2. Theoretical Rationale for Cryonics Procedures

Introduction

Speculations about the ability to preserve human tissue of whole human bodies without deterioration to permit future resuscitation are almost as old as humanity itself. In an April 1773 letter to Jacques Barbeu Dubourg, a person no less than Founding Father of the United States of America Benjamin Franklin, wrote:

> I wish it were possible . . . to invent a method of embalming drowned persons, in such a manner that they might be recalled to life at any period, however distant; for having a very ardent desire to see and observe the state of America a hundred years hence, I should prefer to an ordinary death, being immersed with a few friends in a cask of Madeira, until that time, then to be recalled to life by the solar warmth of my dear country! But . . . in all probability, we live in a century too little advanced, and too near the infancy of science, to see such an art brought in our time to its perfection.

During the 20th century a number of distinct developments gave rise to the contemporary practice of cryonics.

The most fundamental development that permitted meaningful practical discussion of the concept of human cryopreservation was the ability of physicists to achieve cryogenic temperatures and to maintain large volumes of matter at these temperatures. A predictable consequence of the ability to use low subzero temperatures in science was to study the properties of biological matter and microorganisms at such temperatures. These early efforts in low temperature biology gave rise to the science of cryobiology.

The modern era of cryonics followed soon after, when, in the early 1960s, cryonics pioneers Evan Cooper and Robert Ettinger recognized that the freezing damage that occurs when complex organs or whole mammals are cooled to cryogenic temperatures might not exclude meaningful repair and resuscitation, provided the original neuroanatomical basis of identity and memory could be deduced and reconstructed.

The technical feasibility of cryonics was further strengthened when investigations into the pathophysiology of cerebral ischemia showed that loss of cerebral viability does not produce instantaneous ultrastructural decomposition of the brain.

During the last two decades ongoing progress in organ vitrification (solidification without ice formation) and the ability to manipulate and alter human biochemistry at progressively smaller scales have tended to validate the vision of the early cryonics pioneers that cryogenic temperatures might be employed to allow a second diagnosis of the patient by a future physician at a time when more advanced treatments may be available.

The Evolution of Death

One of the distinguishing features of contemporary medical practice is the growing recognition that death is not an event, but a process. As a consequence, it has become increasingly routine to distinguish between legal, medical and biological definitions of death, and more rigorous distinctions are being proposed as our knowledge progresses.

The first step in coming to grips with the phenomenon of death was made when scientists could attribute death to the cessation of specific physiological functions instead of some mysterious force. The next discovery that jumpstarted the science and practice of cardiopulmonary resuscitation was the observation that death is a reversible process, provided that circulation and respiration are artificially maintained while efforts are made to promptly restore circulation. During the 20th century the development of cardiopulmonary bypass allowed man-made devices to control circulation and respiration completely and safely to permit advanced surgical procedures on the heart and the brain.

It was only a matter of time before scientists gradually severed the link between metabolism and life completely. The simple observation that some life forms periodically enter and recover from states of reduced metabolism gave rise to the broader study of depressed metabolism. For example, the extremophile tardigrade (also known as the water bear) can tolerate complete arrest of its normal metabolism. The limiting factor for complete metabolic arrest is not the continued presence of a "vital spark" but an evolved or engineered physiology that can tolerate the conditions that produce metabolic arrest.

During the second half of the 20th century, the practice of general anesthesia and hypothermic circulatory arrest in medicine further corroborated the view that life, metabolism, consciousness, and personal identity can be approached from a unified physicalist perspective. In particular, the practice of therapeutic hypothermic circulatory arrest is of great relevance to the practice of cryonics because it demonstrates that humans can be cooled to profound hypothermic temperatures (as low as +18 degrees C) with stoppage of brain electrical activity, and can be recovered with no adverse neurological consequences. What distinguishes cryonics from these procedures is that the patient's temperature may be lowered just below the glass transition temperature of a perfused vitrification solution to induce complete metabolic arrest, and long-term preservation may be at –196 degrees C, in liquid nitrogen.

As is well known to practicing cryobiologists, complex organized life forms such as humans cannot be lowered to liquid nitrogen temperature without producing substantial freezing damage. To advocates of human cryopreservation this is not necessarily a contraindication for cryopreservation as long as the brain of the person is stabilized in a state that permits reconstruction of the original neuroanatomical state that gives rise to the unique identity and memories of the person. If the original anatomical state of the brain and viability can be restored, the patient can be recovered, similar to patients recovering from hypothermic circulatory arrest.

In his paper "Molecular Repair of the Brain" by Ralph Merkle, first published in the October 1989 *Cryonic*s magazine and currently accessible on

the web site at www.alcor.org, Merkle proposed an *information-theoretic* criterion of death:

> A person is dead according to the information-theoretic criterion if their memories, personality, hopes, dreams, etc. have been destroyed in the information-theoretic sense. That is, if the structures in the brain that encode memory and personality have been so disrupted that it is no longer possible in principle to restore them to an appropriate functional state, then the person is dead. If the structures that encode memory and personality are sufficiently intact that inference of the memory and personality are feasible in principle, and therefore restoration to an appropriate functional state is likewise feasible in principle, then the person is not dead.

The information-theoretic definition of death is not just a rationalization of the cryonics practice but reflects the mainstream view of physics and (bio) chemistry that the function and properties of a substance are defined by the specific organization of its molecules and extends this perspective to the concept of personhood. The criterion also arises in the context of diagnosing brain death or alternatives for cryonics such as chemical brain preservation.

The information-theoretic definition of death is highly relevant to the ethics of performing human cryopreservation under diverse biological conditions, some of which may seem quite poor. However, as we shall discuss below, recent experimental evidence in neural cryobiology supports the position that cryonics as an elective medical procedure may also be able to withstand more conventional medical criteria for diagnosing death.

From Freezing to Vitrification

From its original inception, the objective of cryopreservation technologies in cryonics has been to reduce cellular and ultrastructural injury associated with ice formation. This research program culminated in 2000 with the introduction of the use of vitrification solutions at the Alcor Life Extension Foundation.

Ice formation during cryopreservation presents a challenge for human cryopreservation. Because of ice formation the patient will not just require treatment of his terminal illness and rejuvenation, but extensive repairs to cells

and organized tissue due to ice crystal damage. Since the inception of cryonics, freezing without cryoprotectant chemicals (so called “straight freezing”) has not been rejected as a procedure from which recovery is impossible, but there has been a consensus that the less damage that is done during the cryopreservation process, the better.

As a consequence, there has been a great interest in the use of cryoprotectants and the complete elimination of ice formation through vitrification. The idea of vitrification was discussed by notable early cryobiology pioneers such as Basile J. Luyet, but it was not until the focused research of cryobiologist Gregory M. Fahy and his colleagues in the 1980s and 1990s that the objective of solidification without ice formation was systematically explored for the cryopreservation of organs.

