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EDITORIAL MATTERS

Errata

We apologize for the incorrect use of the words "cell walls" to describe animal cell membranes in the article "A New Theory of Freezing Damage" which appeared in the "Science Updates" column by Thomas Donaldson in the March issue of CRYONICS. As several callers, one of them a biologist who was irate since he has corrected us on this several times before, pointed out: "Only plants have cell walls. They are made of cellulose and they are not injured during

freezing! Animals have cell membranes. Please get this straight since we have enough scientific credibility problems in cryonics already!"

He's right, and it's an error we'll try to avoid making again.

THE ROAD TO THE BEST

Recently I did something the editor of any magazine should do from time to time. I sat down and reviewed CRYONICS from issue #8, which was published in March of 1981, through issue #68, published in March of 1986. It was an eye-opening experience! Issue #8 was 6 pages long, on 8-1/2" by 11" paper, and was run off by copier. That's a far cry from our typical 30+ pages with a quality cover and a heavy commitment to illustrations, art, and photographs. We've come a long way.

But the longer you edit a magazine like CRYONICS, the more you come to realize that the journey is never over. At least, it's never over if you're heart and soul are in it! Part of any successful enterprise is a constant striving for improvement, for expanding horizons. Over the past few years we've made a special effort to improve CRYONICS; its look, its readability, and its content. I think you'll agree we've made some gratifying progress. But there are still some areas where real improvement is possible. And they are areas which many of you, our readers, could help with.

Any magazine quickly builds a pool of regular contributors who are the backbone of the enterprise. That's good and necessary. But variety is also important. We want to see more contributors to CRYONICS and we want to see a wider range of topics covered. In part, I would like to see this because I personally am interested in all sorts of things I don't have the time or the opportunity to research and write about. From conversations with many of our members and readers I know that many of these same issues which fascinate me, fascinate you. What's more, I know that a fair number of you have given these issues a great deal of thought and not only have valuable things to communicate,

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but the skills to communicate them with. I know that this is possible because I've seen our letter column grow. Until about a year ago, we received few letters to the editors. Now, we often get in more than we can print.

To this end, I thought it might be worth the time and space to throw out some of these topics as possible starting points for articles or "Letters to the Editors." I should stress that these areas I'm suggesting are meant to be suggestive, rather than all-inclusive. You may have other, more interesting topics to expound upon:

SAFETY. One of the principal ways young people are likely to die is by accident. Indeed, one recent study indicates

that more than 1% of all people between the ages of 10 and 34 will die in accidents by the year 2000! That's a lot of people, and some of them are going to be us. What is the safest car to drive right now? What are the real risks for accidental death and how can they be minimized? What kind of safety features in automobiles, the home, and industry are on the horizon or could be brought to bear in the intermediate or even distant future to cut accidental death rates? I'm vitally interested in the answers to these questions, and I suspect the overwhelming majority of our readers are, too. So, those of you who know about anti-skid brakes, foam-filled gas tanks, air bags, and fail-safe radar, let's see a thoughtful, well researched article from you.

SLICE OF LIFE. What is it like to be a cryonicist out there in the USA or Australia or England? What kinds of problems do you have, what kinds of social difficulties or personal difficulties result from being invaded by the cryonics meme? There've got to be plenty of good stories here. Stories we can all profit from and learn by. There's no Dear Abby for cryonicists, and yet, from talking to other cryonicists on my travels and by phone I know there's surely a need for one. There are problems out there. I know, in large measure because I face some of them too. Every one of us would like to know how you're coping. Incidentally, feel free to make such submissions anonymously.

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We'll respect your confidence.

THE FUTURE. What kind of a world will we come back to? Will our personalities and our minds be modified or "re-paired" as well as our bodies? What kind of technology will be used to revive us? What impact will molecular technology have on day-to-day life and social and ethical systems? This is a fertile area for thoughtful exploration. Science fiction writers and futurists of the past 20 years

missed all the big world-shapers that have recently come on line: small, affordable computers; women's liberation and the impact of birth control on the presence of women in and out of the home; and the increasing power individuals can bring to bear: now one man can sink a battleship, one terrorist can grind a whole segment of the world to a screeching halt!

