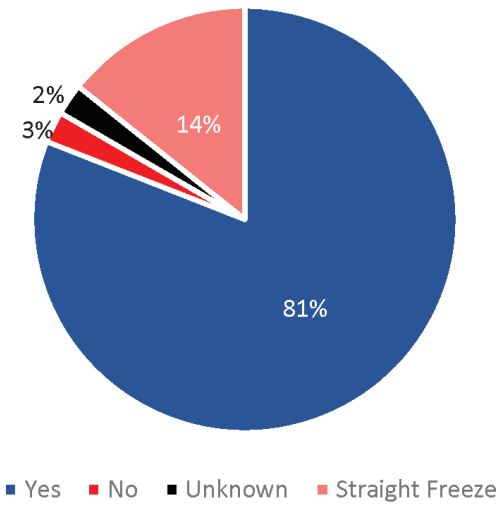

Straight Freeze
3%
14%
83%
Yes
No
Unknown


Medications Administered – Full Protocol
2%
2%
41%
55%
Yes
No
Unknown
NA

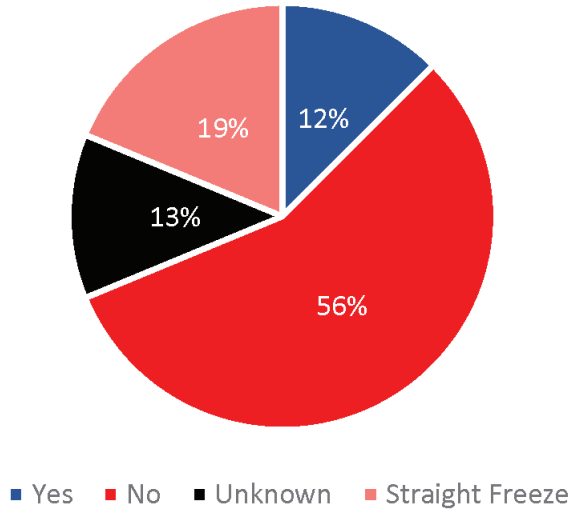

Pre-Mortem Standby
3%
45%
52%
Yes
No
NA


Cardiopulmonary Support (Chest Compressions & Ventilation)
3%
2%
38%
57%
Yes
No
Unknown
NA

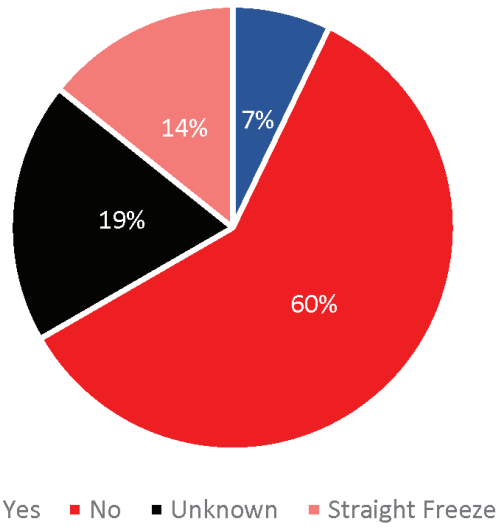
Cryoprotective Perfusion



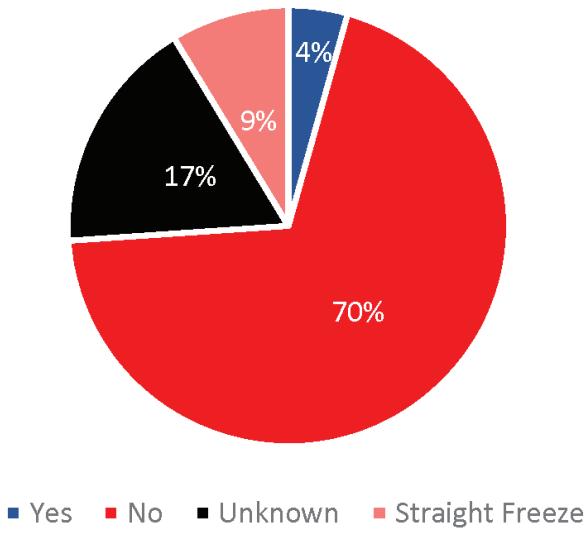
Terminal Cryoprotection Concentration Achieved – Whole Body Cases

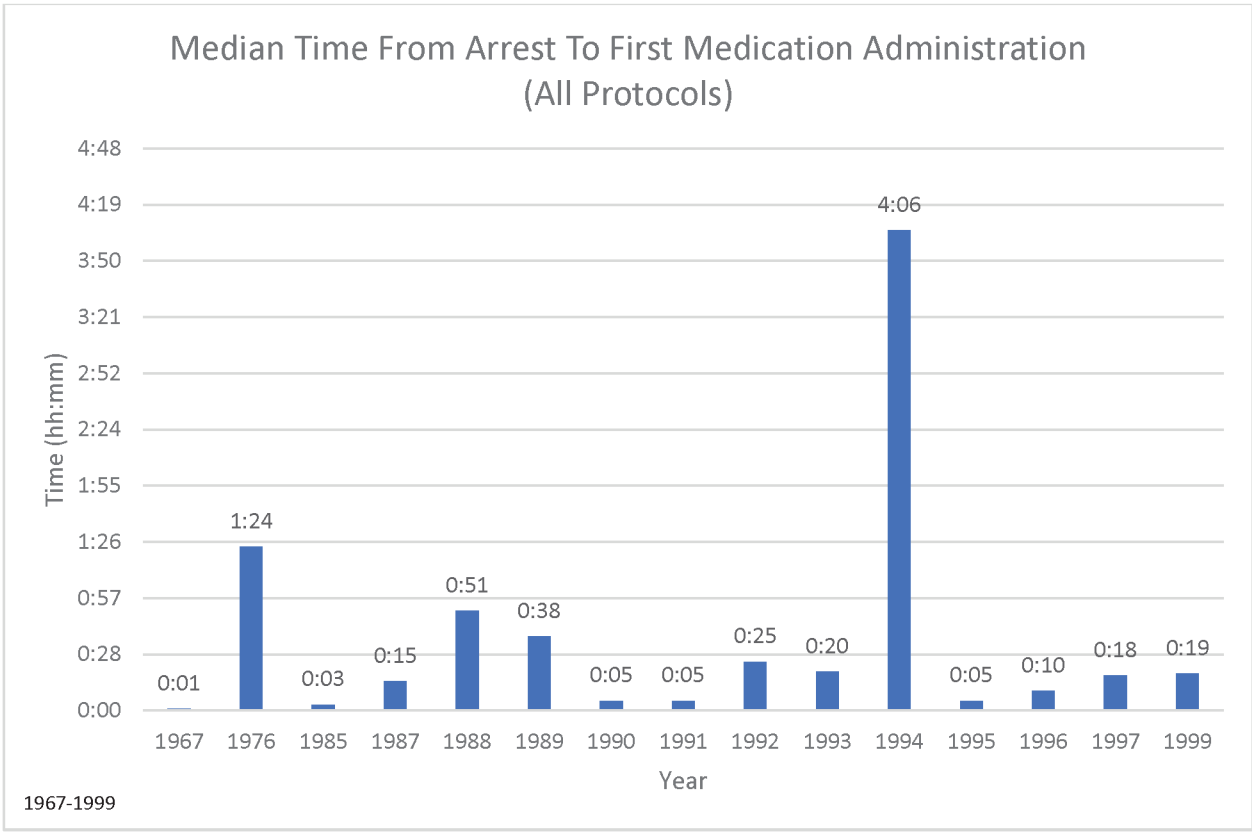


Terminal Cryoprotection Concentration Achieved

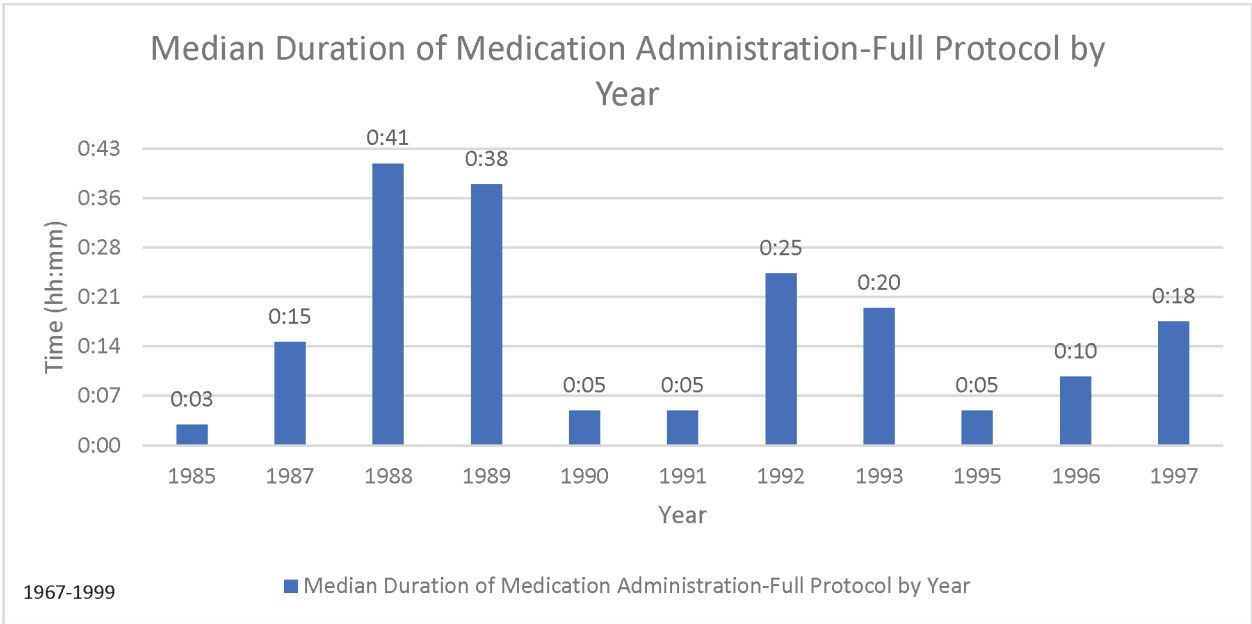


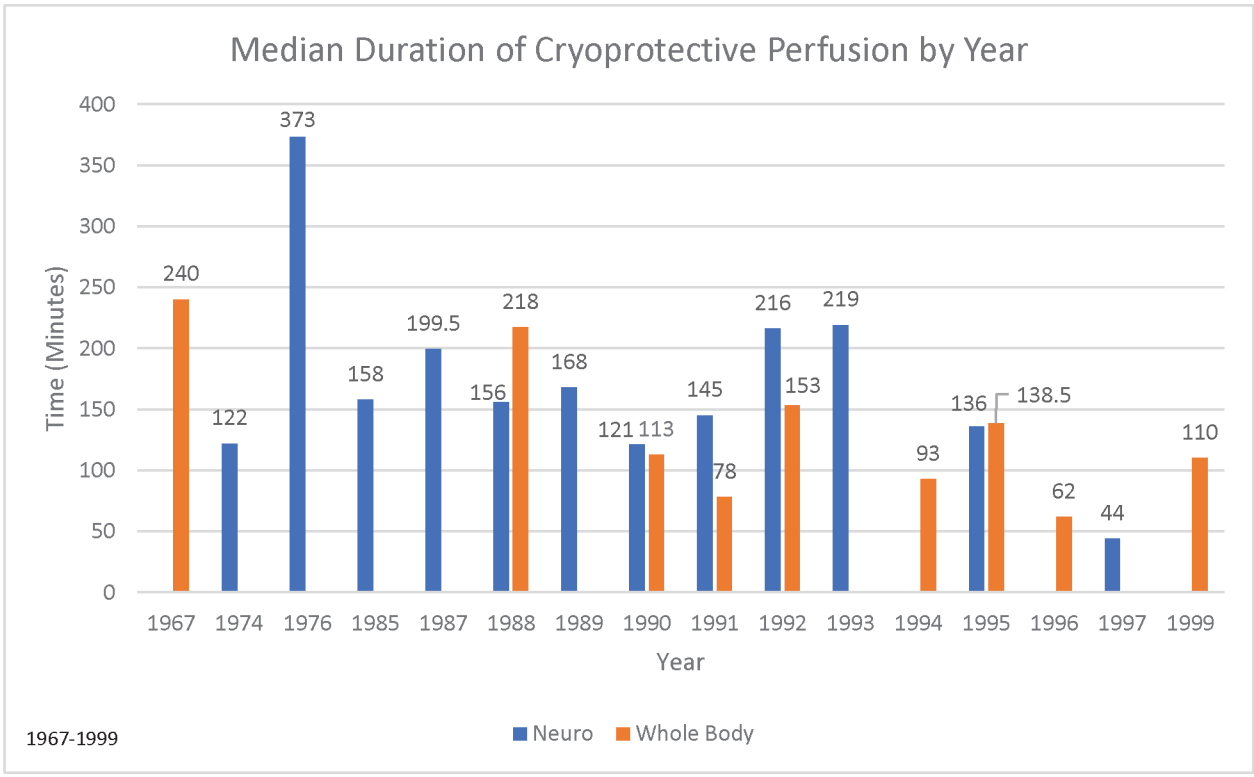
Terminal Cryoprotection Concentration Achieved – Neuro Cases