One of the major misconceptions about vitrification is that this approach requires extremely rapid cooling rates. It is correct that vitrification of pure water requires small samples to be cooled at rates approaching 1,000,000 degrees Celsius per minute, but these requirements are greatly relaxed in the presence of high concentrations of a suitable cryoprotectant.

As a matter of fact, the actual challenge in cryobiology is not to design solutions that resist ice formation at slow cooling rates but to design vitrification solutions with no toxicity. Since the early days of vitrification research the aim of Dr. Fahy and his colleagues has been to discover the mechanisms that rule cryoprotectant toxicity and to design vitrification solutions to mitigate those factors. In 2005 this research culminated in the vitrification (to -135 degrees Celsius), rewarming, and transplantation of a rabbit kidney with good viability and functionality using the proprietary vitrification solution M22. M22 takes advantage of the following vitrification solution design discoveries:

1. High concentrations of a cryoprotective agent (or a mixture of different cryoprotective agents) can prevent ice formation during cooldown and warming.

2. The toxicity of some cryoprotectants can be significantly reduced by combining them with other cryoprotective agents.

3. The general toxicity of a vitrification agent can be predicted by using a measure called qv*, allowing for the rational formulation of less toxic vitrification agents.
4. Within limits, non-penetrating agents can reduce the exposure of cells to toxic amounts of cryoprotectants without reducing vitrification ability.
5. Synthetic “ice blockers” can be included in a vitrification mixture to inhibit the formation of ice, thus enabling a lower concentration of other toxic cryoprotective agents necessary to achieve vitrification.
6. Substituting methoxyl (-OCH3) for hydroxyl groups (-OH) in conventional cryoprotective agents can decrease viscosity, increase permeability, and reduce the critical cooling rate necessary to avoid ice formation.
7. Chilling injury can be eliminated by introducing the vitrification agent with a hypertonic concentration of non-penetrating solutes.
8. In cryonics, with a minor proprietary modification, M22 can be used in whole body perfusion without causing severe edema that has been a problem for some other solutions.

It goes beyond the scope of this text to fully discuss the technical details of each of these discoveries in detail but a number of these breakthroughs are worth mentioning.

Perhaps the most important conceptual breakthrough for formulating vitrification solutions with low toxicity and strong resistance against ice formation was the discovery that high concentrations of (penetrating) cryoprotective agents do not necessarily increase toxicity. Contrary to conventional cryobiology expectations, Fahy et al., found that weaker glass formers favor higher viability. They proposed a new compositional variable called qv* to predict the general toxicity of vitrification solutions. Using qv* they made the counterintuitive decision to substitute a higher concentration of the weaker glass former ethylene glycol for propylene glycol to create a

solution called Veg, which produced a substantial increase in cellular viability over older vitrification solutions. A proposed explanation for this phenomenon is that vitrification solutions containing permeating cryoprotectants with a higher qv* leave less water available for hydrating biomolecules, compromising intracellular viability.

Another important breakthrough was the discovery of synthetic "ice blockers." Naturally occurring antifreeze proteins that inhibit heterogeneous nucleation have been suggested to assist in vitrification of complex biological systems. Limited supply, and the costs of such anti-freeze proteins, have been major obstacles in using them for organ preservation; but in 2000, Brian Wowk et al proposed that the property of selective binding to heterogeneous nucleators could also be achieved by using synthetic polymers. It was found that a copolymer consisting of 80% w/w low molecular weight polyvinyl alcohol (PVA) and 20% vinyl acetate substantially reduced ice formation when added to standard cryoprotectants. This copolymer is now being sold as Supercool X-1000 by the cryobiology company 21st Century Medicine.

Another polymer, polyglycerol (PGL), was found to selectively inhibit bacterial ice nucleation and complement the more general action of PVA in inhibiting ice nucleation. This polymer is currently being sold as Supercool Z-1000, and the combination of the two enables inhibition of ice formation that is superior to either of the two polymers alone. By lowering the minimum concentration of cryoprotectant(s) needed to vitrify, and thus lowering the total viscosity of the solution, the addition of X-1000 and Z-1000 represented another step towards reversible organ vitrification.

It has been long understood that absent ice formation and toxicity there are other forms of injury associated with cooling to low temperatures. One of the distinguishing features of M22 is that it is introduced to organs in a hypertonic concentration of non-penetrating solutes to eliminate this so called "chilling injury."

The remaining challenges in perfecting vitrification for whole organs include further reductions of cryoprotectant toxicity and refining cryoprotectant perfusion and unloading protocols to achieve complete equilibration of the vitrification solution to permit long term storage at cryogenic temperatures and successful recovery. In principle, there is little

difference between the state of the art in today's cryobiology research and the technologies that are utilized in human cryopreservation. As we shall we see later, the practice to improve cryonics procedures has been one of the key drivers of contemporary vitrification research.

Neural Cryobiology

There has been relatively little interest in cryopreservation of the whole brain. Notable exceptions include the feline brain cryopreservation studies by Isamu Suda in the 1960s and more systematic neural cryobiology studies by Gregory M. Fahy in the early 1980s. Robert J. White has discussed the prospects of brain cryopreservation but in his own published work confined himself to whole brain hypothermic preservation. Of related interest are the whole-body high subzero resuscitation experiments of rats and hamsters that were conducted by Audrey Smith, Radoslav Andjus, and James Lovelock.

Two major reasons why neural cryobiology has so remained a relatively ignored part of cryobiology is that practicing researchers fear being associated with cryonics and the controversy surrounding other applications of neural cryobiology such as whole brain transplants.

A good historical and scientific overview of neural cryobiology up until 1988 is available in the article "The Cryobiological Case for Cryonics" that was published in the March 1988 issue of *Cryonics* magazine. This article presented evidence that even the relatively crude cryopreservation techniques of the 1980s could provide robust ultrastructural protection of the brain.

Also, the high-subzero rat and hamster resuscitation studies of Audrey Smith and Radoslav Andjus corroborate the premise of cryonics that brains can be cooled to subzero temperatures and restored to functionality. However, in the chapter "Problems of Resuscitating Larger Animals" in her seminal book *Biological Effects of Cooling and Supercooling*, Audrey Smith wrote:

> So far no technique has been evolved for perfusing individual organs or the whole mammal with glycerol and removing it without damage. If this could be done it might be possible to cool the intact mammal to and resuscitate it from temperatures as low as -70 degrees Celsius. Long term storage of frozen

> mammals might be considered. It must be emphasized that there is no prospect of accomplishing this in the near future.