PHILOSOPHY AND PHYSICS. There are some fascinating things happening in theoretical physics and cosmology that may very well relate to what we're doing. Will the universe last forever or grind to a halt? If the latter is the case, is there anything we can do to stop it? What about quantum mechanics and cryonics? Yes, that's right. There's something called the "many worlds" interpretation of quantum mechanics which, if correct, may have some startling things to say about what really happens to us when we die -- whether we get frozen or not! What about the roots of why we are cryonicists? What is the real, long-term aim of this drive in us for life and the desire to defeat death? Does basic physics and our growing understanding of the universe suggest possibilities other than cryonics for recovering people who've been "given up for dead"?

PROSE AND POETRY. So far, we've avoided running any fiction. We've had three reasons for this: 1) The pressure and backlog of important nonfiction to publish has been great and thus; 2) our standards for fiction are very high; and 3) we've received very little in the way of fiction submissions of any kind. We'd like to see that change. We suspect there may be a few capable fiction writers out there, and we'd like to see your work.

We know there are good poets out there

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because we have seen your work in the pages of cryonics journals in the past -- although not recently. Has the muse withdrawn her touch of inspiration or are there reams of verse out there waiting to be shared? Good poetry makes one think and reflect on what this whole endeavor is all about. At its best, it can open up a new horizon of understanding and meaning. Just recently, as I pored over archival material that had not seen the light of day for nearly two decades, I came across a couple of poems that did all the above things for me. One was by Steven Mandel about his impending suspension. It's mixture of hope and despair, anxiety and calm caught me off guard and left me "softly shaken." It was followed by Jerry White's poem about Steven's subsequent suspension which left me in tears; full of rage and sorrow that the

promise of those words was broken and that Steven didn't make it. Cryonics is a rich field for the chronicler of triumph and tragedy. It would be a terrible shame if in our rush to tomorrow there were none of us who stopped to tell, in simple verse, what the journey was really like.

It's a large part of my job as an editor of CRYONICS to make articles happen. I can't afford to sit back and passively wait for them to come in. I hope this piece has suggested to you as readers that you have an open opportunity. There are great stories to be told out there, much information to be communicated. In the final analysis, you are the only ones who can do that. You are the only people who can keep CRYONICS and cryonics alive. Let us hear from you! -MD-

DON'T DIE TRYING!

Elsewhere in this issue is an article on antioxidants and life extension by Steven Harris, M.D. In the past, we've published a few health related articles, but have by and large avoided covering this area since it is covered well in other periodicals. We've decided to deviate from this a bit this month because we think Dr. Harris' article is interesting and because it offers a rather different perspective on the issue of interventive techniques being practiced by "life extenders" right now. We know from our surveys and from first-hand conversation that many of our readers, if not most, are employing some kind of interventive life extension program which involves ingesting antioxidant drugs, and/or vitamins and minerals. We felt Dr. Harris' article offers a worthwhile word of caution. Furthermore, we feel certain that it is liable to generate some lively debate which just might benefit everyone all the way around. To this end, we are reprinting Dr. Harris' article from the January, 1986 issue of CLAUSTROPHOBIA magazine with the permission of CLAUSTROPHOBIA and Dr. Harris. We invite reader debate and rebuttal and will publish as much of it as space allows.

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DEEP POCKET MADNESS: A WAY OUT?

There is a centuries-old law which in our opinion never should have been on the books in the first place, but which has only really gotten a workout in recent years. Its technical name is "joint and several liability" although it is more commonly known as the "deep pockets" law. It is a classic example of so-called good intentions gone awry in the worst possible way. To those of you with a libertarian or Objectivist background, it will be hard to imagine that this law wasn't drafted by Marx or Lenin.