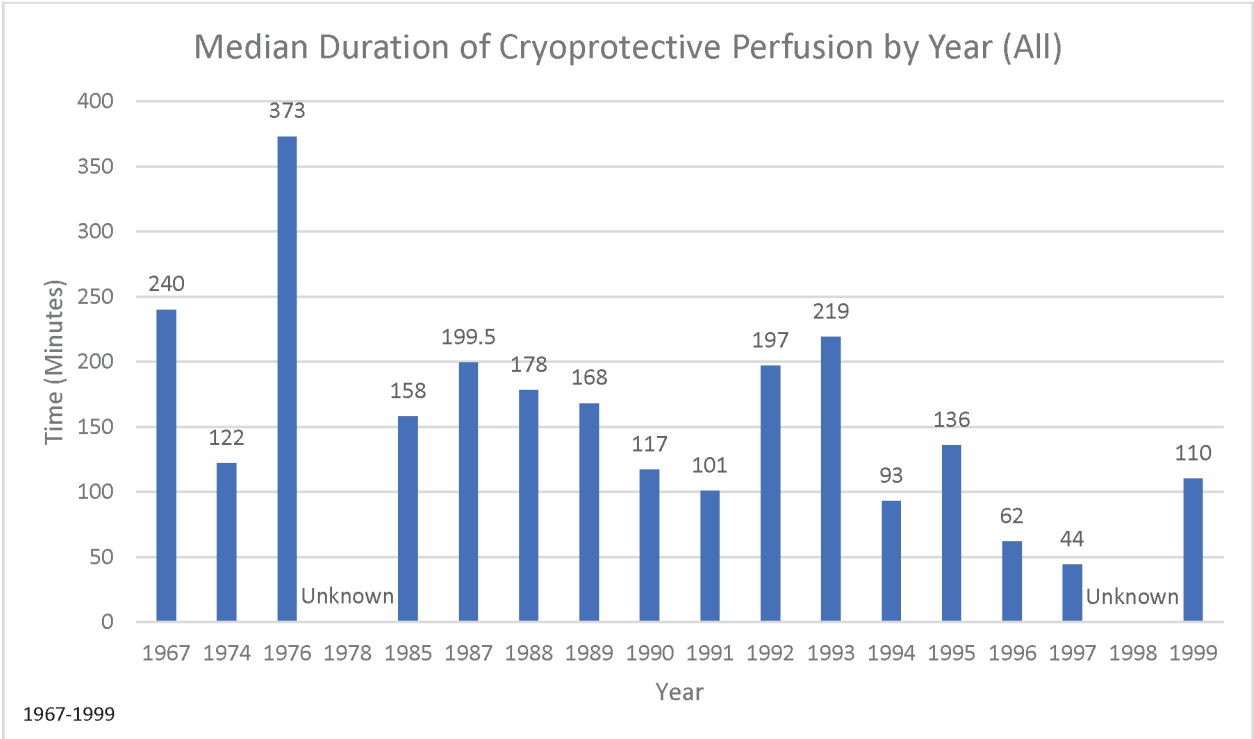


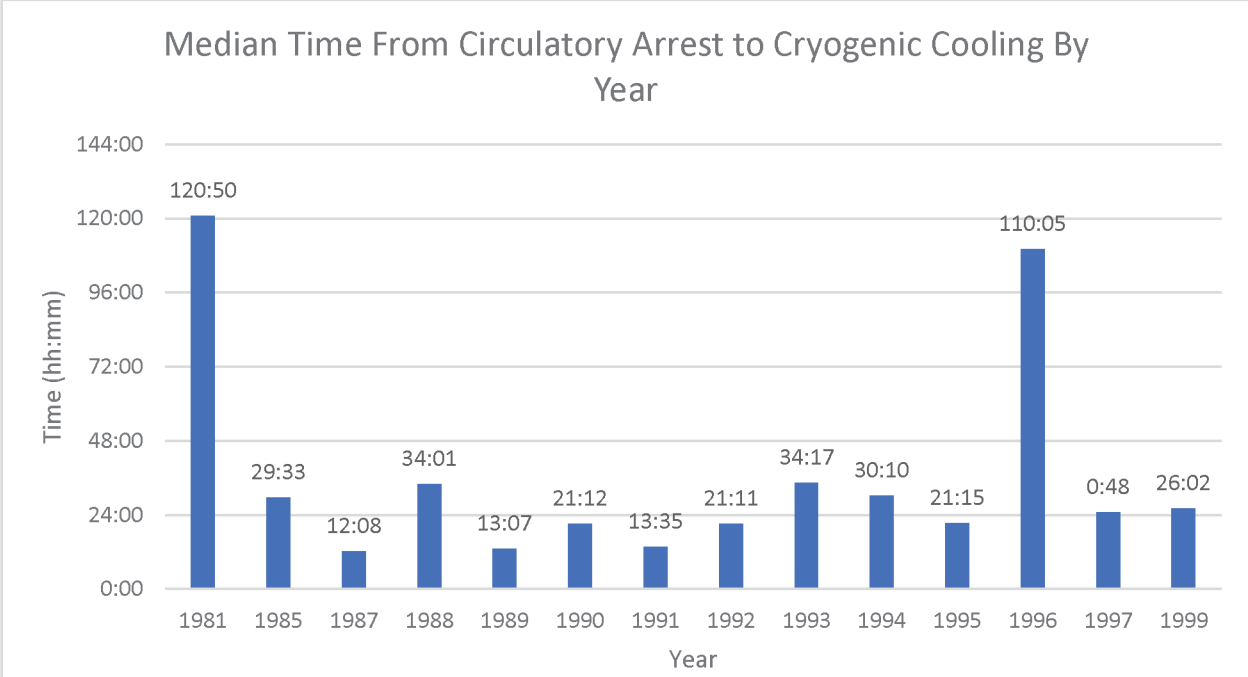


Note: 1994 constitutes one single case, in which only Maalox could be administered post-mortem.

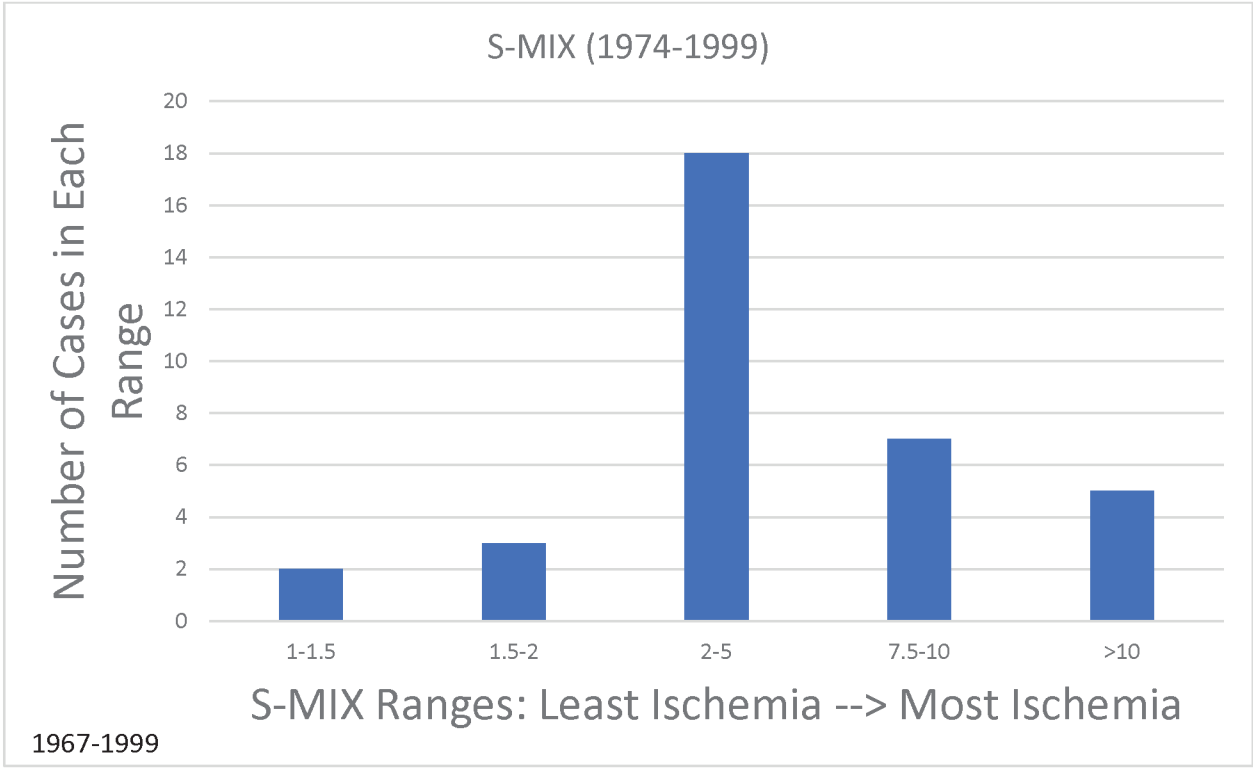



Median Duration of Cryoprotective Perfusion by Year
Time (Minutes)
400
350
300
250
200
150
100
50
0
240
122
373
158
199.5
156
218
168
121
113
145
78
216
153
219
93
136
138.5
62
44
110
1967
1974
1976
1985
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1999
Year
Neuro
Whole Body
1967-1999

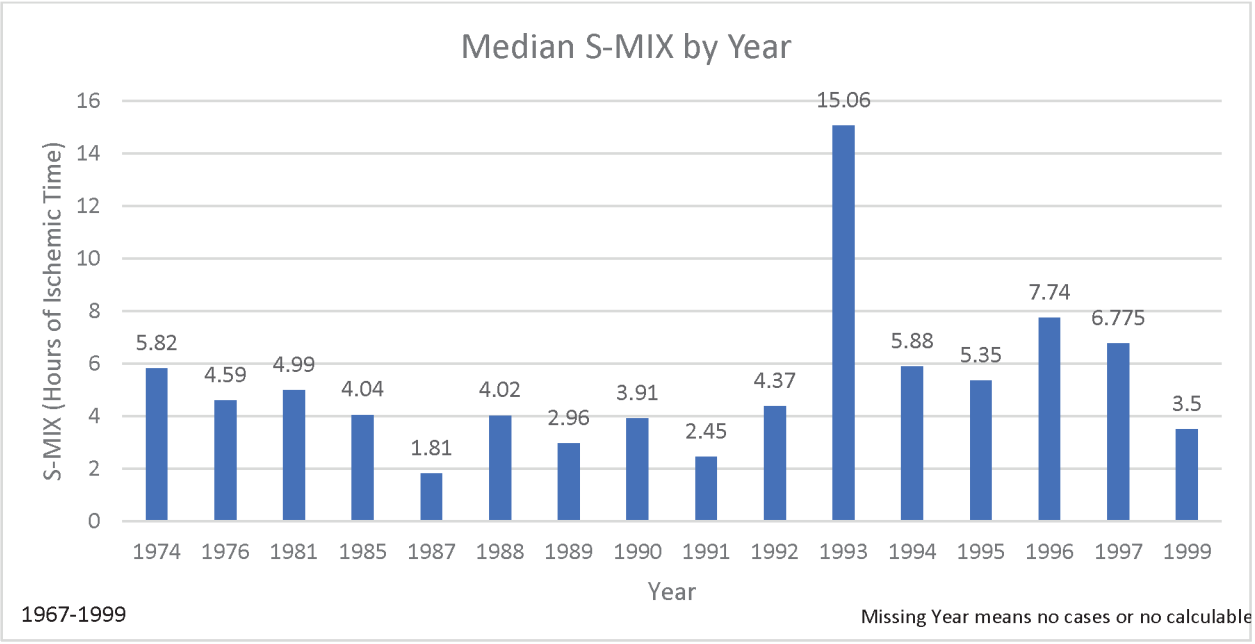

Median Duration of Cryoprotective Perfusion by Year (All)
Time (Minutes)
400
350
300
250
200
150
100
50
0
240
122
373
Unknown
158
199.5
178
168
117
101
197
219
93
136
62
44
Unknown
110
1967
1974
1976
1978
1985
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
Year
1967-1999



1967-1999



1967-1999



Note: Meaningful data collection on the 1967 case (James Bedford) is challenging. For example, Bedford was injected, not perfused with cryoprotectant (DMSO). Calculating the S-MIX is not possible for this case due to a lack of data.

Cryonics and the New Space Age

By Jason Harrow

A new space age is upon us. We in the cryonics community need to capitalize on this moment to form alliances that will accelerate cryonics research.

Recently, Jeff Bezos' Blue Origin and Richard Branson's Virgin Galactic each launched passengers into space and returned safely to Earth. And a few months before that, SpaceX sent four astronauts to the International Space Station. All three companies—and more—are generating not only new excitement, energy, and technology, but are also recalibrating our goals. SpaceX, for instance, says it is on the "road to making humanity multiplanetary." Jeff Bezos has discussed Blue Origin's plans to use the moon as a base for further space travel. But if we truly want to become multiplanetary, cryonic preservation and revival will have to become a reality.

The reason true suspended animation is necessary to interplanetary space travel is obvious: space is big. Really, really big. And that bigness means that it takes a very long time to get anywhere in space. For instance, the minimum distance between Earth and Mars is 33 million miles. During the best launch windows, spacecraft can travel that distance in six to seven months. Perhaps a few people will be able to survive a six-month journey on a spacecraft without going crazy—some very tough astronauts have spent more time than that on the International Space Station—but that trip would be much better if the passengers could enter an unconscious period of stasis and wake up on Mars after what, to them, would be a much shorter period of time. As many science-fiction writers and readers know, that is possible using suspended animation.

But even if a hearty few could make the trip to Mars without some kind of metabolic arrest, that's basically the only place humanity could go without improvements in suspended animation. Trips to the moons of Jupiter or Saturn are at least ten times as long as trips to Mars. Trips to the outer solar system are even longer. And to become an interstellar society and travel light-years away to planets orbiting other stars, we'll need to take trips that will last at least decades or more even with very fast vehicles. Without metabolic arrest, it's hard to imagine that anyone alive at the beginning of the trip would survive to the end.

What is perplexing about the seeming lack of public interest in cryonics research among space travel enthusiasts is that cryonics is surely the best way for those living now to experience a world as different from our current one as Mars would be. While a SpaceX rocket could take a human from Earth to Mars, a viable cryopreservation could take a human from 2021 to 2121. Not only would Earth be vastly different in a hundred years, but other technology may have progressed sufficiently to make humanity a true space-faring society.

And space travel advocates could push for human cryopreservation research on the grounds that it will have benefits outside of cryonics. Just like space exploration programs jump-started several important technologies we use everyday—things like GPS, high-powered solar cells, and even the Dustbuster wouldn't have happened without NASA—cryonics research can lead to breakthroughs outside of life extension. Emerging research shows that cooling trauma patients down substantially can extend their lives by reducing the metabolism of several of their important bodily functions. Indeed, of the people who are revived after being under water for unthinkable periods of time—30 minutes or more—most of them were submerged in icy water, which apparently permits the body to enter a state of depressed metabolism. For now, this research shows promise. But with more resources, who knows what therapies could emerge.

As space travel goes mainstream, it's time for a grand alliance between space travel advocates and cryonicists. If Virgin Galactic is serious about exploring our galaxy, and if Elon Musk is serious about humanity becoming truly "multiplanetary," then they have to begin to get just as serious about human suspended animation and cryonics as they are about booster rockets. To enable that, we in the cryonics community should actively reach out to find fruitful areas of collaboration. It's the only way forward for both cryonics and multiplanetary space travel. ■

Jason Harrow is a civil rights lawyer. He is an Alcor member and a member of the Legal & Regulatory Committee.

He can be reached at jason.harrow@gmail.com.

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Preserving Minds, Saving Lives

The Best Cryonics Writings of The Alcor Life Extension Foundation

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

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

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

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

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

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Afterword • Biographies of Contributors

"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.

How to Argue for Life Extension

By Max More, Ph.D.

Have you been frustrated in discussing cryonics or life extension? Perhaps you were trying to explain your cryonics arrangements. Inevitably that will lead to the question: "But why would you *want* to live longer?" You gave perfectly sensible and persuasive reasons. You were baffled at the response. For every reason you cite your conversation partner had an immediate and apparently reflexive counterargument. If you've had this kind of conversation more than a couple of times, you may have noticed a pattern in the resistance.

I have supported life extension for myself and advocated for life extension as a desirable goal for all who want it. I was still in my teens when I became serious about it. I'm not sure exactly when I first thought about it as a real possibility, but I know the first book I read on the subject was Alan Harrington's idiosyncratic but fascinating, *The Immortalist: How Science Could Give Humanity Eternal Life*. From my notes, I know I read that in June 1982. Being one of those annoying people who enjoy arguing about controversial ideas, I've had that conversation (or argument) thousands of times. That doesn't automatically mean I'm good at it.

For decades, having spent quite a bit of time thinking about how to communicate more effectively, I do think I've learned some things. This showed up in a recent Oxford Union debate. The proposition to be debated was: "This House Would Live Forever". Knowing that the students are constantly blasted with messages of doom and gloom, I expected the pro side to do badly. At the Union debates, votes are counted both before and after the debate. In this case, before the debate, only 29% were in favor, with 71% opposed. After both sides had made their case, the vote was retaken. The results: 59% in favor, with 41% opposed. One of the organizers emailed me and said: "To be honest, such a swing is quite rare!"

Just as in most conversations, I had only eight to ten minutes to make the case. In planning a concise and hopefully compelling argument, I considered the classical rhetorical triangle of pathos, logos, and ethos. Logos comes naturally to many analytically-minded people, which includes most people in life extension circles. Logos is an appeal to logic; persuasion through reason. Intellectual honesty makes logos a crucial part of the discussion, but it isn't enough. Pathos appeals to emotion and attempts to convince an audience of an argument by creating an emotional response. Finally, ethos boosts the message by supporting the speaker's credibility. You will notice that I did a little of that above. A persuasive argument combines logos, pathos, and ethos so that they dovetail and mutually support one another.

In this case, I faced an immediate obstacle: The word "forever" in the motion. I objected to the organizers, but they wouldn't change it. I had to begin by explaining that the audience should understand the motion from my perspective to mean: "This House supports the right of individuals to choose to live for an indefinite number of years in good health and finds that choice appealing." "Indefinite" means that you don't die from old age or age-related diseases (and increasingly less from accidents and violence). The goal is to be able to live for as long as you choose without age-related disease.

Making this point matters because a distressing number of people otherwise think you are talking about people living a very long time while continuing to age. This common mistake stuns me, but it may be due to a long history of literature and myth. Certainly, we don't want to make the Tithonus error. According to the Homeric Hymn to Aphrodite, when Eos asked Zeus to make Tithonus immortal, she forgot to ask that he be granted eternal youth.

Ethos and logos first

Before diving into the many logos-based arguments – and anticipations of objections – I first splashed the audience with a smattering of ethos and pathos to open their minds to reason. Some people will reject your qualifications on the grounds that you live a good life and haven't suffered aging and death (They assume!). I emphasize first that I have pondered the topic for decades. I tell them that my father died when I was 11, that my oldest friend killed himself, and that I have lost several other friends and dear people to disease, accident, or suicide. I'm old enough at 57 to personally experience the effects of aging and saw up close my mother-in-law's descent into dementia before dying at 99. As a champion of life, I'm for reducing suffering and building the capacity to live and love. You probably have similar experiences to draw upon.

Remind your conversant that, in opposing aging, you are opposing the progressive loss of resistance to disease, growing infirmity and disability, the loss of function, the growing collection of aches and pains and sagging skin and loss of sexual function, and you are opposing the loss of each unique mind and person. This deterioration is horrible at any age, whether 70, 90, or 300. It would be better to go out when you feel it's time – if ever.