Since Smith wrote these words, substantial progress has been made in the cryopreservation of complex organs and toward the perfection of loading and unloading the brain with cryoprotective agents. In particular, the development of low toxicity vitrification solutions has greatly reduced the challenges associated with ice formation that were encountered in past whole body and brain cryopreservation research.

In the late 1990s an ambitious research program was launched to investigate and validate the use of the new generation of vitrification solutions in rat hippocampal slices. In these experiments the investigators were able to recover hippocampal brain slices from -130 degrees Celsius without loss of viability and with excellent ultrastructural preservation. The most successful results were obtained using a high molar vitrification solution called VM-3 that incorporates a carrier solution aimed at mitigating chilling injury and two proprietary ice blockers to inhibit ice formation. In 2007, an announcement was made at the Suspended Animation conference that more sophisticated vitrification solutions incorporating the same principles and new insights were successful in demonstrating maintenance of the ability to exhibit Long Term Potentiation (LTP) in rabbit brain slices after cooling below the glass transition temperature of the vitrification solution and rewarming.

The most logical step in neural cryobiology is to seek consistent reversal of whole brain electrical activity after cryopreservation. The only published precedents for this kind of research are the experiments conducted by Isamu Suda et al. In two papers, published in *Nature* (1966) and *Brain Research* (1974), Suda reported that he measured organized electrical activity in cat brains that were rewarmed after being preserved at -20 degrees Celsius for respectively 45-203 days and 7 years (!). He used cryoprotection with 15% v/v glycerol after storage. As encouraging as these results are, the fact that they appear to be at odds with what can be expected from other organs subjected to such cryopreservation regimes is peculiar.

Research aimed at vitrification of complex mammalian organs, and the practice of cryonics, have contributed to a much improved understanding of

the requirements for successful introduction and removal of vitrification solutions from the whole brain. In particular, the use of software-controlled perfusion allows for a gradual equilibration of the vitrification agent in the brain under precise temperature control to mitigate osmotic injury and cryoprotectant toxicity. As can be seen in Figure 2-1, courtesy of 21st Century Medicine, vitrification can confer good ultrastructural preservation to the mammalian brain.

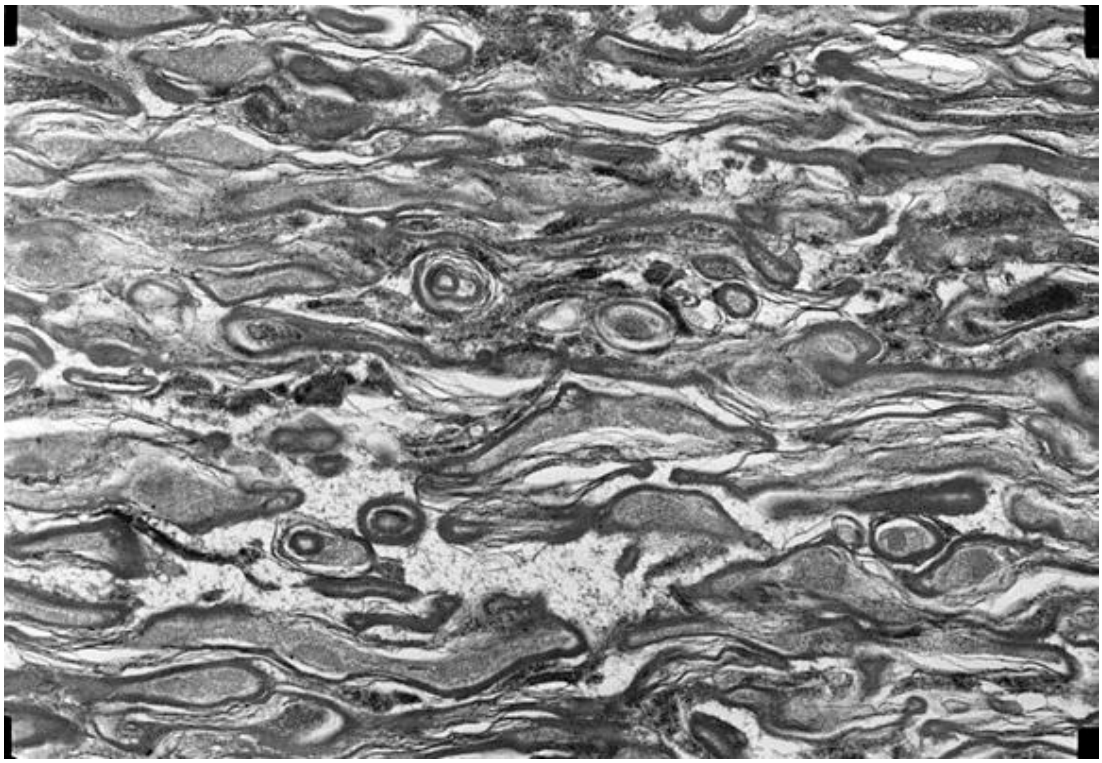

Figure 2-1. Suprahippocampal white matter after perfusion with M22 for 60 minutes at –3 degrees C, cooling to below the glass transition temperature, rewarming, and perfusion fixation.

As the coming decades may witness reports of whole brains being cooled and recovered from below the glass transition temperature without loss of electrical activity, the topic of legal protection of cryonics patients will force itself to the center of bioethical debates about cryonics.

Cell Repair Technologies

The ability to repair cells at the molecular level will almost certainly be necessary before revival of cryonics cases can take place, at least for those who are preserved within the capability of current cryoprotectants. There are four potential targets for cell repair:

1. Treatment of the disease or insult that prompted the cryopreservation of the patient.
2. Repair of ischemic injury resulting from delays between pronouncement of legal death and the start of cryonics stabilization procedures.
3. Repair of damage incurred during the cryopreservation process itself.
4. Reversal of the aging process and associated co-morbidities.

One of the most prevalent misconceptions about cryonics is that its technical feasibility is exclusively wedded to a particular conception of cell repair technologies. While it is correct that advocates and researchers of molecular nanotechnology (MNT) have generally been supportive of cryonics, mechanosynthesis technologies by no means exhaust the options for cell repair. As a matter of fact, there has been an ongoing debate within cryonics about the feasibility and advantages of alternative approaches since its inception.

The biological approach to cell repair starts with the observation that evolution itself demonstrates the technical feasibility of manipulation of matter at the molecular level. The objective of bio-nanotechnology then is to harness, modify, and guide biomolecules to accomplish new tasks. One of the earliest biological proposals to resuscitation of cryonics patients involved using modified viruses to achieve comprehensive cell repair. Another proposal has been to use modified white blood cells to perform reversal of damage. One underappreciated fact about the role of biotechnology is that it can also be utilized prior to the cryopreservation process with the aim of making cells and tissue more tolerant to the cryopreservation process.