What the deep pockets law says is that a plaintiff in a legal action brought for personal injury or wrongful death may be assured of recovering the full extent of his or her rightful damages. It allows plaintiffs to reach into the "deep pockets" of the wealthiest or most heavily insured of several defendants even if the richer or better insured defendant is found to be only minimally at fault. Thus, if a defendant were found to bear only 1% of the responsibility for the loss or injury, and the other defendant(s) were insolvent, then the defendant with only 1% responsibility would have to pay the full amount of the damages -- even if that amount was

millions or tens of millions of dollars.

It is probably not news to anyone who owns a television that many trial lawyers have mounted an aggressive and unrelenting advertising campaign to drum up litigation -- or as they put it, to "protect" the rights of the victim. Ads in Los Angeles run for every kind of injury and malady conceivable. One Los Angeles attorney even runs ads for victims of animal bites with his toll-free number which is 1-800-BIG-BITE! Victims and juries have become persuaded that an injury or damage of any kind can be readily translated into cash, whether the person paying has any significant responsibility for the damage or not.

It would be a waste of time and space here to go over the psychology of such parasitic practices. The reader can find a fuller treatment of such psycho and philosophic pathology in the pages of Ayn Rand's *The Fountainhead* or *Atlas Shrugged*, and of the economic aspects of such parasitism in Mancur Olson's "The Rise and Decline of Nations." That such psychology and practices are spreading is painfully apparent, since despite the existence of the deep pocket law for over 200 years, it is only recently that it has come to be so extensively exploited that it is causing a crisis in insurance. If you are wondering why we are discussing this in the pages of *CRYONICS*, it is because the deep pockets law, and the abuses it encourages, have resulted in a crisis in insurance which has profoundly affected our ability to function.

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ALCOR and Cryovita, as well as Trans Time in northern California, have been unable to get liability insurance for our premises, based on our activities. This means that we face eviction from our current quarters and this has caused us to push up our schedule for acquisition of a permanent Southern California facility and to shelve plans for an ambitious 6200-square-foot complex which was to be built near Perris, California. It also means a major curtailment in research and other operations which involve the traffic of personnel through our facilities.

On June 3, California voters will be given the opportunity to go at least part of the way to redressing the injustice represented by the deep pockets law. There will be an initiative on the ballot to curtail the deep pockets law by stripping away its application to noneconomic damages such as pain and suffering. The initiative would leave intact the provisions of the law which allow victims deep pocket access to resources for actual damages, such as medical costs and lost earnings. This is hardly fair, but it is an improvement. The proposed law, known as the Fair Responsibility Act, deserves your consideration and, we believe, your vote. If this law or similar legislation is not soon enacted, it will not just be cryonics services that you'll be unable to get. Construction, transportation, and other basic economic necessities will soon be disrupted. One of our members who owns a multimillion dollar business is faced with the same problem we are, and will be forced to close his operation down if his state

does not provide similar legislative relief.

For years now, the cost of every aspect of public and private services has been steadily escalating due to skyrocketing insurance costs directly resulting from Alice-In-Wonderland judgements. It is long, long overdue to put a stop to this. On Primary Election day, June 3, 1986 those of us who are California residents will have an opportunity to do so.

LETTERS TO THE EDITORS

Dear Editors:

Regarding "Tightrope" in the February CRYONICS, and the very fact that you are willing to write full reports on suspensions, including problems encountered and inadvertent errors, makes me feel better about choosing ALCOR. It tells me that you have an attitude virtually identical to the rest of the medical profession. Your technical reports have the same flavor as those my wife transcribes for doctors reporting on operations.

Since "Saints, Madmen, and Cryonics" referred to memes, I feel drawn into that discussion. My view of this topic has matured a lot since my last letter (January, 1985), and is still changing.

Marvin Minsky (of artificial intelligence fame) has a new book due out this summer called Society of Mind. In it, he proposes that minds are vast collections of simple "agents" arranged in networks. According to Minsky, mental activity is mostly one agent activating another. Most networks of agents take the form of hierarchies, but for a finite number of agents to be able to accomplish almost anything, they must sometimes be arranged in recursive loops. Loops, as any programmer can tell you, are dangerous.