The pursuit of an indefinite lifespan is – at least for me and most others I know – driven *not* by a fear of death but by a desire for life and all that it makes possible. Consider the tragedy of the human condition as it is and has been so far: We start off with

great vigor and health and the capacity to enjoy and to create. At the same time, we are only just beginning to learn and acquire wisdom. Over time, we increasingly lose those vital qualities just as we are accumulating knowledge and wisdom. What if we could combine vigor with wisdom? What if both could be maintained or built up over time? We would have time to further learn, mature, create, contribute, explore, and experience. We would have the energy and the ability to continue participating in the progress of humanity.

All I know is logos

One of Mr. Spock's classic lines from the original *Star Trek* is "All I know is logic". Of course, that wasn't true. Spock's thinking clearly was guided strongly by emotions, non-rational commitments, and values. Logic tells you about consistency and means to ends; it tells you nothing about which ends to pursue. Spock also confused logic with reason. Logos is more about reason and rational argumentation rather than pure logic. If all you know or use is logos, you will not be persuasive in most situations. Even when focusing on reason-based arguments, it is both sensible and justifiable to blend in elements of pathos and logos, so long as they support rather than conflict with logos. Let's take a look at how logos supports advocacy of life extension and how it anticipates and responds to common objections.

When people hear about life extension, they think of it as living longer than around 70 ("three score years and ten") or 80 years or so. They forget that our current life expectancy differs greatly from that of only a century ago. Make the point that **there is no right age to die**. Our life expectancy has grown radically over time. On a global level it was around 35 a century ago. The world average now exceeds 70 years and in the OECD countries it is 80 years.[1] (About half of this is probably due to reduced child mortality; the rest from longer life spans in adulthood.)

You may think this is too obvious to mention. Mention it anyway. Most people have little awareness of these facts. Even if they have, they may have tucked that knowledge away in the back of their mind and not considered the implications. You need to break apart the idea that there is a right age to die. You also need to demolish the closely related idea that we die at a "natural" time.

Why accept a "natural" termination of your life? We fight natural ends all the time. If you have a cardiovascular problem, you don't say "Ah, well, I'm just going to let it kill me." You get stents put it, or have heart surgery, take statins, or kick your smoking habit and exercise. We don't let infectious diseases kill us when there are safe and effective vaccines available.[2] It used to be common to be killed by tigers, bears, neighboring tribes, falls, or infections. Yet no one believes we acted unnaturally in minimizing those causes of death. Yes, it's wise to accept the truly inevitable (but when is that?) and to acknowledge that we are mortal, but it's a mistake to give this any normative weight.

It's easy to say that we should accept death when "our time" comes. But it is *not* "our time", it's the time of uncontrolled biological entropy. Take almost anyone who reflexively preaches the gospel of departing when our natural time comes. If they fall critically ill, they will desperately try to gain a few more days or weeks of life – even if miserable days – usually at great expense. How, then, can anyone oppose a painless, potent, pleasant, and productive extension of the days of our lives? (This is an appeal to consistency.)

Above, I made the pathos-heavy point about the tragedy of losing our vitality as we gain wisdom. Here's the logos aspect of that. Our personalities and traits change over time. Those changes are limited by our health and well-being. Even so, psychologists have found that there are some important upsides to the gradual changes in our personalities as we reach our 70s and 80s. It seems that the trajectory of what psychologists call "personality maturation" is seen in all cultures. We gain in three of the "Big Five" personality traits by becoming more conscientious and agreeable, and less neurotic.

Older people tend to have more control over their emotions, a better sense of humor, and are more trusting. Anti-social behaviors go down along with levels of the "Dark Triad" traits: Machiavellianism, narcissism, and psychopathy. Late in old age, as people lose friends and relatives and suffer worsening health, there is often a reduction in openness and extraversion. That seems likely to change for the better if we can control the aging process. It's hard to clearly imagine a world of people at the height of their vigor but with a century or two of experience and wisdom. I've sometimes referred to this state as "ultramature" to distinguish it from mere adulthood.

Here's a peculiar phenomenon: Billions of people believe in an eternal "afterlife." They don't seem to have a problem with "after-living" forever. This seems odd to me. To the extent that believers are able to describe how they see the afterlife, it sounds stunningly boring to me. All our needs are taken care of and we are loved unconditionally all the time. There is no creative activity, no striving, no self-improvement, no need to help others. Sounds nice for a break but not for too long and certainly not forever. If those people have no problem with not only very

1 The longest possibly-surviving human being is being cared for in cryopreservation at Alcor: James Bedford, born April 20, 1893, may be counted as still surviving at the chronological age of 128.

2 Resistance by many in numerous countries to the Covid vaccines is not really an exception to the rule. Official mismanagement and poor communication explain some of this. Belief that Covid isn't serious enough is another. And none of the Covid vaccines have been approved for use; they have only an Emergency Use Authorization. For a population long conditioned to rely on a government agency to decide for them which medicines are safe and effective, the lack of FDA approval is unsurprisingly an issue.

long life but endless life in that form, why would they object to a long but non-infinite life of good health?

Anticipate objections

Most objections are extremely flimsy; they are rationalizations, desperate attempts to avoid the existential uncertainty revealed by the possibility of living indefinitely. You can almost count on hearing about boredom and stagnation, meaninglessness, stultification of society, running out of resources, and "inequalities". I don't have the space to provide adequate answers to each of these here (some will be addressed in my "Getting Better" series) but I'll make a few observations.

Boredom: If you live long enough, you will have done everything there is to do and will become bored and stay bored. This common objection comes from some combination of lack of imagination and a static view of the self. Perhaps the most influential statement of this argument was made by philosopher Bernard Williams in his essay, "The Makropulos case: reflections on the tedium of immortality." The essay is based on Janacek's opera The Makropulos Affair in which Elina Makropulos is given the elixir of life by her father. The elixir allows Elina to live for three hundred years at her current biological age. She then has to decide whether or not to take the elixir again and live for another three hundred years. At the end of the first three hundred years, she has become bored with her existence and chooses to die.

Williams argues against the desirability of immortality. However, as others have observed [Dannaher, 2015] if successful, the argument would apply just as well to very long lives. Williams understands immortality to mean an existence that *cannot* come to an end. This is consistent with much historical usage but is not something most of us would want. We want to live *as long as we choose*. If life should become unbearable with no prospect of ever getting better, we might prefer to end our lives. Do you find that unlikely? Suppose all civilization has been destroyed along with all other people and you are in constant agony.

His argument is that we are engaged with life by certain "categorical desires" which are deeper than passing contingent desires. These are long-term commitments and projects. Williams thinks there are a limited number of categorical desires to pursue. Over an immortal (or even merely a super-long) life, you would chase and satisfy every possible categorical desire. With nothing left to make life worth living, you would be bored, listless, apathetic. Williams explicitly bases this argument on a view of the self as having a relatively fixed set of characteristics over time. The problem is avoided by changing the self, but then you cease to exist.

I see four big problems with this line of argument. First, as Donald Bruckner agrees, our memory decays, so we could once again be motivated and entertained by forgotten experiences. Second, even if we retained memories with far more fidelity and vividness, desires that we satisfied in the past often re-emerge or can be rekindled after enough time. [Bruckner, 2012.] Third, we may devise drugs capable of making repeated experiences seem perpetually fresh and exciting. Finally, and most importantly, we have barely started to explore an ever-expanding universe of possibilities. The inventive minds of billions of humans will continue to invent novel careers, pursuits, hobbies, and cultures. Boredom sometimes results from low mood and cognitive energy or from an inability to maintain focus. To the extent that we solve or minimize those problems, we also banish boredom.

Williams tries to convince us that if we change enough to avoid boredom, we will no longer be the same self. This relies on a rather silly and extremely static view of the self. Humans can change over time and retain their identity so long as change is not too drastic and discontinuous at any one time. Small changes over a long time add up to major change but the self is retained.

Planning: A related objection is a reaction to seeing a vast expanse of time lying ahead. "But what would I do with all that time?" When I first heard this, it made me chuckle. I imagine the person pulling out their Day Planner, along with their Weekly, Monthly, Annual, Centennial, and Millennial Planners, scratching their head over how to fill in blocks of time for the next few decades, centuries, and beyond. You don't have to plan your entire long life today!

Meaning: Death gives meaning to life. You've heard it before. It's spoken as if it's a piece of ancient wisdom not to be questioned. "You foolish person! An extended life may be healthy, vital, and interesting but without a limit it would be drained of all meaning." Call me a fool, but I've never been able to make any sense of this argument (or assertion). To the extent that it's founded on the argument from boredom, I've already addressed it. At other times, it's based on an abstract and obscure thought: That life has a shape or structure and is bounded by birth at one end and death at the other.

The "shape" of your life can change, as we have seen happen in recent generations as family and social structures have shifted at a historically rapid pace. The shape of a life can change while still having a shape. Death gives no shape, only a boundary. The meaning we create or attribute to our lives depends on our choices, values, activities, and commitments and not on having an inevitable end. On the contrary, I would argue that, other things being equal, longer lives would be or could be more meaningful. Each action you take at any time will have a longer future trajectory to echo down and influence. You can build on each action and reach greater heights. Your life can amount to more.

If the "meaning" argument relies on literal immortality, we need not concern ourselves with it. At least, we can return to it in a trillion billion years or so, which is an infinitesimal fraction of

forever. Even with the abolition of aging, you would not know how long you're going to live. There's always some chance that you will be murdered, catastrophically damaged beyond repair in an accident, struck by an asteroid, or evaporated by a gamma ray burster. If it's the expectation of death that gives meaning to life, is life more meaningful or less if you believe you have almost no time left? Did the shorter-lived people of the past have more meaningful lives? Should we take a lesson from *Logan's Run* and require everyone to die at 30 (or 21 in the book) to ensure a super-meaningful life? I think not.

> **Historical note:** I covered some of the above objections 30 years ago in this very magazine. [More, 1991]

Stagnation of society: Conservative bioethicist Leon Kass worries that delaying retirement will "clog the promotional ladders and block opportunities for young people just starting out." [Kass, 1983] He wonders who would do the "numerous tedious, unrewarding, or degrading jobs." He suggests that to avoid resulting strains and disasters, great changes in social patterns and institutions would have to be compelling by central "planning." As economist Brian Kaplan put it: "Since he's writing in 1983, I have to take the last paragraph as a thinly-veiled warning that, 'Immortality will end in communism'. I've heard of 'Better dead than Red,' but this is ridiculous!" [Caplan, 2009]

There might be a real worry in rigid caste systems (or mediocre academic departments, notes Caplan), but in advanced capitalist economies "talented young people don't have to wait for retirements to get promoted. If their current employer won't pay them their marginal productivity, somebody else will." If unchanging hierarchies ruled existing firms, the results would be creative destruction by new entrants. Caplan also points out that "in the first two weeks of graduate macroeconomics, students learn all about the infinitely-lived agent model". "Economies with immortal agents… are the benchmark case, and their efficiency is easy to prove."

Entropy: Leonard Hayflick (discoverer of 'Hayflick limit' on cell divisions) dismissed longevity research because "aging is inevitable – it is obvious from the Second law of thermodynamics – the entropy always goes up!" This is just as mistaken as the idea that our civilization is doomed because the Earth is subject to entropy. Entropy increases in a closed system. Like the Earth, living organisms are not *closed* systems. It is actually part of the definition of living systems that they take in and excrete matter and energy from their environment.

Population and resources: This is a big one. Not only is this objection raised often, it takes quite a bit of explanation to overturn it – if the listener is even willing to let you try. The short answer is that the rate of population growth peaked in the late 1960s and has been slowing ever since. This seems to happen in every society that reaches a certain level of income and education. Within 50 years, demographers expect global population to stop growing and to decline. In wealthy countries, that point will be reached sooner and has already come for quite a few countries.

Even a growing population is not a problem so long as you have the resources to meet their needs and methods to handle side-effects such as pollution. Most people have been inculcated with the belief that resources are limited and that larger populations mean running out of resources sooner. This complex issue has been addressed well by plenty of writers. (Simon, 1981; Goklany, 2007; McAfee, 2019.) I'm addressing it in my "Getting Better" series for this magazine. Some quick points: Resources have become *more* available, not less, over time thanks to new technologies and incentives in the economic system. A growing population may, counterintuitively, *increase* resource availability. [More, 2021] We seem to have reached a point where economic growth is continuing even as we use fewer physical resources (in total, not just per capita). Earth is not a closed system. The potential resources beyond our gravity well are immense.

Only for the rich: You've heard this one, over and over. Life extension is a bad idea because only the rich could afford it and it would widen the wealth gap. The short answer is that most new technologies and treatments start off being expensive. The richer people create a market and then competition and new discoveries drive down prices. This is happening faster in cases where government regulation doesn't prevent it.

In the end, being able to effectively communicate the life extension idea – and the cryonics idea beyond that – takes engagement and practice. Don't shy away from these conversations unless inappropriate. Pay attention to the way your interlocutor responds. You may be able to sense when they are merely parroting what they have heard and when they really mean what they say. Use some humor if you can but don't force it. It's okay to be passionate although how much passion is good will depend on your conversant or audience. Avoid being combative for the most part. However, this can be okay within reason – especially when you are trying to persuade an observer rather than the person you're speaking to.

I welcome feedback on any of the above, based on your personal experiences. ■

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Alcor's First Half Century

Part 1: 1970-1976

By R. Michael Perry, Ph.D.

A few months from now, as I write this, Alcor will mark its 50th anniversary as a cryonics organization. Here we explore some highlights of this long, eventful history, including a brief but interesting "prehistory" before the incorporation of the stand-alone organization in 1972. Our report will take the form of a series of vignettes, each covering a few years at a time and spread over multiple issues of the magazine. We start (where else?) at the beginning.

Technical matters: Arial Narrow typeface *is used for longer quotations, which I've very lightly edited in places to correct minor errors such as spelling or punctuation. Inserted material is enclosed in square brackets* []*, deleted material is indicated by ellipsis ....*

In the Beginning[3]

Alcor owes its existence to the vision and dedication of two individuals: Fred and Linda Chamberlain. Independently they became involved in the Cryonics Society of California, met, and married in 1970. Their stories are interesting in different ways.