An alternative paradigm for cell repair is to use mechanosynthesis, by which molecules are directed towards desired configurations through the use of mechanical means, as opposed to chemosynthesis which involves the interaction of molecules through random motion in an aqueous medium. The most rudimentary proof of concept of mechanically-directed positioning of atoms was achieved in 1988 when researchers at IBM's Zurich Research Institute successfully spelled the letters “IBM” in xenon atoms on a cryogenic copper surface. In 2000 Robert Freitas and Ralph Merkle founded the Nanofactory Collaboration, an effort of researchers associated with various organizations to initiate a focused experimental agenda towards positionally-controlled diamond mechanosynthesis and diamondoid nanofactory development.

The requirements of such envisioned repair technologies in cryonics are a function of the degree of damage that needs to be addressed. For example, for some cryonics patients a combination of protein renaturation, organ replacement and gene therapy may suffice to restore the patient to good health. For cryonics patients with extensive ischemic and cryopreservation damage, cell repair technologies as envisioned by mechanosynthesis researchers will be required.

Rejuvenation

Interventions aimed at rejuvenation will be required in most cryonics patients to prevent the patient succumbing to another age-related disease shortly after revival. For a small subset of cryonics patients, halting or slowing the aging process might be sufficient, but it is reasonable to assume that many patients would also prefer to bring their biological age to a level of their own choice.

There are broadly two modes of thought about rejuvenation in cryonics. One perspective argues that technologies that are powerful enough to repair cell damage at the molecular level will also be powerful enough to control and reverse the aging process. In this scenario, control of aging and morbidity will be one of the medical applications of molecular nanotechnology. This reasoning has also played an important role in the decision of some cryonics advocates to elect neuropreservation under the assumption that molecular

technologies that permit repair of the brain can also grow a new body. Ultimately, a very mature nanotechnology could be used to induce warm biostasis, which would bring all the elements of the cryonics program under the nanotechnology rubric.

Not all advocates of cryonics are persuaded by such appeals to the power of mature nanotechnology. They advocate separate research into interventive biogerontology and rejuvenation. Absent the perfection of nanomedicine, achieving control over the human aging process will provide additional corroboration for the cryonics program. A separate argument for such research is that if the aging process can be slowed or reversed in humans, the need to cryopreserve people who are afflicted with age-associated illnesses will be reduced. As a consequence, the practice of human cryopreservation would be confined to diseases and insults that are resistant to control over the aging process.

The most ambitious and well-publicized research program that aims to use regenerative medical procedures to defeat aging is SENS (Strategies for Negligible Senescence). The SENS approach, as advocated by Aubrey de Grey and his colleagues, distinguishes itself from most conventional biogerontology research by emphasizing a results-driven approach to repair age-associated damage as opposed to conducting research to elucidate the mechanisms that drive the aging process. The advantage of aiming at actual rejuvenation is that the efficacy of interventions can be assessed in a relatively short time-span, as opposed to interventions that aim to slow down the aging process or extend the maximum life span.

The SENS program identifies the following biological manifestations of aging for clinical intervention:

1. Cell loss and tissue atrophy.

2. Oncogenic nuclear mutations and epimutations.

3. Cell senescence (death resistant cells).

4. Mitochondrial mutation.

5. Intracellular aggregates.

6. Extracellular aggregates.

7. Random extracellular cross-linking (tissue stiffening).

The SENS program has been criticized along two lines, which I will call "external" and "internal" criticisms. At the most general level, SENS, and its most prominent advocate Aubrey de Grey, has been charged with raising expectations that this program can succeed in the absence of experimental results, within an optimistic projected timeline. Essentially, since all the research objectives of SENS are falsifiable in principle, this debate concerns not so much the technical credibility of the project as the question of how researchers should communicate their objectives and projected achievements.

Internal criticisms are concerned with the internal coherency of the SENS program and its technical details. Cryonics advocate Benjamin Best has argued that two of the seven strategies of the SENS program, making copies of mitochondrial DNA in the nucleus (and importing the resulting proteins back into the mitochondria) and deletion of genes that contribute to cancer, should not be considered "repair" but strategies to prevent aging. A more fundamental objection he raises is that SENS ignores the role of nuclear DNA damage as a cause of (brain) aging. Other objections question whether SENS is actually the most results-oriented approach considering the possibility that the aging program is controlled by a finite number of upstream genes that are susceptible to modification. A more conceptual criticism is that, in practice, the difference between the traditional biogerontology approach and the engineering approach that SENS advocates is a matter of degree, not principle. Interventions that aim to restore an organism to a youthful state allow for short-term validation but longer term adverse consequences cannot be ruled out. As such, the practical implementation of the SENS approach may require substantial modifications in how society thinks about patient autonomy and regulating new therapies.

Historical Development of Cryonics Procedures

From the moment of its original conception, the practice of cryonics has relied upon past and future progress in the science and practices of mainstream

cryobiology and medicine. The commonly held view of cryonics as the practice of freezing humans without any form of cryoprotection has not been endorsed by any of the major cryonics providers. Cryopreservation without protection against ice formation (a so called “straight freeze”) is only practiced in cases where extensive ischemia prevents cryoprotectant perfusion. Even before the first attempted cryopreservation of a human, the biophysicist Dr. Dante Brunol had outlined a protocol that incorporated the use of cardiopulmonary support after legal pronouncement of death, extracorporeal perfusion, and the use of cryoprotective agents.

During the late 1970s and early 1980s myocardial recovery researcher Jerry Leaf and kidney dialysis technician and cryonics researcher Michael Darwin introduced contemporary extracorporeal bypass techniques and equipment to the practice of cryonics. Extracorporeal circulation is used during cryoprotectant perfusion of the patient and, in remote cases, a portable perfusion unit may be used to replace the blood of the patient with an organ preservation solution. In the mid-1980s the Alcor Life Extension Foundation formulated a whole-body blood substitute called MHP, a high potassium “intracellular” solution that incorporates hydroxyethyl starch, mannitol, HEPES and a number of components to protect against free radical damage and support metabolism during the hypothermic (above 0 degrees C) phase of cryonics.

During the early years of cryonics DMSO was routinely used as the cryoprotective agent of choice, but this practice was progressively abandoned in favor of glycerol because DMSO was observed to increase edema during the cryoprotective perfusion of whole-body patients. Ultrastructural studies of brains perfused with glycerol indicated that patients could benefit from higher concentrations of glycerol. Unlike DMSO, in a suitable carrier solution (such as MHP) glycerol can be used as a mono-agent at high concentrations. In the 1990s the target concentration for glycerol perfusion at the Alcor Life Extension Foundation was increased to ~7.5M until this agent was eventually replaced by the new generation of vitrification solutions.