A meme may be considered the information from which we construct one of

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these mental agents. The ability to build agents from information is also called learning, and without more of this ability than any other species we could not have left the tropics. But it is not an unmitigated blessing. We have become hosts for evolving information patterns ranging from outright parasites to symbiotes whose survival is only loosely coupled to our own. One need only consider the People's Temple for a vivid example.

Incidentally, I have become very appreciative of well-established religions that have evolved a long way in the direction of symbiotes. A positive aspect of religious agents is to protect the people they "possess" from dangerous parasitic cults.

The agents memes of the religious class build often get very high priorities in the mind, sometimes seriously interfering with survival. Why is this? It is at least consistent with Minsky's view that the agents built by religious memes activate primitive survival agents. The primitive survival agents may in turn activate the very agents that activated them in a loop that gets out of control.

Your correspondent's remarkable experiences are consistent with this model. The things that we have found that break up the state he found himself in -- drugs, electroshock, and the passage of time -- would be

expected from this model. While this model may prove incorrect, it may provide a new viewpoint toward mental aberration and perhaps some aspects of normal behavior as well.

In his book, Minsky remarks that reasoning by analogy lies at the very heart of our abilities to solve complex problems, by comparing them with problems that we can already solve. Certain agents may fit into preexisting mental sites in the mind analogous to the way hormones and other chemicals fit receptor sites on a cell.

The analogy should not be expected to be exact. For example, the agents memes build should be less distinctive in their effects on a person's behavior than molecules are on a receptor site since all agents compete to some extent for attention. A new agent should be expected to modify the agent society into which it fits. This may create susceptibility to memes that build additional agents. Minsky views the learning process as the acquisition of large numbers of agents, starting with those that are understandable as "just hardware."

Molecular biologists investigate receptor sites on cells indirectly by determining which molecules fit sites well enough to displace each other, since a "lock" can hold only one "key" at a time. With less precision, we can apply similar techniques to investigating possible agent sites.

One class of agents to examine by this method would be those built by religious memes. We can take self-identification of Catholics or Southern Baptists as evidence of possessing -- or being possessed by -- religious agents built by competing memes. Cases of a person claiming membership in both organizations are rare indeed, but conversions from one to the other, while uncommon, do happen. This suggests that there are a variety of functionally equivalent religious memes that can build agents that occupy a religious agent site (RAS) in a person's mental space.

Just as molecular biologists can measure the competition or exclusion among the various molecules that bind to receptor sites, we can measure the

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competition for sites among memes.

One way to measure this competition for the RAS is to determine how much possession of an agent built by a particular meme reduces the probability (compared to the general population) of an individual's having this site occupied by something that is clearly a religious agent. Belonging to a religious organization can be taken as evidence for a person's RAS being filled by a religious agent built by a particular meme.

To take an arbitrary (and to my knowledge untested) example, I would be surprised to find that whatever agents are built by taking up bowling had much influence on the rate of claiming membership in a religion.

On the other hand, the agents built by the communist meme (as indicated by membership in the Communist Party) must reduce the probability of being in any religious organization by 90% or more. Membership in the L5 Society was found to reduce the probability of membership in a religion to about half the general population, though there may be other factors at work. While neither L5 or communism would ever be considered religions, these memes may build agents that mildly to strongly compete for the religious agent site. I suspect that the agents the cryonics meme builds in the mind

can also occupy this site.

Richard Dawkins in "The Selfish Gene" ascribes to religious memes the function of anxiety reduction about situations (especially death) over which a person has no control. Put in agent terms, religious memes build agents which reduce anxiety about death. At least for me this is a good description of the way I feel about cryonics.