Fred (Frederick Rockwell Chamberlain III) grew up on a farm in World War II, and traced his interest in life extension to his childhood, when he watched in dismay as his aging grandmother gradually weakened. "She wasn't very mobile to begin with," he later recalled, "but I could see her falling apart at the seams. I guess my first contact with death was seeing her stretched out in the funeral home and recognizing that, if you don't do something about it, it's going to get you." He read in the paper about an experiment that allegedly doubled the lifespan of a dog by "artificially cleaning" its blood by washout and replacement. "Of course the article was probably inaccurate, but it stimulated me to consider that what was going to happen to my grandmother possibly could have been postponed a long time if there had been some sort of therapy." Attaining adulthood, he obtained a bachelor's degree in electrical engineering from the University of Virginia, and pursued a military career, first in the Navy, then in the Air Force. In the Air Force he worked thirteen years at the Jet Propulsion Laboratory in Pasadena, California, his main focus being "research and development concerning high-velocity reentry vehicles, ostensibly to carry nuclear weapons …"[5]

Fred encountered cryonics by reading Robert Ettinger's *The Prospect of Immortality* around 1965, shortly after its publication, and was greatly impressed. Around the same time, he discovered Harold Meryman's book, *Cryobiology*, and eagerly started to devour it also. "But I was quite disappointed, as I began to read it carefully, with the [state] of the art at that time, which of course had really nothing to offer other than freezing of blood and perhaps some sperm and that sort of thing." Soon he joined the newly established Cryonics Society of California (CSC), based in the Los Angeles area and headed by Robert Nelson, and in 1970 became its vice president.[4,5]

Linda Lee McClintock, the future Mrs. Chamberlain, was born and grew up in a small mountain town, with one brother. She became an atheist "in about the third grade, abandoning the Christianity I was raised on." In college she wanted to be a philosophy professor but was put off by classes that focused on Plato, "a mystic, as opposed to Ayn Rand, a rationalist." Randian Objectivism greatly appealed to her, with one caveat: "it didn't offer you any kind of immortality, the way most religions do." In early 1969 her brother sent her a copy of *Prospect*. "When I picked up Ettinger's book, it was obvious the hole was there and that cryonics was the way to fill it. I didn't hesitate – I just laid down the book and called Bob Nelson, thinking he was somebody who could do something for me if I were to die, and I immediately joined CSC."[6]

In 1968 a series of annual cryonics conferences was begun by the Cryonics Society of New York (CSNY). The first one was held in New York City and sponsored by CSNY, the second (1969) in Ann Arbor, sponsored by Ettinger's group, the Cryonics Society of Michigan. The third conference would be in Los Angeles with CSC as sponsor, and Linda was heavily involved with the preparations. Fred meanwhile was showing interest in CSC and Nelson urged him to come to a meeting. That is how, in February 1970, Linda met Fred, who proved to be a libertarian like herself, and shared many views. The conference was held in May 1970 and the following September they became a couple.[3,7,10]

Manrise Corporation and the First 'Alcor'

Ironically, given what would happen later, it was Robert Nelson who proposed to Fred that he start a "rescue group" within CSC, and Fred agreed. The team would be on 24-hour alert and available to all members. "This would be the same type of thing I was involved with in the service," Fred remembered. "It must

include communications, necessary equipment and chemicals, and especially training."[4] Fred gave a talk at a CSC dinner meeting in October 1970, and "said that this rescue team was going to be named Alcor." The name was chosen for two reasons. Alcor is a faint star in the Big Dipper, and needs a good eye to spot it, so it is a "test for clear vision." Additionally, "ALCOR" can be taken as an acronym for "ALlopathic CryOgenic Rescue" where "allopathic" refers to the "right" kind of medicine as opposed to something like homeopathy. Fred and Linda were eager to get started with their newly named concept, but there was a snag. As Fred reported, "Nelson obstructed every attempt we made to implement any kind of rescue procedure, so nothing was ever developed within the context of CSC." Increasingly, Fred and Linda became dissatisfied.[4,5,7]

So, what to do? In March 1971 they started Manrise Corporation, an organization to provide cryopreservation services and storage of patients, along with carrying out research. Manrise would publish two newsletters. *The Hourglass* aimed at a popular audience and effectively became the newsletter of CSC for a short while. The other, *Manrise Technical Review* (MTR), was devoted to mathematical and scientific work at a more advanced level. In the second issue of MTR (a combined issue covering Mar.-Jun. 1971, with a long, mathematical article by Art Quaife on perfusion modeling) there is a short editorial by Fred Chamberlain. It well expresses the rationale and difficulties of cryonics, and still has relevance today. It can be taken as an indication of what the focus of Manrise would be, as well as an underpinning for the new stand-alone Alcor that was about to be formed:[13]

Editorial

It has been proposed that all dying persons be frozen, pending the development of means for their reanimation.[1] It has also been suggested that this should not be done at all until the capability for reanimation has been demonstrated.[2] Perhaps there is a third position which can bridge that gap.

First, a glance at current capabilities. Cells of most types can be frozen and thawed with some retention of viability, in an isolated state. With tissue samples, there is a lesser degree of success. Attempts to freeze whole organs or organisms and revive them have largely failed. "Freeze now" advocates assert that the difficulties encountered with larger specimens generally stem from thawing damage and from a lack of understanding of how to correct and repair freezing damage. This contention may be correct, but it has not yet been satisfactorily proven. On the positive side, were this premise verified, then fundamental feasibility of the "freeze now" approach could be validated.

Several considerations are involved in this demonstration of feasibility. First, highly controlled methods of freezing whole organisms must be developed, along with similarly sophisticated means for extracting small samples and rewarming them. Experimentation must then be pursued until a whole organism freezing protocol exists which can be verified by rewarming samples of all important types of cells with essentially complete retention of viability. At this point, it will have been established that a low temperature state can be induced in whole organisms where cells are potentially viable. This level of confidence is expected to be sufficient to induce the necessary long-term research for development of the means of reanimation.

It is expected to be sufficient, since many persons will understand that the rest of the task is primarily a matter of technological development. Each cell of an organism frozen by the verified method will be able to be restored to a normal living state, individually. No cell of such an organism can then be regarded as fundamentally "dead." The research that follows will result from the fact that many will want it done, and will support it.

The next hundred years or so, barring a catastrophic end to civilization, should include advances in medicine and gerontology opening up the eyes of everyone to a proper view of human life, as potentially endless, full of activity, enjoyment, and growth. Accidental deaths and residual fatal illnesses will be handled in a way that seeks to return life to those who die. Whether or not the means of reanimation have been developed, those who are dying will be frozen.

But few persons will be frozen without a demonstration of feasibility such as that described above. Most will demand proof that the procedures used will, at the very least, lead to a state in which all cells are potentially viable. This much we must do alone, now, without the general support of society. If we do not take this first step, we may not have a chance to take many others. We must offer proof that what we are doing produces results.

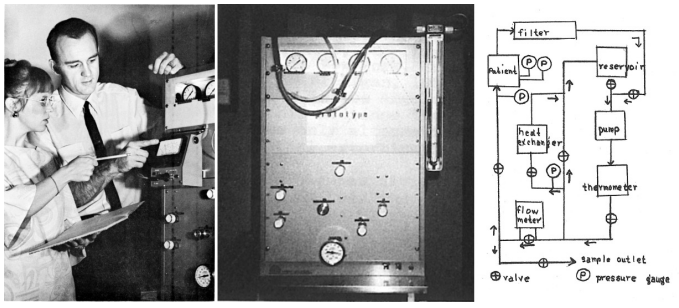
Have you noticed how fast the years keep going by? There is no time to waste!

To comment briefly on the present state of cryonics: Some of the goals Fred outlines in this article of fifty years ago have now been achieved. Though he doesn't say it, the brain is recognized as the organ of paramount importance to preserve, a philosophy he himself and Linda would follow in a few years with the first neuropreservation, Fred's father, described below. Other body parts, arguably, are in principle replaceable through some form of tissue regeneration or cloning-like procedure. In either case it appears that modern cryopreservation techniques can yield viable cell samples throughout the body, plus showing preservation of ultrastructural details in the brain that should be important in defining the personality of the patient. Much is still unknown, of course, and issues have been identified that are still not fully resolved, yet nothing is known that would preclude the success of cryonics, at least in the better cases.

There was a cryonics conference in San Francisco, in June 1971, hosted by the Bay Area Cryonics Society (now American Cryonics Society), and reported in the following month's *Outlook*, the mouthpiece of the Cryonics Society of Michigan. (At this time *The Outlook* was almost the only cryonics

newsletter still publishing. Today the newsletter continues as *Long Life* magazine, with essentially continuous publication since it started in 1970.) Among the problems considered at the conference was the ever-present one of minimizing ice crystal formation in tissues as the temperature is lowered to the cryogenic range. This problem has generally been addressed by replacing the body fluid with an antifreeze mixture or cryoprotectant. The replacement process uses the vascular system and is called perfusion. As an active researcher through Manrise Corporation, Fred Chamberlain had devised his own perfusion machine which was exhibited at the conference and reported enthusiastically.[8,10,12]

One of the biggest attractions and sensations of the meeting was the prototype perfusion machine built and exhibited by Fred Chamberlain. It is a response to the many problems already encountered and to be encountered in perfusing patients in a carefully controlled and measured way under changing conditions and with different requirements at different stages of the perfusion process and in different parts of the body.



From left: Linda and Fred Chamberlain with perfusion machine Fred designed; machine, front view, the "prototype" shown at the conference; block diagram.

In a writeup in the *Hourglass* quoted in the article, Fred has this to add:[14]

The system block diagram shown above presents a "two-loop" system with perfusion and heat exchanger circuits driven through a common pump. The perfusion circuit embodies a flow meter, perfusion flow valve, pressure gauges, and return filter, while the heat exchanger with bypass and a main reservoir are located in a second loop. Instrumentation currently installed includes a thermometer while projections for future improvements include a thermistor sampling network and a device measuring pH, specific gravity, and refractive index. In future models, a drip chamber and isolation reservoir will be added to the perfusion circuit.

In mid-August, 1971, Fred resigned as the CSC vice president.[17] Soon the Chamberlains severed all ties with the organization, and started one of their own, the Rocky Mountain Cryonics Society, incorporated in Washington State. As they reported: "The articles and by-laws of this organization specifically provided for 'Alcor Members,' who were to be the rescue team core of activity." Difficulties quickly surfaced, however, in securing non-profit status, and the Chamberlains decided to reincorporate their organization in another state under another name.

In this way, the Alcor Society for Solid State Hypothermia came into being in the State of California on Feb. 23, 1972. It was a stand-alone organization with "Alcor" in the name, and it's been that way ever since. (There was a minor change of name to the present Alcor Life Extension Foundation in 1977.[19]) Linda Chamberlain was the first president, while Fred meanwhile was president of Manrise. It might be wondered why yet another cryonics organization had to be started up. What about Manrise itself? Couldn't it have served the purpose? The answer had to do with the type of corporate entity used on one hand at the membership level, and on the other at the level of services offered, including long-term cryogenic storage. It was desirable to make the membership organization (in this case Alcor) a non-profit, so it could accept anatomical donations (cryonics patients) while the service organization (Manrise) would be for-profit. This plan had been followed before (CSNY was the membership organization, CryoSpan its associated for-profit; CSC was the membership organization; Cryonic Interment the for-profit. Today Alcor sometimes contracts with outside organizations for cryoprotection services, generally when done in a remote location, but does its own low-temperature storage, a model that is found elsewhere.)

Corporate seal impressions of Manrise and the early Alcor, showing dates of incorporation.

The November-December 1972 issue of *Manrise Technical Review* contains a several-page summary of Alcor covering everything from choice of the name to directorate structure, scientific research and data compilation, training, and rescue capabilities. Written/arranged by Julianne Schultz, one of the earliest Alcor activists besides the Chamberlains,[9] it is highly informative and interesting and is included here in full. It is remarkable how the state of affairs in Alcor so long ago so well approaches what we would like to believe we have today, granted the organization was a miniature one by today's standards and could only serve a local area. (This would have centered around Verdugo City, an L.A. suburb and Alcor's first address).[18]

ALCOR ACTIVITIES AND SYSTEMS

by Julianne N. Schultz

Director, The Alcor Society for Solid State Hypothermia

Alcor is the small companion star to Mizar, the second star in the handle of the Big Dipper. It has been used for thousands of years as a critical test of vision. As an acronym, Alcor represents "Allopathic Cryogenic Rescue". Allopathy is basically that form of medicine which (as opposed to homeopathy) treats the disease by any and all means that may possibly lead to a favorable outcome. Alcor, the organization, was designed to accomplish very specific and unconventional goals. These are discussed.

The Alcor Society for Solid State Hypothermia is a non-profit, tax-exempt "scientific-educational" organization engaging in and promoting technological and scientific research in cryopreservation, cryoinjury, gerontology and cryogenics. In pursuing these objectives, Alcor's Board of Directors is supported by three classes of membership and an auxiliary advisory group.

The organization's activities and systems of operation are rigorously dictated by its purpose and are therefore interrelated. For the sake of definition and clarification, both activities and systems shall here be treated as if separate.

ALCOR ACTIVITIES

Alcor activities include membership, research, and cooperation with outside groups and peoples of similar direction. A brief description of each follows:

1. Membership

The Alcor *General Member* is a dues-paying individual who has made legal (anatomical donation) and financial (insurance, trust fund, etc.) provisions for rescue procedures and suspended animation. The General Membership classification is applicable to each member's first year of association with Alcor and can, by choice, be maintained indefinitely with payment of insurance policy premiums and increased annual dues.

It is the option of the General Member, during the first year, to train for qualification as a Working Member. This is accomplished by successfully completing the Alcor Training Program. The Working Member pays reduced annual dues, and is obligated to volunteer 40 hours of personal effort per year in maintaining skills through refresher courses.

The *Director Electorate*, a third classification of membership, is an annually elected body of Working Members having the only power within the corporation to elect Directors and members of the Director Electorate. In essence, this is the controlling body of Alcor. The Director Electorate allows for a broad but stable basis for control outside the Board of Directors.

2. Research

Research is the means to the achievement of Alcor's goals involving the development of extensive scientific understanding and expertise. To date, the major portion of Alcor's research activities has been dedicated to program formulation and the accumulation and compilation of established scientific and medical data.

Alcor will soon begin development of a fully equipped facility and laboratory to implement research studies supporting a full range of investigation in suspended animation. Priorities will be given to determinations of viability in hundreds of biological cell samples taken from frozen whole organisms.

3. Cooperation with outside groups...

It is of natural importance for Alcor to enjoy the benefit of association with other organizations, societies and individuals having similar scientific objectives. Typically, such groups or peoples are engaged in life extension, preventive medicine, aging reversal, the low temperature sciences, mental and physical health, neurology and space technology programs in hibernation and suspended animation.

Alcor's research results will be coordinated with similar studies by others in whole organ storage for donor transplant, fetal organism freeze-thawing, and so forth. In this, Alcor expects to work closely with Trans Time, Inc. and Manrise Corporation.

As far as association with other cryonics societies, a close working relationship exists between Alcor and the Bay Area Cryonics Society in Berkeley, California. Similar associations will be sought with other cryonics societies striving to develop and maintain high standards.

ALCOR SYSTEMS OF OPERATIONS

Developing Alcor systems has taken the better part of the first year following incorporation in February 1972. In devising these systems the future had to be provided for while planning for the present – logically, the future depends largely upon the flexibility and operational efficacy of the systems designs.

As a first step, Alcor engaged the cooperation and services of two mortuary facilities, providing a redundant 24-hour availability. Although the mortician and his staff have not been required to assume overall responsibilities, assistance and familiarity with the procedures are an integral part of their involvement. More mortuaries will be taken into consideration to fulfill maximum geographical coverage as time permits.

At a second step in providing for effective Alcor operations, a communication network was planned and instituted. An around-the-clock monitoring system now provides for the protection of members at all times. This system involves a number of interrelated elements, including radio-paging devices and membership identification bracelets.

Each new member in Alcor is issued a specially engraved bracelet. This bracelet gives a brief set of emergency instructions to the rescuer or finder of a member in distress, as well as the member's personal code number and Alcor's emergency phone numbers.

Hopefully, the phone call will be one of the first emergency actions taken by rescuers on the scene. Under most circumstances, the number directly connects the caller with trained Alcor Representatives (Working Members). If Alcor does not promptly answer the call, an emergency medical answering service does. The service operator follows special instructions in receiving and deciphering all calls taken; if the call is an emergency, the operator immediately contacts a paging service (radio transmitting station) which transmits a designated radio signal assigned only to Alcor. Portable receivers carried by members of the Alcor rescue team then emit audio beeping sounds. Each team member carrying a paging receiver calls the answering service as quickly as possible and is connected into a "conference call" with the person at the scene. Emergency procedures are explained to the caller and assignments are given to team members.

Presently, three paging devices are carried "on-person" at all times; radio coverage extends over approximately 3000 square miles. Alcor can be alerted and a rescue team with emergency equipment dispatched within minutes of receiving a call. At this time, short of equipping each Donor with an emergency transmitter, a maximum communication capability is in being.

The beeper-bracelet communication system has been planned to accommodate growth on a national scale by extending-services to members of other cryonics societies. In response to this type of-emergency call, Alcor would contact the appropriate people anywhere in the United States. The bracelet bearing membership code number facilitates this endeavor in indexing such vital information as member's name, his organization, and the emergency team to be contacted.

The success of an emergency communication system relies heavily upon a qualified emergency rescue team; this is one of the principal purposes of Alcor's Training Program and the Working Membership classification, the next system to be discussed.

Training and qualification of members for responsible roles is a major Alcor system. As previously stated, each member may attempt to qualify for Working Membership by completing the Alcor Training Program. Annually given, it is a four part course educating the member in all phases of administering emergency aid and the procedures for inducing solid state hypothermia.

The first part of the course is primarily concerned with life saving techniques. It covers standard first aid, advanced first aid and cardiopulmonary resuscitation taught by qualified Red Cross and Heart Association instructors.

In part two, training concentrates upon the many facets of cryonics rescue, including sustained cardiopulmonary resuscitation (perhaps over many hours following death), external body cooling, and legal procedures for protecting the member.

Part three of the training course includes learning Phase I of the actual procedure for inducing the low temperature state, and developing the skills for using all applicable equipment. The student will be aided by a detailed instruction manual which contains a thorough and up-to-date treatment of all procedures for inducing solid state hypothermia in humans.

The final part of the course trains the student in all the sophisticated aspects of Phase II (sub-zero) perfusion and the transition to extremely low temperatures for long term storage. This and all parts of the training program will be taught with visual aids, actual rescue equipment, and perfusion apparatus with simulated (hydrodynamic) models.