One other important consequence of the introduction of extracorporeal perfusion technologies is that it allowed for introducing the cryoprotectant in a controlled, linear fashion to avoid osmotic shock. Such ramped cryoprotectant

perfusion requires the addition of a recirculating reservoir to the perfusion circuit. A typical ramped cryoprotectant perfusion starts with the perfusion of the carrier solution or low concentration of the cryoprotectant agent in carrier solution and gradually pumps the high concentration solution to the recirculating reservoir where it is mixed with the carrier solution and introduced to the patient. Inline and manual refractometry measurements are taken to monitor and control the progressive increase of the cryoprotective agent. Cryoprotectant perfusion is complete when the refractometry readings of the venous effluent indicate that equilibration of the tissues at the target concentration has been achieved.

In 2000 the Alcor Life Extension Foundation replaced glycerol with the vitrification agent B1C for neuropatients. To reduce viscosity, B1C was quickly followed by the nearly-identical solution B2C, a hyper-stable multi-component vitrification agent that incorporates many recent discoveries in cryobiology, such as the use of high concentrations of weak glass-formers and the addition of ice blockers to increase resistance against ice formation with reduced toxicity. B2C was introduced in a carrier solution that is optimized for inhibiting chilling injury and for enhanced performance of the ice blockers.

In 2005, B2C was replaced by M22, the least toxic vitrification solution usable at high concentrations in the cryobiology peer reviewed literature to date. In addition to the discoveries embodied in B2C, M22 incorporates the use of methoxylated cryoprotectants to further reduce toxicity and to improve equilibration. An alternative formulation of M22 is available for whole body patients that permits the use of this agent without increasing edema during cryoprotective perfusion. Initial perfusion of M22 is conducted ~0 degrees C and the temperature is further dropped to ~ -3 degrees C when 50% of target concentration has been reached.

After cryoprotectant perfusion the patient is gradually cooled to liquid nitrogen temperature. Older cooling protocols used a combination of dry ice and silicone oil to cool the patient (Alcor) or the gradual lowering of the patient into the dewar to minimize thermal stress and fracturing.

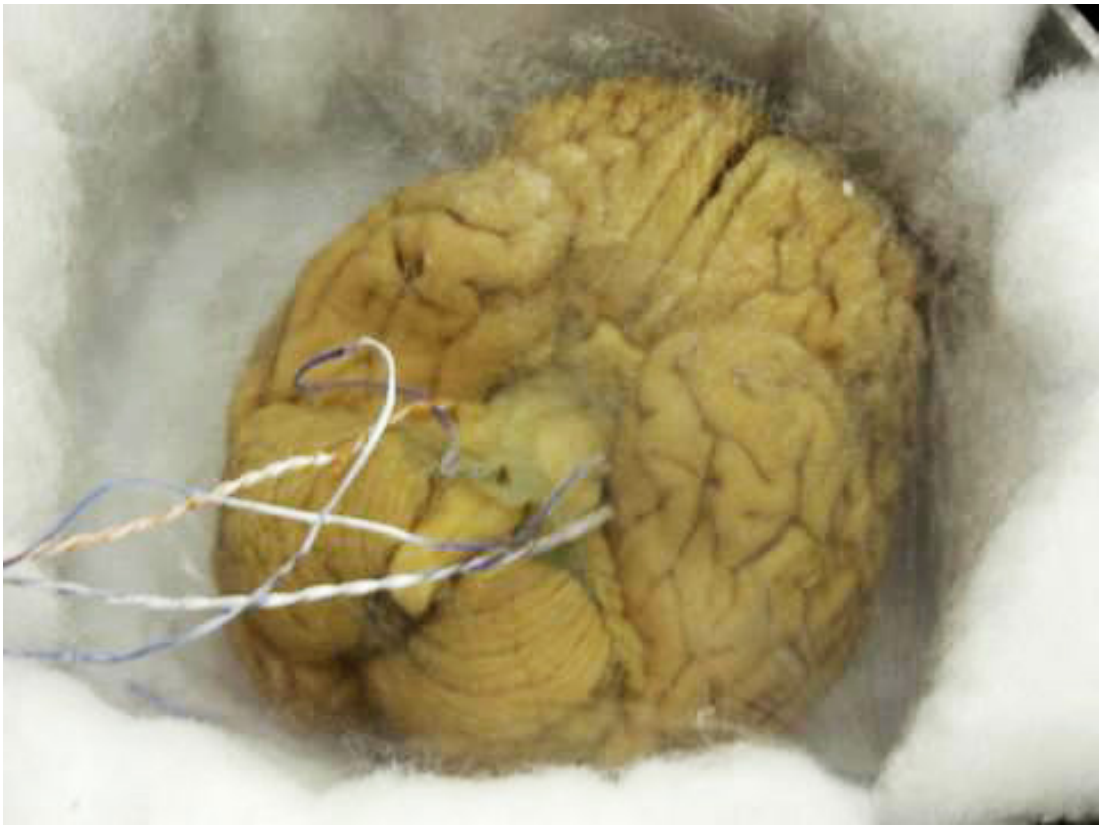

Figure 2-2. Vitrified human brain of Alcor patient A-2077 under liquid nitrogen.

Since the mid-2000s both major cryonics organizations have used a computer-controlled cooling box that injects liquid nitrogen vapor to cool the patient down to liquid nitrogen temperature. The protocol for patients who have been perfused with a vitrification solution is to lower the temperature as fast as possible to near the glass transition temperature of the vitrification solution and then to slowly lower the temperature over days to minimize fracturing. Patients are either maintained in a hard vacuum dewar (Alcor) or a soft vacuum cryostat (Cryonics Institute) for long term care.

Effective cryopreservation requires prompt intervention after cardiac arrest and pronouncement of legal death. To achieve this, Alcor attempts to arrange a “standby” for a member when there is advance notice or high risk of legal death. During standby a team of staff members and medical professionals is deployed to the location of the terminal patient to minimize

the delay between legal pronouncement of death and the start of cryonics stabilization procedures.

The objective of cryonics stabilization procedures is to maintain viability of the brain by contemporary medical criteria. Modern stabilization technologies consist of three distinct procedures:

1. Cardiopulmonary support to restore circulation and respiration, circulate medications and enhance external cooling.

2. Induction of hypothermia to depress metabolism and protect the brain.

3. Administration of medications to depress metabolism, increase cerebral blood flow, prevent and reverse blood clotting, protect the brain, rehydrate the patient, maintain physiological pH and prevent edema.

In remote cases where the patient requires transport to the cryonics facility, usually by air, a whole body blood washout is performed to enhance cooling and protect the brain against ischemia-induced perfusion impairment during cryoprotective perfusion.