The student who successfully completes this training program, as evaluated by standards set by the Alcor Board of Directors, becomes a Working Member and is qualified as an Alcor Representative. From that time forward, assuming he maintains the qualification, he is able to assume full responsibility for rescue and other procedures required in cryonics operations.

The completion of Alcor's emergency systems is providing for a fully equipped emergency vehicle. This unit will be a mobile laboratory in every respect, equipped for rescue procedures as well as all operations required in the induction of solid state hypothermia. For example, capabilities will include mechanical heart-lung resuscitator, electrocardiograph, telemetry systems and other medical equipment consistent with the qualifications of Alcor's rescuers. Cryonics related instrumentation will provide for remote monitoring of temperature at many points, automatic determination of pH, conductivity, and specific gravity in perfusates. Controlled temperature cryogenic environmental chambers, heat exchangers, and other apparatus will be incorporated into the vehicle. The objective is the most complete cryonics capability possible in a mobile unit.

THE FUTURE

Alcor represents today, 1972, the organization not just seeking the funds to buy and equip their own emergency vehicle and gain more research space, but rather, the organization having the functional intention to gain the technological insight needed in the induction of solid state hypothermia. The tangible realism of this intention is admittedly far reaching, however, Alcor does as[pire] to the unlimited application of man's scientific brainpower in control of his universe.

Reading the above, it is surprising to me how advanced Alcor seemed to be less than a year after its incorporation! Its personnel were trained in perfusion operations, had walkie-talkies or something similar, and could operate over "3000 square miles" or about a 30-mile radius. (Limited, yes, but this particular circle included much of the greater Los Angeles area, encompassing millions of people. You could, of course, relocate there if you were serious about wanting to be a part of Alcor and have their services available to you.) Its corporate structure deserves some comment. Today Alcor has a self-perpetuating Board: Directors elect other Directors.[20] At the start, though, Alcor had a Director Electorate which elected itself and the Directors. The Director Electorate, however, was not the general membership, far from it, or even the specially trained Working Members who had to pass refresher courses each year. Instead, it was specially chosen

from the latter group, people who had already demonstrated their commitment and training.

The next few years: 1972-76

With the organization off to a good start, suddenly there was a lull in publications. Manrise stopped publishing *The Hourglass* with the September, 1971 issue, before the formation of Alcor. *Manrise Technical Review* was last published in March 1973; the *Outlook* reported in December that year:[22]

Manrise Technical Review has suspended publication, and Fred and Linda Chamberlain, after years of Herculean effort, seem discouraged and disappointed about some aspects of it as does Curtis Henderson [then the long-serving president of CSNY]. But our guess is that, in due time they will gird their loins again and renew their efforts, since it's the only game in town.

For two or three years Alcor seemed dormant to the outside world. At the beginning (January) of each year, from 1972 through 1976, *The Outlook* published a Directory of cryonics organizations. The newly formed Alcor is listed in 1973 and '74 but not in '75 or '76, even though it did exist. But apparently it was "keeping quiet" and not advertising itself, though rather important things were happening. Fred and Linda would report in 1998:[9]

In the beginning Alcor's resources were mostly the resources of Manrise Corporation, including a 100+ page manual on suspension procedures and the first specialized equipment for cryonics perfusion which had ever been designed and fabricated [Fred's perfusion machine shown above]. Our medications were primitive, by today's standards, but they represented the best advice of the cryobiological community at that time, plus all the consulting we'd been able to beg and borrow.

For the first two years or so, there were only five members. Fred Chamberlain, Linda Chamberlain, Dick Jorgensen, and Julie Schultz were Alcor's initial "active members." Fred's father, a stroke victim of many years, was not only Alcor's fifth member, but literally its "reason for being." Were it not for "Fred Jr.'s" state of declining health, Alcor might never have been formed.

…

From '72 to '76, Alcor primarily sought membership from libertarian sources. First, mailing lists were used to conduct a well-advertised seminar (30 people came.) Then Alcor members became closely allied with the Free Enterprise Institute (FEI) of Andrew J. Galambos. Galambos was lecturing throughout the Los Angeles Basin and elsewhere (his lectures firmly stated that cryonics was going to be an integral part of future society.) When Fred Jr. was frozen in 1976, virtually all of the team were "FEI'ers"!

During this period, also, Mike Darwin (then a teenager) moved to California for approximately a year and a half. He conducted viability research, supported by Manrise Corporation, and contributed heavily

Andrew J. Galambos, a libertarian thinker and promoter who started the Free Enterprise Institute (FEI), was an early supporter of Alcor and cryonics, though by appearances soon lost interest.

to the outfitting of a surgical laboratory within a large van, and in the acquisition and modification of a small "retrieval vehicle" (not exactly an ambulance, but close) with on-board gurney and [heart-lung resuscitator (]HLR[)].

As noted, Linda Chamberlain was the first president of Alcor, Fred meanwhile serving in that capacity at Manrise. A switch of CEOs occurred in February 1973, a year after the formation of Alcor, with Fred now presiding at Alcor and Linda at Manrise. Another switch occurred, August or September 1975, with Linda returning to control at Alcor. A year later Allen McDaniels, M.D., became president of Alcor.[11,15,22]

Alcor's First Cryopreservation, 1976

1976 was something of a memorable year. Alcor started its first newsletter, *Alcor News*, in May, and in July had its first case, Fred Chamberlain Jr., father of Alcor cofounder Fred III. In earlier life Fred II had a distinguished military career, reaching the rank of colonel and serving on the staff of Gen. George S. Patton in the crucial, closing months of World War II in Europe.

Interesting additional details of the cryopreservation are given in the composite citation that follows, from the August 1976 newsletter which reports the case, and the 1998 communication.[9,15] (The term "suspension" or "cryonic suspension" is used for what today is more often called "cryopreservation.")

Fred Jr. was Alcor's first member, and indirectly has been its greatest benefactor from an operational standpoint. Manrise Corporation is

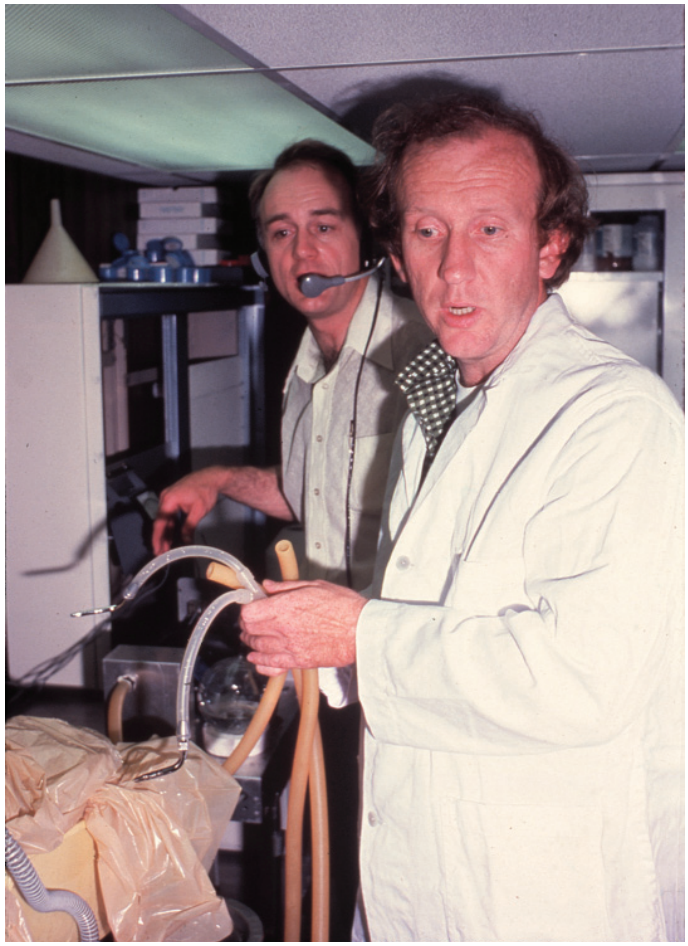
Col. Fred Chamberlain (Fred Jr.), Alcor's first cryopreservation case.

the result of a sustained effort by a number of persons over the last five years to achieve the existing state of capability, but behind every organization there is a financial foundation. Fred Jr. furnished nearly all the hardware that Manrise owns – he covered its operating expenses during periods when otherwise there would have been no facilities, no communications system, etc. Of course, Fred Jr. also was the most probable person to benefit from this capability buildup. ….

Alcor's first suspension took place on July 16, 1976, when Fred Jr. was placed in a state of neurosuspension (the first of its kind.) At that time, the President of Alcor was Allen McDaniels, M.D. Although Dr. McDaniels is no longer an Alcor Member, it is interesting that Alcor's first suspension was directed by a medical doctor who was also its President. Also as Medical Director and by virtue of being a physician, Dr. McDaniels was able to legally take possession (on behalf of Alcor) of the patient, as an anatomical donation.

A respiratory infection resulted in Fred Jr.'s clinical death. Immediate heart-lung resuscitation and cooling were effected and maintained throughout an initial 20°C drop in temperature. Acidosis was minimal and physical signs evidenced excellent oxygenation throughout this phase. A balanced intracellular salt solution was used as the carrier for cryoprotective agents. Within 24 hours, temperatures were dropped to -110°F, and then to -320°F within 90 hours.

By [the time of this first case], Manrise Corporation had rented industrial space and had moved its "mobile operating room" inside, so that it could have running water and electric power. Theoretically, the large vehicle could have been deployed to a distant location, but it was recognized that this was unlikely to be practical. We found, during that first suspension, that getting a team of 4-5 people into the cramped quarters of a "laundry van-sized" operating room made moving about nearly impossible, especially during surgery, when it was necessary to have surgeon and assistant surgeon on opposite sides of the table.



From left: Fred Chamberlain (Fred III), Allen McDaniels, M.D., at the cryopreservation of Fred's father, July 16, 1976.

Manrise Corporation's future services to Alcor, while still including preparedness for emergencies, will probably be concentrated heavily in the area of research. Plans are already underway for animal experimentation, with inputs as to protocols and analyses of results being coordinated with other cryonics organizations. Thus, the capabilities established through Fred Jr.'s support will still be employed for his benefit – in furthering the search for knowledge which might someday enable him to open his eyes, realize that he has somehow been flung through time into a young, strong, healthy body, and experience the world we are all reaching for – a world where "death from natural causes" is the rarest of occurrences. …

(End of Part 1.)

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IMAGE CREDITS:

1. Fred and Linda Chamberlain with perfusion machine: *The Outlook* 3(1) (Jan. 1972) cover.

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5. Col. Fred Chamberlain (Fred Jr.) Alcor News 1(4) (Jul. 1976) 1, image sharpened and colorized with help of myheritage.com. Color of uniform from online sources.

6. Fred Chamberlain III, Allen McDaniels at cryopreservation of Fred II, Alcor archives.

The author thanks Linda Chamberlain for reviewing the manuscript before publication and offering helpful comments.

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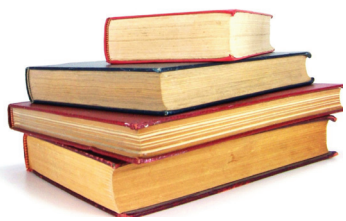

No one knows better than you what you will want to have with you.

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

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Alcor Associate Membership

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

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

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

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

Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

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

The Binarized Transcriptomic Aging Clock

March, 2021

Patterns of epigenetic regulation of gene expression (and thus RNA and protein levels) change constantly in response to cell state and environment. Some of those changes are characteristic responses to the damage and dysfunction of aging. Since the demonstration of the first epigenetic clocks, those that predict age based on an algorithmic combination of the status of DNA methylation at CpG sites on the genome, researchers have produced any number of new clocks based on mining epigenomic, transcriptomic, proteomic, and other databases for correlations with age. This open access paper is yet another example of a new transcriptomic clock.

It remains the case that in none of these clocks is there is a good, well understood connection between specific mechanisms of aging and specific components of the clock algorithm. This makes it hard to make good use of aging clocks: it isn't at all clear that any given result is meaningful. If one applies a potentially rejuvenating or age-slowing intervention, and it produces a change in the clock measurements taken before and after treatment, what does that change mean? Is a drop in measured age a sign that the therapy is great, or a sign that the clock is overly weighted towards the subset of mechanisms of aging that are targeted by the intervention? If the clock shows little to no change, does that mean the therapy is useless, or the clock is unhelpful for this class of intervention? And so forth.

Thus clocks and therapies will have to be calibrated against one another in order to make the clocks useful. This process is only in the earliest stages, where it is occurring at all. As matters progress, this calibration will most likely mean running the slow, costly life span studies that we'd all like to avoid by using the clocks instead. There is no free lunch here.

BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy

Aging biomarkers that predict the biological age of an organism are important for identifying genetic and environmental factors that influence the aging process and for accelerating studies examining potential rejuvenating treatments. Diverse studies tried to identify biomarkers and predict the age of individuals, ranging from proteomics, transcriptomics, the microbiome, frailty index assessments to neuroimaging, and DNA methylation. Currently, the most common predictors are based on DNA methylation. The DNA methylation marks themselves might influence the transcriptional response, but aging also affects the transcriptional network by altering the histone abundance, histone modifications, and the 3D organization of chromatin. The difference in RNA molecule abundance, thereby, integrates a variety of regulation and influences resulting in a notable gene expression change during the lifespan of an organism. These changes sparked interest in the identification of transcriptomic aging biomarkers, an RNA expression signature for age classification, and the development of transcriptomic aging clocks.

While a large variety of data, techniques, and analyses have been used to identify aging biomarkers and aging clocks in humans, issues remain with regard to pronounced variability and difficulties in replicability. Indeed, a recent analysis of gene expression, plasma protein, blood metabolite, blood cytokine, microbiome, and clinical marker data showed that individual age slopes diverged among the participants over the longitudinal measurement time and subsequently that individuals have different molecular aging patterns, called ageotypes. These interindividual differences show that it is still difficult to pinpoint biomarkers for aging in humans.

Model organisms, instead, can give a more controllable view on the aging process and biomarker discovery. Caenorhabditis elegans has revolutionized the aging field and has vast

advantages as a model organism. To date, no aging clock for C. elegans has been built solely on RNA-seq data and been shown to predict the biological age of diverse strains, treatments, and conditions to a high accuracy. In this study, we build such a transcriptomic aging clock that predicts the biological age of C. elegans based on high-throughput gene expression data to an unprecedented accuracy. We combine a temporal rescaling approach, to make samples of diverse lifespans comparable, with a novel binarization approach, which overcomes current limitations in the prediction of the biological age. Moreover, we show that the model accurately predicts the effects of several lifespan-affecting factors such as insulin-like signaling, a dysregulated miRNA regulation, the effect of an epigenetic mark, translational efficiency, dietary restriction, heat stress, pathogen exposure, the diet-, and dosage-dependent effects of drugs.

This combination of rescaling and binarization of gene expression data therefore allows for the first time to build an accurate aging clock that predicts the biological age regardless of the genotype or treatment. Lastly, we show how our binarized transcriptomic aging (BiT age) clock model has the potential to improve the prediction of the transcriptomic age of humans and might therefore be universally applicable to assess biological age.

Link: https://onlinelibrary.wiley.com/doi/10.1111/acel.13320

A Non-Invasive Biomarker to Measure the Effectiveness of Senolytic Drugs

April, 2021

Researchers here note the discovery of a non-invasive biomarker that can measure the pace of destruction of senescent cells. This could be used to more rapidly quantify the effectiveness of potential senolytic treatments, those capable of destroying senescent cells, thus speeding up development of the next generation of senolytic drugs. Readily available small molecule treatments (such as the dasatinib and quercetin combination) can destroy a fraction of senescent cells throughout the body, and in doing so produce rejuvenation in animal studies. Alongside bringing those first treatments to the clinic, the next goal in line is to achieve a much greater level of clearance. A great deal of work lies ahead in that optimization process.

Researchers have discovered and are developing a novel, non-invasive biomarker test that can be used to measure and track performance of senolytics: a class of drugs that selectively eliminate senescent cells. "The list of age-related diseases definitively linked to cellular senescence keeps growing, as does the number of biotech companies racing to develop drugs to eliminate senescent cells. While the field has never been more promising, the lack of a simple biomarker to measure and track efficacy of these treatments has been a hindrance to progress. We are excited to bring this new biomarker to the field and look forward to it being used in the clinic."

This work, performed in human cell culture and mice, shows that senescent cells synthesize a large array of oxylipins, bioactive metabolites derived from the oxygenation of polyunsaturated fatty acids. "Lipid components of the senescence-associated secretory phenotype (SASP) have been vastly understudied. The biosynthesis of these signaling lipids promotes segments of the SASP and reinforces the permanent growth arrest of senescent cells." Oxylipins are implicated in many inflammatory conditions including cardiovascular disease and pain response. Many commonly used drugs, such as aspirin and ibuprofen, act by preventing oxylipin synthesis.

Senescent cells change their fatty acid metabolism and they do it in such a way that free polyunsaturated fatty acids accumulate inside the arrested cells where they are used to manufacture oxylipins. Researchers identified one of these fatty acids, 15-deoxy-delta-12,14-prostaglandin J2 (dihomo-15d-PGJ2), as unique to senescent cells; it accumulates inside senescent cells and is released when the cells die. In this study, mice were given chemotherapy which induces widespread senescence, followed by a senolytic drug. The biomarker was only detected in the blood and urine of mice treated with both chemotherapy and the senolytic, but not with either on its own, confirming specificity for senolysis.

Link: https://www.buckinstitute.org/news/the-first-non-invasive-biomarker-to-track-and-verify-efficacy-of-senolytic-drugs/

The Latest Data from the Interventions Testing Program: Nicotinamide Riboside has No Effect on Mouse Life Span

April, 2021

The Interventions Testing Program (ITP) at the National Institute on Aging runs very rigorous, costly life span studies in large numbers of mice, picking a few interventions to test each year. The usual outcome is that a treatment with some interesting past results is found to have absolutely no effect on life span when run through the rigor of the ITP process. We should all bear this in mind whenever modest life span extension in mice is reported by researchers elsewhere in the community. Based on past ITP data, a great many such results are the result of chance or poor experimental design.

Will the ITP ever get around to testing senolytics or other potential rejuvenation therapies? They are dosing a group with fisetin, but overall their bias is towards approved drugs and existing supplements, calorie restriction mimetics, and similar classes of intervention that affect metabolism in well-explored ways: insulin signaling; blood pressure; inflammation; and so forth. Senolytics are likely not yet a well trodden enough path for most to get past the selection process.

This open access paper reports the latest set of interventions to have shown minimal, gender specific, or no effects at all on mouse life span in the ITP process. Of interest to the community here, nicotinamide riboside supplementation is one of these, and does not extend mouse life span. We might compare that outcome to the 2016 paper in which mouse life span does increase modestly, the human trial in which benefits to cardiovascular function result, and all of the other data showing improved stem cell and tissue function in mice and humans.

We might view the ITP as a steamroller encouraging us to run faster, to aim higher, to stop messing around with approaches to aging that do not and cannot have large enough effects to matter at the end of the day. The only goal worth aiming for is robust, sizable rejuvenation of the old. We have excellent starting points in the form of the SENS proposals for repair of cell and tissue damage, and the existence of the senolytics industry indicates just how fast things can move once impressive data is produced in animal studies. More of that sort of thing is much needed if we are to realize the promise of modern biotechnology.

17-a-estradiol late in life extends lifespan in aging UM-HET3 male mice; nicotinamide riboside and three other drugs do not affect lifespan in either sex

The interventions for the present study were chosen for the following reasons:

(a) 17-α-estradiol (17aE2) is a relatively "non-feminizing" estrogen which shows reduced activation of classical estrogen receptors compared with 17-β-estradiol. It was reported that in UM-HET3 mice fed 4.8 mg 17aE2/kg (4.8 ppm) diet from 10 months of age, median male lifespans increased 12%, while 17aE2 did not alter female lifespan. Other researchers showed that using a threefold higher dose (14.4 ppm) from 10 months of age, pooled median male lifespans increased 19%; the 90% lifespan increased 12%, but females still did not benefit. Thus, only males were tested in the present study. To determine whether 17aE2 treatment is effective when initiated in older mice, males were treated beginning at 16 or 20 months of age, choosing middle age, and early old age before many natural deaths.

(b) Nicotinamide riboside (NR) is a precursor of nicotinamide adenine dinucleotide (NAD) via the cell's salvage pathway. Total NAD levels decline with age, in a wide range of species. Importantly, increasing NAD levels benefit a wide variety of tissues in species including mice and human beings. it has been suggested that NAD+ boosters may "..delay aging and age-related physical decline." It was reported that NR delays senescence of neural stem cells (SCs) and melanocyte SCs and increases mouse life span, even when given in old age (5% increase at 20 months of age).

It was reported that in mice and humans NR is bioactive when given by mouth, unlike most other nicotinamide derivatives. In a 2016 study NR improved liver function and protected against diabetic neuropathy. When fed to C57BL/6 J mice from 10 weeks of age, NR protects against high-fat diet (HFD)-induced obesity and promotes oxidative metabolism by increasing the NAD+/NADH ratio in muscle, liver, and brown adipose tissue. Researchers found that increasing NAD+ stores with NR supplementation improved muscle function and alleviated heart defects in a mouse model of muscular dystrophy. It was reported that an NR metabolite, nicotinamide, did not increase lifespan when started at 12 months in C57BL/6 J mice but improved some health outcome measures. Due to its benefits in a variety of diseases, and reports of benefits in mouse lifespans, NR treatment was proposed to increase lifespan in UM-HET3 mice.

c) Candesartan cilexetil (CC) is an angiotensin-receptor blocker, which lowers blood pressure and improves cardiovascular function and insulin sensitivity in obese, hypertensive patients. Importantly, angiotensin-receptor knockout increases lifespan of mice. Because CC is effective against age-related diseases, and sensitizes the body to insulin, and because the angiotensin-receptor knockout increases lifespan of mice, treatment with CC was hypothesized to increase lifespan.

(d) To maintain good quality protein in the body, heat shock proteins (HSPs) are vital. Geranylgeranylacetone (GGA) induces heat shock protein (Hsp70) in mammalian tissues and promotes insulin sensitivity in old mice, while it increases HSP expression in atrial tissue after heart surgery. Long-lived species, compared with related short-lived species within the same order, have elevated HSP levels in conjunction with better proteostasis. To test whether treatment with an established HSP inducer can increase lifespan in a mammalian model, UM-HET3 mice were treated with GGA.

(e) MIF098 ((3-(3-hydroxybenzyl)-5-methylbenzo[d]oxazol-2(3H)-one) is a macrophage migration inhibition factor (MIF) antagonist that regulates CD44 binding. MIF is a proinflammatory cytokine, so MIF098 reduces inflammation. This may include the chronic inflammation that increases with age, as suggested by the finding that MIF-knockout mice live significantly longer than controls. Because it is orally bioavailable and shows MIF inhibitory activity in mouse models of hyperoxic lung injury, as well as in other diseases, treatment with MIF098 was proposed to increase lifespan by decreasing chronic inflammation and disease.

Our new data show that nicotinamide riboside (NR) failed to increase lifespan. Only 17aE2 increased lifespan, and benefits in males occurred even when the drug was not fed until late middle or early old age (16 and 20 months of age, respectively). The range of ages for which treatment is effective suggests that benefits from 17aE2 do not depend on effects earlier in life, such as growth alteration. Interventions that are effective when started at a late age have considerable translational potential.

Link: https://onlinelibrary.wiley.com/doi/10.1111/acel.13328

Tau Immunotherapy for Alzheimer's Disease is Proving to be as Challenging as Amyloid Immunotherapy

Alzheimer's disease is characterized by the aggregation of first amyloid-β and then tau protein in later stages. It took many years and many attempts to produce immunotherapies capable of clearing amyloid-β from the brain, only to find that this doesn't in fact help patients to any great degree. Amyloid-β may be a side-effect of the causative mechanisms - such as infection, or chronic inflammation - or only important in the earliest stages of the development of Alzheimer's. By the time tau aggregation happens, a different disease process has become dominant. One of the next options is to target tau protein with the same sorts of immunotherapy technologies. So far this is proceeding in much the same way, with the first attempts failing to achieve meaningful levels of clearance.

With anti-amyloid antibodies now consistently hitting their target, tau immunotherapy represents the next frontier. In Alzheimer's disease, tau tangles correlate far more closely with cognitive decline than plaques do, and tau aggregates are the main pathology in many related disorders. As with amyloid, however, initial trials of anti-tau antibodies have been beset by failures. Already, several antibodies that bind the N-terminus or C-terminus of tau have been scuttled after not doing recipients any good. Meanwhile, preclinical evidence suggests that antibodies that go after the protein's mid-section, particularly its microtubule-binding region (MTBR), may be better at preventing aggregates from spreading. Several such antibodies have now entered Phase 1 or 2.

At the 15th International Conference on Alzheimer's and Parkinson's Diseases, researchers discussed a number of these programs. Roche offered a first look at biomarker data from the negative Phase 2 trial of the N-terminal-targeting antibody semorinemab. Other speakers touted MTBR-binding antibodies. Pinteon Therapeutics showed preliminary Phase 1 findings for PNT001, while the Technical University of Munich presented on UCB's beprenemab, also in Phase 1. Prothena's MTBR-binder PRX005 is still preclinical, but the company offered mechanistic data on how it might inhibit the transfer of pathological tau.

Time will tell if this newest crop can perform in the clinic. Researchers believe the field is making progress in figuring out how to target the protein, and are encouraged by data linking cerebrospinal fluid MTBR tau with tangles, and specific tau phospho-species with plaques. "That's really exciting for us as a field. We're learning so much more about this target."

Link: https://www.alzforum.org/news/conference-coverage/n-terminal-tau-antibodies-fade-mid-domain-ones-push-fore

Are Some Amyloid Plaques Protective in Old Age and Alzheimer's Disease?

April, 2021

Researchers here provide evidence to suggest that some of the amyloid-β deposits in the brain that are characteristic of Alzheimer's disease are in fact beneficial and protective, the efforts of immune cells to remove harmful amyloid-β from contact with cells and deposit it elsewhere. This may or may not help to explain why amyloid clearance therapies have so far failed to produce benefits in patients: it is always hard to say just how large a contribution any one given mechanism has to disease progression. It seems likely that amyloid-β aggregates are either a moderately but not severely harmful side-effect of the real core disease processes - such as chronic infection and its consequences - or that amyloid-β aggregation is only relevant in the early stages of Alzheimer's disease. In the later stages of the condition, a feedback loop of inflammation, cellular senescence, and immune system dysfunction drives the condition.

Alzheimer's disease is a neurological condition that results in memory loss, impairment of thinking, and behavioral changes, which worsen as we age. The disease seems to be caused by abnormal proteins aggregating between brain cells to form the hallmark plaques, which interrupt activity that keeps the cells alive. There are numerous forms of plaque, but the two most prevalent are characterized as "diffuse" and "dense-core." Diffuse plaques are loosely organized, amorphous clouds. Dense-core plaques have a compact center surrounded by a halo. Scientists have generally believed that both types of plaque form spontaneously from excess production of a precursor molecule called amyloid precursor protein (APP).

But, according to a new study, it is actually microglia that form dense-core plaques from diffuse amyloid-beta fibrils, as part of their cellular cleanup. This builds on earlier research showing that when a brain cell dies, a fatty molecule flips from the inside to the outside of the cell, signaling, "I'm dead, eat me." Microglia,

via surface proteins called TAM receptors, then engulf, or "eat" the dead cell, with the help of an intermediary molecule called Gas6. Without TAM receptors and Gas6, microglia cannot connect to dead cells and consume them.

The team's current work shows that it's not only dead cells that exhibit the eat-me signal and Gas6: So do the amyloid plaques prevalent in Alzheimer's disease. Using animal models, the researchers were able to demonstrate experimentally for the first time that microglia with TAM receptors eat amyloid plaques via the eat-me signal and Gas6. In mice engineered to lack TAM receptors, the microglia were unable to perform this function.

Digging deeper, they traced the dense-core plaques using live imaging. Much to their surprise, the team discovered that after a microglial cell eats a diffuse plaque, it transfers the engulfed amyloid-beta to a highly acidic compartment and converts it into a highly compacted aggregate that is then transferred to a dense-core plaque. The researchers propose that this is a beneficial mechanism, organizing diffuse into dense-core plaque and clearing the intercellular environment of debris.

"Some people are saying that the relative failure of trials that bust up dense-core plaques refutes the idea that amyloid-beta is a bad thing in the brain. But we argue that amyloid-beta is still clearly a bad thing; it's just that you've got to ask whether dense-core plaques are a bad thing." The researchers suggest that scientists looking for a cure for Alzheimer's should stop trying to focus on breaking up dense-core plaques and start looking at treatments that either reduce the production of amyloid-beta in the first place or therapies that facilitate transport of amyloid-beta out of the brain altogether.

Link: https://www.salk.edu/news-release/in-surprising-twist-some-alzheimers-plaques-may-be-protective-not-destructive/

Further Confirming Data on the Failure of Fullerenes in Olive Oil to Extend Life in Rodents

April, 2021

The years of work that went into investigating the effects of fullerenes (spherical assemblies of carbon molecules, specifically C60 in this case) on life span in rodents are an example of the waste that can occur following the publication of a badly designed study that produces misleading data. The original 2012 study that led to the claim that supplementation with fullerenes dissolved in olive oil increases rat life span was carried out using only a small number of animals and was published in a journal that did not specialize in aging research. This is perhaps because the size of the life span extension claimed was large enough that it would have been rejected by reviewers familiar with past results. It is too large to be taken at face value without resulting from a much larger and more rigorous study.

Later work showed that fullerenes in oil are in fact quite toxic unless very carefully manufactured, a hurdle requiring some years to pass, and not accounted for at all in the original paper. When tested robustly, using non-toxic formulations, fullerenes in olive oil were found to fail to extend rodent lifespan. The original study did not control for calorie intake, and so may have been reporting a disguised calorie restriction effect, or simply the result of an artifact of poor study design and execution.

We might then look at the following paper by a different group, in which the authors suggest that the problem is that olive oil on its own is quite harmful to rodent lifespan, while putting fullerenes into the olive oil counteracts some of these effects. The mechanisms of interest here revolve around oxidation of the lipid molecules in oils, as oxidized and otherwise altered lipids are harmful to cells, versus the sizable antioxidant capacities of fullerenes. At this point there is still at least one next step to conduct, which is to run life span studies based on delivery of water-soluble fullerenes without involving olive oil. This sort of approach has been tested in a preliminary way by a few groups for their ability to assist in control of localized inflammation, but not extensively.

Given the poor performance of systemic antioxidants to date in extending life in animal models, versus benefits for some types of antioxidant shown in inflammatory conditions, I wouldn't expect much to result from this work. The only antioxidant compounds that have produced increased life span are those that specifically target the mitochondria (such as MitoQ, SkQ1, and so forth), and even there the gains in life span in short-lived species are modest at best. These compounds have so far found their greatest success in localized treatment of inflammatory conditions, such as those of the eye.

Effect of long-term treatment with C60 fullerenes on the lifespan and health status of CBA/Ca mice

Several studies claimed C60 fullerenes as a prospective geroprotector drug due to their ability to capture free radicals effectively and caused a profound interest in C60 in life extension communities. Multiple additives are already sold for human consumption despite a small body of evidence supporting the beneficial effects of fullerenes on the lifespan. In order to test the effect of C60 fullerenes on lifespan and healthspan, we administered C60 fullerenes dissolved in virgin olive oil orally to 10-12 months old CBA/Ca mice of both genders for seven months and assessed their survival.

To uncover C60 and virgin olive effects, we established two control groups: mice treated with virgin olive oil and mice treated with drinking water. To measure healthspan, we conducted daily monitoring of health condition and lethality and monthly

bodyweight measurements. We also assessed physical activity, glucose metabolism, and hematological parameters every three months.

We did not observe health deterioration in the animals treated with C60 compared with the control groups. Treatment of mice with C60 fullerenes resulted in an increased lifespan of males and females compared with the olive oil-treated animals. The lifespan of C60-treated mice was similar to the mice treated with water. These results suggest that the lifespan-extending effect in C60-treated mice appears due to the protective effect of fullerenes in opposition to the negative effect of olive oil in CBA/Ca mice.