In ideal circumstances where there is a negligible delay between pronouncement of legal death and the start of cryonics stabilization procedures, viability of the brain by contemporary criteria can be maintained until the early stages of cryoprotective perfusion, after which the aim becomes excellent ultrastructural preservation of the brain. In general, the objective of applied cryonics research is to delay the loss of cerebral viability to progressively later stages. One recent development that aims to prevent fracturing is to maintain patients at a temperature just below the glass transition temperature of the vitrification solution (-123 degrees C for M22). Prototypes of such intermediate temperature storage units have been designed for neuro and whole body patients. A number of neuropatients at Alcor are stored at intermediate temperatures.

Anticipated near-term developments in cryonics technologies include the use of cyclic lung lavage with chilled perflurocarbon liquid to increase the cooling rate of cryonics patients during stabilization, enhanced computer control of whole-body cryoprotectant perfusion, and the conduction of

cryoprotectant perfusion with vitrification solutions at remote locations, with subsequent transport of the patient at dry ice temperatures.

Cryonics and Suspended Animation

The most controversial aspect of cryonics is the likely delay between stabilization of the patient and treatment. It is often assumed that cryonics would gain in credibility if this separation between stabilization and treatment could be overcome.

This belief rests on the confusion of the ideas of suspended animation and cryonics. It is certainly the case that the technological feasibility of cryonics will appear more plausible if humans can be recovered from liquid nitrogen temperatures without any adverse effects, but perfecting human suspended animation would not make cryonics redundant because the defining feature of cryonics is to stabilize patients that cannot be treated by contemporary medicine. As long as there are diseases and traumatic events for which there are no cures or treatments, cryonics will remain available as an experimental form of critical care medicine.

A related misunderstanding is the failure to distinguish between the practice of cryonics and the science of cryobiology. Almost as old as the idea of cryonics is the objection that it is unethical and unscientific to offer a procedure that has not been proven to work. As should have become clear from the preceding exposition, cryonics cannot be proven to work because its defining feature is to stabilize a patient who cannot be treated by contemporary medicine in anticipation of future medical advances. As such, cryonics should not be evaluated as an experimental science but as a form of decision-making under conditions of uncertainty.

In its most abstract form the argument in favor of cryonics is a variant of Pascal's wager: People who do not make cryonics arrangements are in the control group, and those who make cryonics arrangements are in the experimental group. So far the control group is not doing very well and the fate of those who have made cryonics arrangements is uncertain.

A variant of this argument is to present cryonics as the conservative medical course of action. We do not know if critically ill patients can be

resuscitated and restored to health in the future, but we cannot err on such serious matters of life and death.

Some advocates (and critics) of cryonics have gone a step further and have assigned probabilities to the prospect of successful resuscitation of cryonics patients. This approach raises a lot of complicated issues. For example, should such estimates concern only scientific and technical events or should social and legal events be included as well? Obviously, it is important to distinguish between events that are independent and dependent to perform meaningful probability calculations, which pose a non-trivial problem.

A more fundamental objection was raised by the mathematician and cryonics activist Thomas Donaldson, who argued that revival is not an independent event that will occur beyond our control but will be subject to the efforts of cryonics advocates. It should also be noted that the very question about the probability of revival is problematic because cryonics patients have been cryopreserved under a wide variety of circumstances raging from cases with minimal ischemic delay, rapid cooling, and good equilibration of the vitrification solution to cases where the patient has been frozen in the absence of a cryoprotective agent after a long ischemic interval.

As a form of decision making under uncertainty, cryonics cannot be comprehensively proven, but progress in experimental science can progressively move conditions that must be met to resuscitate cryonics patients from the domain of informed speculation to science fact. Ultimately, the only element of uncertainty left in the cryonics program will concern the fate of a patient whose condition cannot be treated by the prevailing state of medicine.

Cryonics as an Elective Medical Procedure

Our growing understanding and recognition of the neuroanatomical basis of identity, and progress in neural cryobiology and regenerative medicine, will progressively pressure medicine to abandon cardiovascular criteria for pronouncement of death in favor of procedures to preserve personhood until medical treatment will be available in the future. The growing recognition that

patients should not be abandoned simply because other organs give out will increase demand to accept cryonics as an elective medical procedure.

Broader acceptance of this concept will also transform the nature of human cryopreservation from a form of emergency medicine to a form of experimental critical care medicine. As a consequence, the ischemic delays and improvised volunteer-driven care that characterizes contemporary cryonics will give way to the performance of cryonics procedures in the hospital, and the development of human cryopreservation as an evidence-based branch of medicine.

Although current cryonics organizations try to make the best of an unfavorable situation by employing standby teams to reduce brain injury, much improved quality of care would be possible if cryonics procedures could start at a point where medical professionals (with informed consent of the patient and/or family) would determine that further treatment of the patient with contemporary technologies would be futile, or even counter-productive.

When this determination is made, conventional life support for the patient would be terminated and deep hypothermia would be induced using cardiopulmonary bypass. At deep hypothermic temperature, the patient's blood would be substituted with an organ preservation solution to reduce blood complications associated with lower temperatures. When the patient's core temperature approached the freezing point of water, the organ preservation solution would be replaced by a vitrification agent to allow an ice-free descent to cryogenic temperatures for long term care. After lowering the patient's temperature below the glass transition point, the patient would be maintained at intermediate temperatures to reduce the risk of thermal stress and fracturing that would occur at lower cryogenic temperatures.

Cryonics as an elective medical procedure will not just be an option for those who have been diagnosed with a terminal disease, but will also present a new paradigm to treat patients who suffer severe ischemic attacks or traumatic brain insults. In current medical practice, when such patients are successfully resuscitated, the predominant outcome is a persistent vegetative state or minimally conscious state (MCS). Such outcomes trigger much debate among medical caregivers, lawmakers, and bioethicists concerning the moral status of

such patients, the authority of relatives to withhold treatment, and the allocation of medical resources.

It is now a well-established scientific finding that brain cells do not immediately "die" after severe hypoxic insults such as stroke or cardiac arrest. Actual necrosis (or apoptosis) takes many hours, or sometimes even days (as a result of a phenomenon called "delayed neuronal death"). Unfortunately, ischemic insults to the brain exceeding 5-10 minutes are often sufficient to set parts of the brain on an irreversible path to destruction, even if resuscitation of the patient is possible. Currently, there is no single approved neuroprotective agent that can protect these brain cells. Although hyperacute combination therapy and postresuscitation hypothermia may offer hope for people suffering severe hypoxic insults, most of such patients currently would be better served by placing them in a state of biostatis before the complete ischemic cascade can complete its course.

Although cryonics is often dismissed as speculative, it can be persuasively argued that long term preservation of the neuroanatomy of such patients through vitrification offers better prospects for recovery of the person than the current practice of resuscitation after the insult. Such a practice could also offer a truce between those who advocate that life should be maintained at all cost and those who advocate a definition of death that involves the presence of personhood.

Legal Recognition of Cryonics

We may assume that as cryonics continues to grow it will at some point be covered by specific regulations. So far there has been little consensus about the legal framework that cryonics will need to operate in. As a consequence of publicity surrounding the cryopreservation of baseball legend Ted Williams by Alcor, the Cryonics Institute in Michigan was legally designated as a cemetery. Such a regulatory approach treats cryonics patients as dead people without legal protection beyond the regulations that cover cemeteries. Another consequence of this unfortunate designation is that cryoprotectant perfusion needs to be performed under the supervision of a licensed funeral director. An alternative approach has been pursued by the Alcor Life Extension

Foundation, which receives its patients under the Uniform Anatomical Gift Act (UAGA).

The current lack of meaningful legal recognition of people in cryostasis presents two problems. First, it prevents patients for employing the most effective stabilization procedures to inhibit brain injury after pronouncement of legal death. This reinforces the perception that cryonics is a futile attempt to preserve the brain. In fact, the ischemic delays that are routinely associated with contemporary cryonics are not an intrinsic property of cryonics itself, but the logical consequence of the lack of legal protection of cryonics patients.

If cryonics is recognized as an elective medical procedure, or the practice of cryonics is recognized at least to such a degree that there can be a smooth transition between the terminal phase of the patient and the start of cryonics procedures, such undesirable events will be greatly reduced. In the case of unexpected death, homicide, or other unnatural events, mandatory autopsy requests will seriously interfere with efforts to protect the brain of the patient.

The second problem following from the lack of legal recognition of cryonics patients is that medical and legal practice will be increasingly out of sync with scientific and bioethical developments. One of the two accepted criteria for determination of death—irreversible cessation of all functions of the brain—requires a serious reconsideration of the legal status of cryonics patients in light of recent developments in neural cryobiology. If scientists, medical practitioners, and bioethicists learn more about the ability to restore organized electrical activity after vitrification of brain slices and, in the foreseeable future, whole brains, cryonics patients can no longer be considered dead using brain death criteria. Cardiorespiratory criteria will also be inadequate, just as patients undergoing hypothermic circulatory arrest procedures are not considered dead.

One important issue in the upcoming debate concerning the legal status of cryonics patients will revolve around the concept of reversibility. The question of whether cryonics patients will be revived in the future cannot be answered by consulting contemporary scientific and medical knowledge. This characteristic of cryonics would seem to set cryonics apart from other medical procedures, but upon closer inspection such a distinction fails to recognize that

all medical prognoses are probabilistic in nature. The question, therefore, is what kind of expectations can be considered reasonable in light of the existing experimental research and what the ethical consequences are if we come down on either side of the issue.

The issue of reversibility also draws attention to the question of what should be considered a successful resuscitation. In contemporary medicine it is not conventional wisdom to consider a treatment for a serious disease or insult a failure if the person is not restored in exactly the same state as before the event. As a matter of fact, significant segments of modern society believe that medical care should be continued even if there is empirical evidence that the neuroanatomical basis of personhood has been irreversibly damaged. From this perspective, the objective of cryonics looks relatively modest in comparison because it incorporates a modern recognition of what it means to be human.

Contributions of Cryonics Research

Many scientists who are sympathetic to the objectives of human cryopreservation nevertheless claim that cryonics research risks reallocation of resources from more legitimate research efforts. This is a misunderstanding, for two important reasons. The first reason is that it cannot be assumed that cryonics research funding is competing with mainstream cryobiological research. Most of the financial support aimed at researching cryonics procedures has originated from individuals and organizations who have taken an interest in cryobiology for the sole reason of developing and perfecting technologies to place critically ill people in cryopreservation.

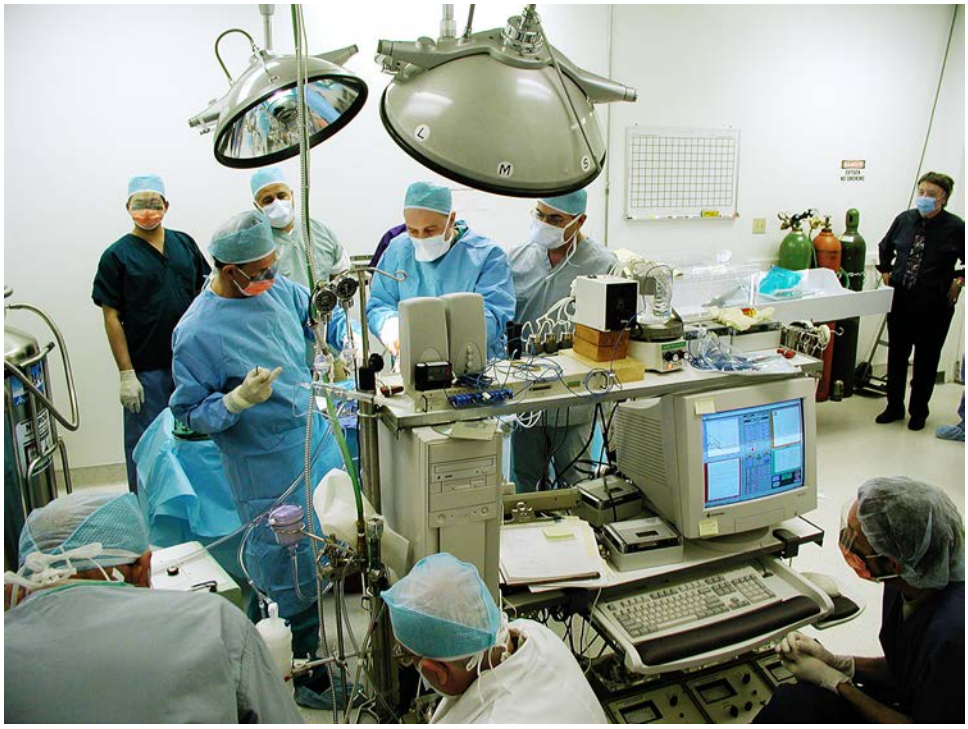

Figure 2-3. Cryoprotective perfusion preparations at Alcor in mid-2002.

The second reason, which has more profound implications, is that cryonics research in practice aims to solve many of the same problems that are currently being investigated in mainstream cryobiology research and stroke research. Cryonics research is not just comprised of experimental work to resuscitate complex organisms from subzero temperatures, but includes research efforts such as vitrification of organs, eliminating cryoprotectant toxicity, automation of cryoprotectant perfusion equipment, multi-modal pharmacological treatment of cerebral ischemia, and other related topics.