Link: https://www.liebertpub.com/doi/10.1089/rej.2020.2403

Putting Some Numbers to Senescent Immune Cell Counts in Humans by Age

May, 2021

In this open access paper, the authors report on inroads in counting senescent immune cells in blood samples from human patients of different ages. Accurate determination of senescence status isn't cut and dried for many types of immune cell, but the researchers believe they have produced good numbers for cytotoxic T cells, showing that older people have many more senescent cells in this category. I'd like to see more of this sort of research, establishing some sort of baseline of expectations for levels of cellular senescence in various tissues by age, leading towards assays that can be used to directly the measure the outcome of treatment with senolytic drugs to selectively destroy senescent cells.

The results here suggest surprisingly high levels of cellular senescence in some important immune cell populations, more than half of the cells in a sample being senescent by the criteria used. In the broader context, it would make sense for numbers to be high relative to tissues. After the thymus atrophies significantly in late life, nearly all new T cells – needed to maintain the observed constant T cell population across a lifetime – are created by replication of existing T cells. Eventually cells hit the Hayflick limit and either self-destruct or become senescent.

Will treatment with senolytics produce benefits to immune function in this scenario? It will kill senescent T cells, and more cells will become senescent in the course of replicating to make up the numbers. The outcome will most likely be a lower count of senescent immune cells than existed prior to treatment, and the benefits of clearing senescent cells throughout the body should be sizable, but it is something to consider. Replication stress on the immune system is to be avoided if possible. One would have to test this scenario in larger mammals than mice: one big difference between mice and people is that mice do not rely on replication of existing T cells to maintain overall T cell population size, so there is little to be learned from existing mouse data.

Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans

Aging leads to a progressive functional decline of the immune system, rendering the elderly increasingly susceptible to disease and infection. The degree to which immune cell senescence contributes to this decline remains unclear, however, since markers that label immune cells with classical features of cellular senescence accurately and comprehensively have not been identified.

Using a second-generation fluorogenic substrate for β-galactosidase and multi-parameter flow cytometry, we demonstrate here that peripheral blood mononuclear cells (PBMCs) isolated from healthy humans increasingly display cells with high senescence-associated β-galactosidase (SA-βGal) activity with advancing donor age. The greatest age-associated increases were observed in CD8+ T-cell populations, in which the fraction of cells with high SA-βGal activity reached average levels of 64% in donors in their 60s. CD8+ T cells with high SA-βGal activity, but not those with low SA-βGal activity, were found to exhibit features of telomere dysfunction-induced senescence and p16-mediated senescence, were impaired in their ability to proliferate, developed in various T-cell differentiation states, and had a gene expression signature consistent with the senescence state previously observed in human fibroblasts.

Based on these results, we propose that senescent CD8+ T cells with classical features of cellular senescence accumulate to levels that are significantly higher than previously reported and additionally provide a simple yet robust method for the isolation and characterization of senescent CD8+ T cells with predictive potential for biological age.

Link: https://onlinelibrary.wiley.com/doi/10.1111/acel.13344

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

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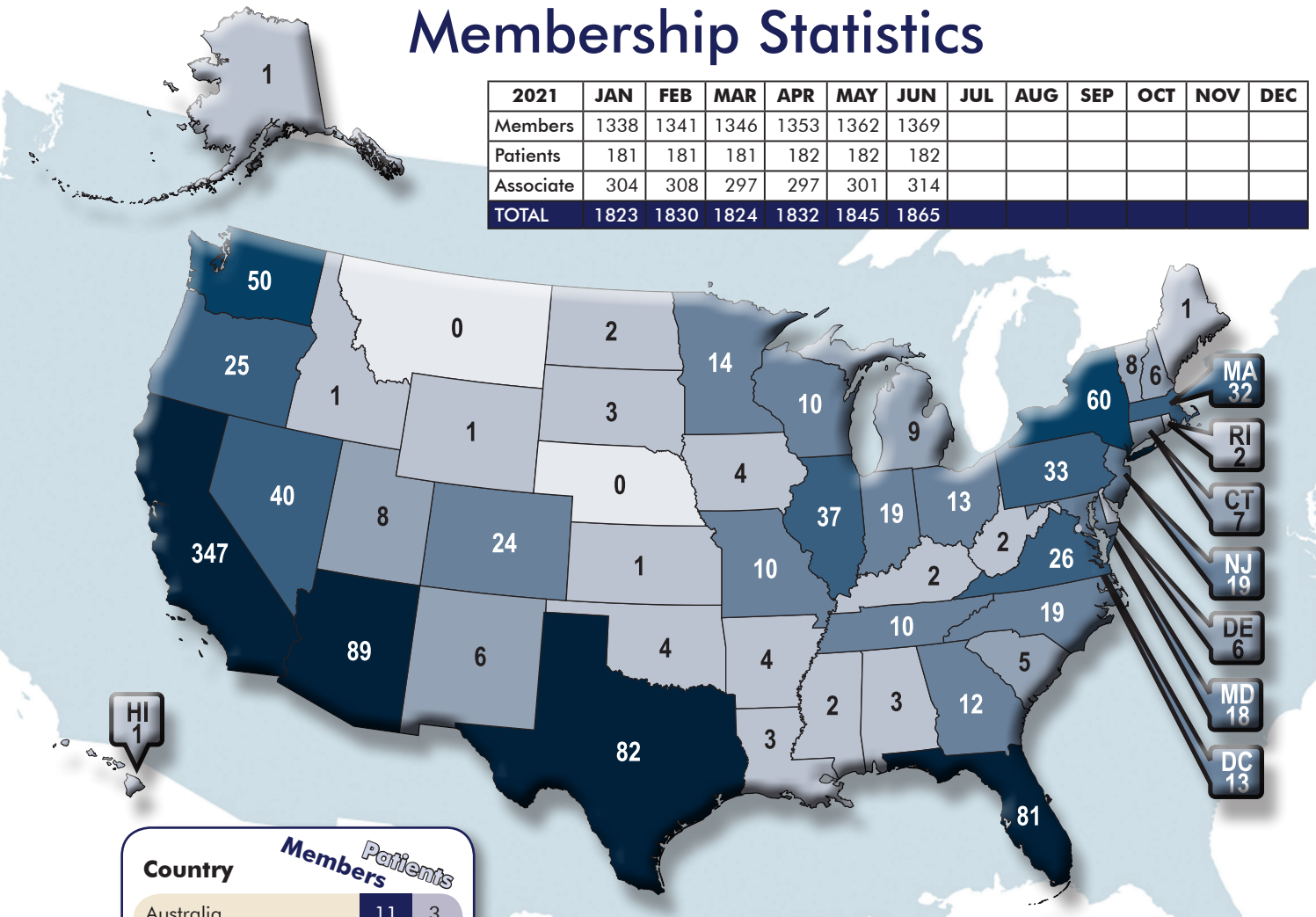
Membership Statistics

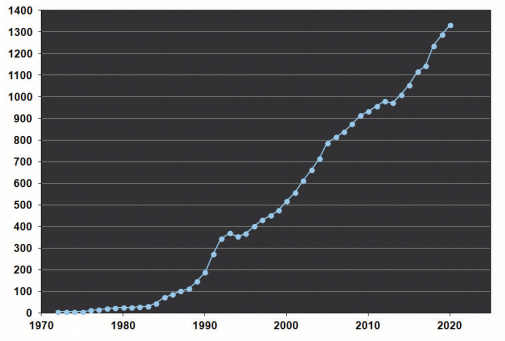
2021	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1338	1341	1346	1353	1362	1369						
Patients	181	181	181	182	182	182						
Associate	304	308	297	297	301	314						
TOTAL	1823	1830	1824	1832	1845	1865						



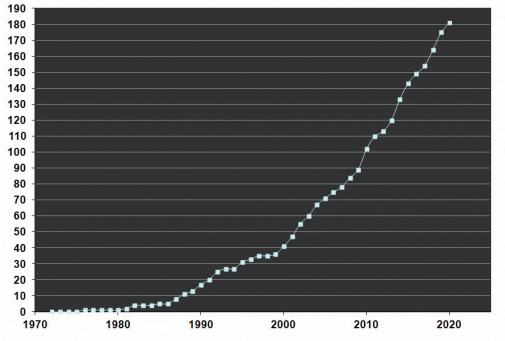
International Members & Patients

Country	Members	Patients
Australia	11	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	70	4
China	2	1
Finland	1	0
France	3	1
Germany	19	0
Hong Kong	2	0
Hungary	1	0
Israel	1	1
Italy	1	0
Japan	6	0
Luxembourg	1	0
Malaysia	1	0
Mexico	5	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	2	0
Portugal	4	1
Puerto Rico	3	0
Spain	5	1
Sweden	1	0
Switzerland	2	0
Taiwan	1	0
Thailand	3	1
United Kingdom	42	3
TOTAL	194	16

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



Number of Alcor members



Number of Alcor patients

Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Control and Readout of a Superconducting Qubit Using a Photonic Link

F. Lecocq, F. Quinlan, K. Cicak, J. Aumentado, S. A. Diddams, J. D. Teufel

Nature, 24 Mar. 2021, https://www.nature.com/articles/s41586-021-03268-x, accessed 11 Apr. 2021.

Abstract

Delivering on the revolutionary promise of a universal quantum computer will require processors with millions of quantum bits (qubits). In superconducting quantum processors, each qubit is individually addressed with microwave signal lines that connect room-temperature electronics to the cryogenic environment of the quantum circuit. The complexity and heat load associated with the multiple coaxial lines per qubit limits the maximum possible size of a processor to a few thousand qubits. Here we introduce a photonic link using an optical fibre to guide modulated laser light from room temperature to a cryogenic photodetector, capable of delivering shot-noise-limited microwave signals directly at millikelvin temperatures. By demonstrating high-fidelity control and readout of a superconducting qubit, we show that this photonic link can meet the stringent requirements of superconducting quantum information processing. Leveraging the low thermal conductivity and large intrinsic bandwidth of optical fibre enables the efficient and massively multiplexed delivery of coherent microwave control pulses, providing a path towards a million-qubit universal quantum computer.

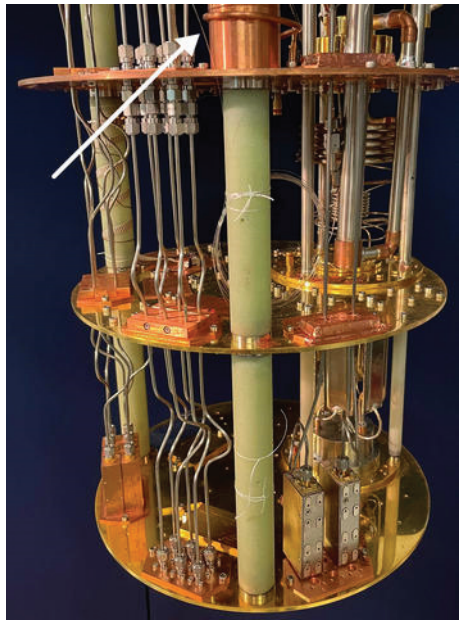
From: **Optical Fiber Could Boost Power of Superconducting Quantum Computers**

Unattributed, *NIST News*, 24 Mar. 2021, https://www.nist.gov/news-events/news/2021/03/optical-fiber-could-boost-power-superconducting-quantum-computers, accessed 11 Apr. 2021.

The secret to building superconducting quantum computers with massive processing power may be an ordinary telecommunications technology – optical fiber.

Physicists at the National Institute of Standards and Technology (NIST) have measured and controlled a superconducting quantum bit (qubit) using light-conducting fiber instead of metal electrical wires, paving the way to packing a million qubits into a quantum computer rather than just a few thousand. The demonstration is described in the March 25 issue of *Nature*.

Superconducting circuits are a leading technology for making quantum computers because they are reliable and easily mass produced. But these circuits must operate at cryogenic temperatures, and schemes for wiring them to room-temperature electronics are complex and prone to overheating the qubits. A universal quantum computer, capable of solving any type of problem, is expected to need about 1 million qubits. Conventional cryostats – supercold dilution refrigerators – with metal wiring can only support thousands at the most.



NIST physicists measured and controlled a superconducting quantum bit (qubit) using light-conducting fiber (indicated by white arrow) instead of metal electrical cables like the 14 shown here inside a cryostat. By using fiber, researchers could potentially pack a million qubits into a quantum computer rather than just a few thousand. ***Credit: F. Lecocq/ NIST***

Optical fiber, the backbone of telecommunications networks, has a glass or plastic core that can carry a high volume of light signals without conducting heat. But superconducting quantum computers use microwave pulses to store and process information. So the light needs to be converted precisely to microwaves.

To solve this problem, NIST researchers combined the fiber with a few other standard components that convert, convey and measure light at the level of single particles, or photons, which could then be easily converted into microwaves. The system worked as well as metal wiring and maintained the qubit's fragile quantum states.

"I think this advance will have high impact because it combines two totally different technologies, photonics and superconducting qubits, to solve a very important problem," NIST physicist John Teufel said. "Optical fiber can also carry far more data in a much smaller volume than conventional cable."

Incorporation of a Nucleoside Analog Maps Genome Repair Sites in Postmitotic Human Neurons

Dylan A. Reid, Patrick J. Reed, Johannes C. M. Schlachetzki, Ioana I. Nitulescu, Grace Chou, Enoch C. Tsui, Jeffrey R. Jones, Sahaana Chandran, Ake T. Lu, Claire A. McClain, Jean H. Ooi, Tzu-Wen Wang, Addison J. Lana, Sara B. Linker, Anthony S. Ricciardulli, Shong Lau, Simon T. Schafer, Steve Horvath, Jesse R. Dixon, Nasun Hah, Christopher K. Glass, Fred H. Gage

Science, 2 Apr 2021, https://science.sciencemag.org/content/372/6537/91, accessed 9 Apr. 2021.

Abstract

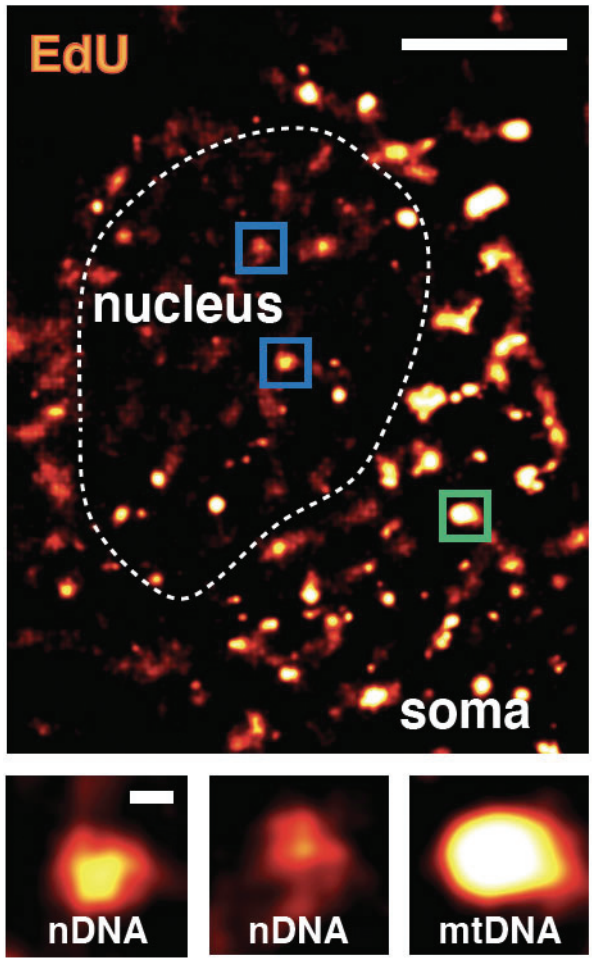
Neurons are the longest-lived cells in our bodies and lack DNA replication, which makes them reliant on a limited repertoire of DNA repair mechanisms to maintain genome fidelity. These repair mechanisms decline with age, but we have limited knowledge of how genome instability emerges and what strategies neurons and other long-lived cells may have evolved to protect their genomes over the human life span. A targeted sequencing approach in human embryonic stem cell-induced neurons shows that, in neurons, DNA repair is enriched at well-defined hotspots that protect essential genes. These hotspots are enriched with histone H2A isoforms and RNA binding proteins and are associated with evolutionarily conserved elements of the human genome. These findings provide a basis for understanding genome integrity as it relates to aging and disease in the nervous system.

From: **How Brain Cells Repair Their DNA Reveals "Hot Spots" of Aging and Disease**

unattributed, *Salk News*, 1 Apr. 2021, https://www.salk.edu/news-release/how-brain-cells-repair-their-dna-reveals-hot-spots-of-aging-and-disease/, accessed 8 Apr. 2021.