The most profound example where the practice of cryonics has stimulated great strides in mainstream cryobiology research is the design of low toxicity vitrification agents. The desire to completely eliminate ice formation in cryonics has triggered ongoing research efforts to achieve this goal. This, in turn, has produced a stream of experimental work and peer reviewed papers that are of great practical importance to cryobiology as such. Even in the case of neural cryobiology it is hard to underestimate the importance of being able to store neural tissue without loss of viability and

ultrastructural alterations at low temperatures for neuroanatomical and pharmacological studies.

Another example of the lasting contributions cryonics can make to society is the design and experimental validation of whole body hypothermic organ preservation solution. The goal to lower a patient's body temperature to just above 0 degrees Celsius without neurological damage during cryonics stabilization procedures finds a close counter-part to efforts in emergency and military medicine to stabilize cardiac arrest patients and severe trauma victims. Efforts to design universal organ preservation solutions in cryonics have great relevance to such efforts and vice versa.

There are a number of research areas where cryonics researchers and practitioners have not only contributed to mainstream science, but where their efforts have also anticipated subsequent developments in medicine. For example, the technologies that are now being proposed to stabilize legally dead people who have elected to donate their organs have been routine in cryonics for decades; also consider the use of mechanical cardiopulmonary support devices, the induction of hypothermia, and the use of anticoagulants and neuroprotective interventions.

One researcher involved with the Alcor Life Extension Foundation anticipated and built a prototype of an inspiratory impedance threshold valve to improve cardiac output during external chest compressions before this technology was brought to the commercial market and endorsed by the American Heart Association. Cryonics research led to the development of Hextend, an artificial blood plasma substitute now used in clinical medicine. In the mid-1990s researchers associated with cryonics used combinational pharmacotherapy to resuscitate dogs from up to 16 minutes of normothermic ischemia, anticipating the growing embrace of multi-component pharmacological strategies to limit brain injury after cardiac arrest and stroke.

The importance of rapid cooling in cryonics cannot be overestimated, and cryonics researchers and engineers have put a lot of time and effort in developing practical strategies. As a consequence, the typical cooling rates that are achieved during cryonics stabilization procedures in the field routinely outperform those observed in emergency medicine and the treatment of heat stroke. Researchers who participate in the field of cryonics continue to

develop more powerful cooling methods such as the use of cyclic lung lavage, also known as liquid ventilation. When applied as a cooling method, this uses the lungs as an endogenous heat exchanger with chilled perfluorocarbon liquid. Because it does not require invasive surgery and can be achieved with endotracheal intubation, it can be applied by paramedics in the field. The most recent cyclic lung lavage technologies can produce cooling rates approaching those that were previously only possible with the use of extracorporeal bypass.

As this short survey of cryonics to the general body of knowledge and medical practice shows, there are important benefits of cryonics research that benefit science, medicine and society in general.

The Cultural Reception of Cryonics

When cryonics first entered the public conscious in the 1960s, its early advocates believed that advances in cryobiology would give rise to a growing acceptance of cryonics among the general public, scientists, and medical practitioners. The expectation was that if more elements of the cryonics program would be supported by experimental science, the number of people making cryonics arrangements would continue to grow. As we know now today such an optimistic vision did not materialize. As a matter of fact, discussion of cryonics in the popular media seems strangely disconnected from the scientific, technological, conceptual, and organizational advances in cryonics. Comments from cryobiologists and bioethicists do not indicate even the most basic understanding of contemporary cryonics practices.

A persistent misconception about advocates of cryonics is that they want dead people to be frozen so that they will be revived in the future. There are no public advocates of cryonics who would phrase the case for cryonics in this matter, and not a single existing cryonics organization is offering cryonics services with a guarantee of future revival.

The objective of cryonics organizations is not to revive the dead, but to stabilize patients at low temperatures to prevent death. To accomplish this objective, existing major cryonics organizations offer stabilization services to prevent neurological damage after pronouncement of legal death and use vitrification solutions to eliminate freezing. Because even the most superficial

investigation of contemporary cryonics practices could remove these misconceptions, one wonders why such incorrect misconceptions about cryonics persist.

Having no informed opinion on the matter, an expert who is consulted on the technical feasibility of cryonics usually expresses a form of popular bias. In his own field, an ill-informed statement could cost him dearly, but in the case of cryonics there are no significant costs. Because there are no costs to holding irrational beliefs about cryonics, (presumed) experts can be rationally irrational, to use a phrase from the economist Bryan Caplan.

Another factor that contributes to the poor public quality of cryonics is that humans have not evolved to think in probabilistic terms and accept uncertainty. As a consequence, cryonics is not discussed as a subset of rational decision making under uncertainty but as a set of scientific conjectures that should be resolved first before the practice can be endorsed. In the absence of that, cryonics organizations are accused of "selling false hope." But the fact that humans generally endorse the view that decision making can be rational in absence of absolute knowledge of future events indicates that more basic psychological mechanisms may prevent a more dispassionate assessment of the cryonics protocol.

One school of thought in cryonics attributes the limited appeal of cryonics to the temporal separation between patient stabilization and patient treatment. A decision to make cryonics arrangements is a conscious expression to permit resuscitation in a far and unknown future. In this sense, cryonics is fundamentally distinct from contemporary medical practice where no contemplation of the nature of a future existence is required as a part of medical treatment. The anxiety produced by the concept of cryonics is not confined to the person contemplating cryonics but extends to family members and close relatives.

There are numerous documented cases where partners and hostile relatives have resisted the cryonics arrangements of family members. Often such resistance is motivated by financial gain, but feelings of abandonment and lack of closure contribute as well. After a long struggle with disease, a natural response is to seek closure. Because cryonics does not provide this kind of closure, it can be seen as something that fundamentally changes the

nature of human bereavement. As such, the hostility that is sometimes encountered in public debates about cryonics does not reflect informed skepticism but anxiety that is produced by the prospect that cryonics is credible.

Figure 2-4. James Hiram Bedford (born on 20 April 1893), a psychology professor, was the first person whose body was cryopreserved in 1967 and who remains a patient at Alcor today.

As a consequence, advocates of cryonics are increasingly investigating the psychological, sociological, and moral topics surrounding cryonics. One notable perspective is that when the expected lifespan is inherently indeterminate, there will be a growing disposition towards human cooperation, because there will be no fixed limit to the number of individual encounters between individuals. Public policies will increasingly be aimed at long term goals and stability instead of aiming at short-term gratification on the assumption that we are all dead in the long run. In this sense, cryonics has profound transformative properties, but it would seem these will further the progress of mankind.