Neurons lack the ability to replicate their DNA, so they're constantly working to repair damage to their genome. Now, a new study by Salk scientists finds that these repairs are not random, but instead focus on protecting certain genetic "hot spots" that appear to play a critical role in neural identity and function.

The findings, published in the April 2, 2021, issue of Science, give novel insights into the genetic structures involved in aging and neurodegeneration, and could point to the development of potential new therapies for diseases such Alzheimer's, Parkinson's and other age-related dementia disorders.



In this image of a neuron nucleus, bright spots show areas of focused genetic repair.
Credit: Salk Institute/Waitt Advanced Biophotonics Center

"This research shows for the first time that there are sections of genome that neurons prioritize when it comes to repair," says Professor and Salk President Rusty Gage, the paper's co-corresponding author. "We're excited about the potential of these findings to change the way we view many age-related diseases of the nervous system and potentially explore DNA repair as a therapeutic approach."

Unlike other cells, neurons generally don't replace themselves over time, making them among the longest-living cells in the human body. Their longevity makes it even more important that they repair lesions in their DNA as they age, in order to maintain their function over the decades of a human life span. As they get older, neurons' ability to make these genetic repairs declines, which could explain why people develop age-related neurodegenerative diseases like Alzheimer's and Parkinson's.

To investigate how neurons maintain genome health, the study authors developed a new technique they term Repair-seq. The team produced neurons from stem cells and fed them synthetic

nucleosides – molecules that serve as building blocks for DNA. These artificial nucleosides could be found via DNA sequencing and imaged, showing where the neurons used them to make repairs to DNA that was damaged by normal cellular processes. While the scientists expected to see some prioritization, they were surprised by just how focused the neurons were on protecting certain sections of the genome.

"What we saw was incredibly sharp, well-defined regions of repair; very focused areas that were substantially higher than background levels," says co-first and co-corresponding author Dylan Reid, a former Salk postdoctoral scholar and now a fellow at Vertex Pharmaceutics. "The proteins that sit on these 'hot spots' are implicated in neurodegenerative disease, and the sites are also linked to aging."

The authors found approximately 65,000 hot spots that covered around 2 percent of the neuronal genome. They then used proteomics approaches to detect what proteins were found at these hot spots, implicating many splicing-related proteins. (These are involved in the eventual production of other proteins.) Many of these sites appeared to be quite stable when the cells were treated with DNA-damaging agents, and the most stable DNA repair hot spots were found to be strongly associated with sites where chemical tags attach ("methylation") that are best at predicting neuronal age.

Previous research has focused on identifying the sections of DNA that suffer genetic damage, but this is the first time researchers have looked for where the genome is being heavily repaired.

"We flipped the paradigm from looking for damage to looking for repair, and that's why we were able to find these hot spots," Reid says. "This is really new biology that might eventually change how we understand neurons in the nervous system, and the more we understand that, the more we can look to develop therapies addressing age-related diseases."

Quantum Phases of Matter on a 256-Atom Programmable Quantum Simulator

Sepehr Ebadi, Tout T. Wang, Harry Levine, Alexander Keesling, Giulia Semeghini, Ahmed Omran, Dolev Bluvstein, Rhine Samajdar, Hannes Pichler, Wen Wei Ho, Soonwon Choi, Subir Sachdev, Markus Greiner, Vladan Vuletić, Mikhail D. Lukin

Nature **595**, 227–232 (2021) 7 Jul. 2021, https://www.nature.com/articles/s41380-021-01208-9, accessed 17 Aug. 2021.

Abstract

Motivated by far-reaching applications ranging from quantum simulations of complex processes in physics and chemistry to quantum information processing, a broad effort is currently underway to build large-scale programmable quantum systems. Such systems provide insights into strongly correlated quantum matter, while at the same time enabling new methods for computation and metrology. Here we demonstrate a programmable quantum simulator based on deterministically prepared two-dimensional arrays of neutral atoms, featuring strong interactions controlled by coherent atomic excitation into Rydberg states. Using this approach, we realize a quantum spin model with tunable interactions for system sizes ranging from 64 to 256 qubits. We benchmark the system by characterizing high-fidelity antiferromagnetically ordered states and demonstrating quantum critical dynamics consistent with an Ising quantum phase transition in (2 + 1) dimensions. We then create and study several new quantum phases that arise from the interplay between interactions and coherent laser excitation, experimentally map the phase diagram and investigate the role of quantum fluctuations. Offering a new lens into the study of complex quantum matter, these observations pave the way for investigations of exotic quantum phases, non-equilibrium entanglement dynamics and hardware-efficient realization of quantum algorithms.

From: **Harvard-Led Physicists Take Big Step in Race to Quantum Computing**

Juan Siliezar, *Harvard Gazette*, 7 Jul. 2021, https://news.harvard.edu/gazette/story/2021/07/harvard-led-physicists-create-256-qubit-programmable-quantum-simulator/, accessed 17 Aug. 2021.

A team of physicists from the Harvard-MIT Center for Ultracold Atoms and other universities has developed a special type of quantum computer known as a programmable quantum simulator capable of operating with 256 quantum bits, or "qubits."

The system marks a major step toward building large-scale quantum machines that could be used to shed light on a host of complex quantum processes and eventually help bring about real-world breakthroughs in material science, communication technologies, finance, and many other fields, overcoming research hurdles that are beyond the capabilities of even the fastest supercomputers today. Qubits are the fundamental building blocks on which quantum computers run and the source of their massive processing power.

"This moves the field into a new domain where no one has ever been to thus far," said Mikhail Lukin, the George Vasmer Leverett Professor of Physics, co-director of the Harvard Quantum Initiative, and one of the senior authors of the study published today in the journal Nature. "We are entering a completely new part of the quantum world."

According to Sepehr Ebadi, a physics student in the Graduate School of Arts and Sciences and the study's lead author, it is the combination of system's unprecedented size and programmability that puts it at the cutting edge of the race for a quantum computer,

which harnesses the mysterious properties of matter at extremely small scales to greatly advance processing power. Under the right circumstances, the increase in qubits means the system can store and process exponentially more information than the classical bits on which standard computers run.

"The number of quantum states that are possible with only 256 qubits exceeds the number of atoms in the solar system," Ebadi said, explaining the system's vast size.

Already, the simulator has allowed researchers to observe several exotic quantum states of matter that had never before been realized experimentally, and to perform a quantum phase transition study so precise that it serves as the textbook example of how magnetism works at the quantum level.

These experiments provide powerful insights on the quantum physics underlying material properties and can help show scientists how to design new materials with exotic properties.

Highly Accurate Protein Structure Prediction with AlphaFold

John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Žídek, Anna Potapenko, Alex Bridgland, Clemens Meyer, Simon A. A. Kohl, Andrew J. Ballard, Andrew Cowie, Bernardino Romera-Paredes, Stanislav Nikolov, Rishub Jain, Jonas Adler, Trevor Back, Stig Petersen, David Reiman, Ellen Clancy, Michal Zielinski, Martin Steinegger, Michalina Pacholska, Tamas Berghammer, Sebastian Bodenstein, David Silver, Oriol Vinyals, Andrew W. Senior, Koray Kavukcuoglu, Pushmeet Kohli, Demis Hassabis

Nature (2021) 15 Jul. 2021, https://www.nature.com/articles/s41586-021-03819-2, accessed 17 Aug. 2021. [DeepMind researchers]

Abstract

Proteins are essential to life and understanding their structure can facilitate a mechanistic understanding of their function. Through an enormous experimental effort, the structures of around 100,000 unique proteins have been determined, but this represents a small fraction of the billions of known protein sequences. Structural coverage is bottlenecked by the months to years of painstaking effort required to determine a single protein structure. Accurate computational approaches are needed to address this gap and to enable large-scale structural bioinformatics. Predicting the 3-D structure that a protein will adopt based solely on its amino acid sequence, the structure prediction component of the 'protein folding problem', has been an important open research problem for more than 50 years. Despite recent progress, existing methods fall far short of atomic accuracy, especially when no homologous structure is available. Here we provide the first computational method that can regularly predict protein structures with atomic accuracy even where no similar structure is known. We validated an entirely redesigned version of our neural network-based model, AlphaFold, in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14), demonstrating accuracy competitive with experiment in a majority of cases and greatly outperforming other methods. Underpinning the latest version of AlphaFold is a novel machine learning approach that incorporates physical and biological knowledge about protein structure, leveraging multi-sequence alignments, into the design of the deep learning algorithm.

Accurate Prediction of Protein Structures and Interactions Using a Three-Track Neural Network

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Science 15 Jul 2021, https://science.sciencemag.org/content/early/2021/07/19/science.abj8754, accessed 17 Aug. 2021. [University of Washington researchers]

Abstract

DeepMind presented remarkably accurate predictions at the recent CASP14 protein structure prediction assessment conference. We explored network architectures incorporating related ideas and obtained the best performance with a three-track network in which information at the 1D sequence level, the 2D distance map level, and the 3D coordinate level is successively transformed and integrated. The three-track network produces structure predictions with accuracies approaching those of DeepMind in CASP14, enables the rapid solution of challenging X-ray crystallography and cryo-EM structure modeling problems, and provides insights into the functions of proteins of currently unknown structure. The network also enables rapid generation of accurate protein-protein complex models from sequence information alone, short circuiting traditional approaches which require modeling of individual subunits followed by docking. We make the method available to the scientific community to speed biological research.

From: **Protein Folding AI Is Making a 'Once in a Generation' Advance in Biology**

Shelly Fan, 20 Jul. 2021, https://singularityhub.com/2021/07/20/new-protein-folding-ai-just-made-a-once-in-a-generation-advance-in-biology/#:~:text=Topics-,Protein%20Folding%20AI%20Is%20Making%20a%20'Once,a%20Generation'%20Advance%20in%20Biology&text=Similar%20to%20Transformers%2C%20many%20protein,functional%20needs%20at%20the%20moment, accessed 17 Aug. 2021.

Thanks to AI, we just got stunningly powerful tools to decode life.

In two back-to-back papers last week, scientists at DeepMind and the University of Washington described deep learning-based methods to solve protein folding – the last step of executing the programming in our DNA, and a "once in a generation advance."

Proteins are the minions of life. They form our bodies, fuel our metabolism, and are the target of most of today's medicine. They start out as a simple ribbon, translated from DNA, and subsequently fold into intricate three-dimensional architectures. Similar to Transformers, many protein units further assemble into massive, moving complexes that change their structure depending on their functional needs at the moment.

Misfolded proteins can be devastating, causing health problems from sickle cell anemia to cancer and Alzheimer's disease. One of biology's grandest challenges for the past 50 years has been deciphering how a simple one-dimensional ribbon-like structure turns into 3D shapes, equipped with canyons, ridges, valleys, and caves. It's as if an alien is reading the coordinates of hundreds of locations on a map of the Grand Canyon on a notebook, and reconstructing it into a 3D hologram of the actual thing – without ever laying eyes on it or knowing what it should look like.

Yeah. It's hard. "Lots of people have broken their head on it," said Dr. John Moult at the University of Maryland.

It's not just an academic exercise. Solving the human genome paved the way for gene therapy, CAR-T cancer breakthroughs, and the infamous CRISPR gene editing tool. Deciphering protein folding is bound to illuminate an entire new landscape of biology we haven't been able to study or manipulate. The fast and furious development of Covid-19 vaccines relied on scientists parsing multiple protein targets on the virus, including the spike proteins that vaccines target. Many proteins that lead to cancer have so far been out of the reach of drugs because their structure is hard to pin down.

With these new AI tools, scientists could solve haunting medical mysteries while preparing to tackle those yet unknown. It sets the stage for better understanding our biology, informing new medicines, and even inspiring synthetic biology down the line.

"What the DeepMind team has managed to achieve is fantastic and will change the future of structural biology and protein research," said Dr. Janet Thornton, director emeritus of the European Bioinformatics Institute.

"I never thought I'd see this in my lifetime," added Moult.

Chondroitin 6-Sulphate Is Required for Neuroplasticity and Memory In Ageing

Sujeong Yang, Sylvain Gigout, Angelo Molinaro, Yuko Naito-Matsui, Sam Hilton, Simona Foscarin, Bart Nieuwenhuis, Chin Lik Tan, Joost Verhaagen, Tommaso Pizzorusso, Lisa M. Saksida, Timothy M. Bussey, Hiroshi Kitagawa, Jessica C. F. Kwok, James W. Fawcett

Molecular Psychiatry (2021) 16 Jul. 2021, https://www.nature.com/articles/s41380-021-01208-9, accessed 17 Aug. 2021.

Abstract

Perineuronal nets (PNNs) are chondroitin sulphate proteoglycan-containing structures on the neuronal surface that have been implicated in the control of neuroplasticity and memory. Age-related reduction of chondroitin 6-sulphates (C6S) leads to PNNs becoming more inhibitory. Here, we investigated whether manipulation of the chondroitin sulphate (CS) composition of the PNNs could restore neuroplasticity and alleviate memory deficits in aged mice. We first confirmed that aged mice (20-months) showed memory and plasticity deficits. They were able to retain or regain their cognitive ability when CSs were digested or PNNs were attenuated. We then explored the role of C6S in memory and neuroplasticity. Transgenic deletion of chondroitin 6-sulfotransferase (*chst3*) led to a reduction of permissive C6S, simulating aged brains. These animals showed very early memory loss at 11 weeks old. Importantly, restoring C6S levels in aged animals rescued the memory deficits and restored cortical long-term potentiation, suggesting a strategy to improve age-related memory impairment.

From: **Scientists Reverse Age-Related Memory Loss in Mice**

Sarah Collins, University of Cambridge, 22 Jul. 2021, https://www.cam.ac.uk/research/news/scientists-reverse-age-related-memory-loss-in-mice, accessed 17 Aug. 2021.

Scientists at Cambridge and Leeds have successfully reversed age-related memory loss in mice and say their discovery could lead to the development of treatments to prevent memory loss in people as they age.

In a study published in Molecular Psychiatry, the team show that changes in the extracellular matrix of the brain – 'scaffolding' around nerve cells – lead to loss of memory with ageing, but that it is possible to reverse these using genetic treatments.

Recent evidence has emerged of the role of perineuronal nets (PNNs) in neuroplasticity – the ability of the brain to learn and adapt – and to make memories. PNNs are cartilage-like structures that mostly surround inhibitory neurons in the brain. Their main

function is to control the level of plasticity in the brain. They appear at around five years old in humans, and turn off the period of enhanced plasticity during which the connections in the brain are optimised. Then, plasticity is partially turned off, making the brain more efficient but less plastic.

PNNs contain compounds known as chondroitin sulphates. Some of these, such as chondroitin 4-sulphate, inhibit the action of the networks, inhibiting neuroplasticity; others, such as chondroitin 6-sulphate, promote neuroplasticity. As we age, the balance of these compounds changes, and as levels of chondroitin 6-sulphate decrease, so our ability to learn and form new memories changes, leading to age-related memory decline.

Researchers at the University of Cambridge and University of Leeds investigated whether manipulating the chondroitin sulphate composition of the PNNs might restore neuroplasticity and alleviate age-related memory deficits.

To do this, the team looked at 20-month old mice – considered very old – and using a suite of tests showed that the mice exhibited deficits in their memory compared to six-month old mice.

For example, one test involved seeing whether mice recognised an object. The mouse was placed at the start of a Y-shaped maze and left to explore two identical objects at the end of the two arms. After a short while, the mouse was once again placed in the maze, but this time one arm contained a new object, while the other contained a copy of the repeated object. The researchers measured the amount of time the mouse spent exploring each object to see whether it had remembered the object from the previous task. The older mice were much less likely to remember the object.

The team treated the ageing mice using a 'viral vector', a virus capable of reconstituting the amount of 6-sulphate chondroitin sulphates to the PNNs and found that this completely restored memory in the older mice, to a level similar to that seen in the younger mice.

The team have already identified a potential drug, licensed for human use, that can be taken by mouth and inhibits the formation of PNNs. When this compound is given to mice and rats it can restore memory in ageing and also improves recovery in spinal cord injury. The researchers are investigating whether it might help alleviate memory loss in animal models of Alzheimer's disease. ■

A Roadmap to Revival

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

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

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

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

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

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

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

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

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

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

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

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

What is Cryonics?

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

How do I find out more?

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

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

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

How do I enroll?

Signing up for cryopreservation is easy!

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

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

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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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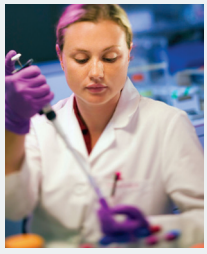

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