The question about cryonics taking the organizational form of a religion may be something to answer on terms of legal advantages and disadvantages. However, a better understanding of memes, mental agents, and the minds they form in might lead us to design a "religion," or a functional and legal equivalent, that embraced cryonics. It could also build strong agents into the mental site (or sites) of its members, especially the younger ones, for protection against dangerous cults and other harmful mental parasites. Just what memes it would take to build these agents would take considerable thought, but this "meme about memes and mental agents" might make up one component.

Sincerely,
H. Keith Henson
San Jose, CA

TRANS TIME MOVES IN

From Saturday to Saturday -- February 15 thru February 22nd, Trans Time moved into its new headquarters on Pearmain Street in Oakland, about 3 miles East of Oakland Airport. According to Trans Time President Art Quaife, the move went smoothly in spite of the fact that it was carried out during one of the worst storms in recent Northern California history. Despite torrential downpours, rough winds, and flooding the volunteers showed up and the move was carried out smoothly.

The general move-in, which consisted of transferring office furniture,

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files, and boxed supplies, was carried out on February 15th and 16th. A crew of helpers consisting of John Day, Art Quaife, Jim Yount, Ron Viner, Jerry White, Hal Sternberg, Thomas Donaldson, Lee Simondet, Margaret Bradshaw, and Bette Symanski moved tons of items to the new facility and helped situate them.

On Monday, February 22nd the work of preparing for the move of the storage dewars was begun. Since both of these containers are "upright" 8' to 9' tall open-mouth "whole body" dewars, the task was not a small one. Trans Time currently has two whole body patients and three neuro patients. However, the neuropatients are also stored in a "whole body" container.

According to Trans Time director John Day, the dewars were moved by a 15,000 lb capacity flatbed truck with removable metal "stakebed" type fencing. The snap-together steel framework which normally supports the patient dewars was first loaded onto the truck, reinforced with 4"x4"s and heavily secured to the truck bed with ropes and chains. A 4"x4" lumber framework was then attached to the plywood box with contains the smaller of the two patient dewars, and this was then hoisted by forklift onto the bed of the truck, where it was secured into the steel framework with ropes and

chains.

The second, larger dewar was moved a few days later. This larger dewar, made by MVE Cryogenics, was first encased in a protective plywood flashing to protect it from damage from the forklift. Cables were then run from the flashing under the wheel supports to a framework of 4"x4"s on the sides of the dewar. This allowed the forklift to pick up the dewar from the sides while the weight of the container was in reality supported from the bottom.

John said that there were several important lessons learned from this undertaking, fortunately all of them the easy way. First of all, taking plenty of time to meticulously plan things was of critical importance. John estimated that the total amount of time involved in moving the dewars alone was in the vicinity of 350 to 450 man hours! Additionally, they took their time to make the physical move. They drove slowly, taking 3 hours to cover 12 miles of road. Since the height of the truck/dewar assembly was 14' even, they had to carefully scout out the route in advance to exclude overpasses -- most of which are only 13'6" high. A necessary factor in covering the route as slowly as they did was that entire move be carried out between 2:30AM and 5:30AM on a weekend morning. Conducting the move at night during adverse weather conditions was yet another hassle in an already hair-raising job.

According to John, the dewars appear to have made it OK, although it's really too early to know for sure if subtle damage to vacuum integrity occurred as a result of the move. John said that he felt that patient security was excellent throughout the move and that by far the most difficult aspect of the operation -- and the most dangerous, was avoiding injury to the dewars. The dewar moving crew consisted largely of tried and true personnel such as John Day, Jim Yount, Ron Viner, and of course, TT president Art Quaife.

The Editors of CRYONICS congratulate Trans Time on a safe and productive move.

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THE QUESTION COLUMN

I have made cryonic arrangements with ALCOR as a "neuro" and am wondering if there isn't some way I could leave the rest of my body, which I'll have no further use of, to someone who might be in more immediate need? Can cryonic patients donate organs or tissues?

F. M.
Los Angeles

This question is a tough one, and a complicated one to answer well. In principal, there is no reason why organs and tissues not being "taken along" can't be donated for use by someone else, right now. In practice, this turns out to almost never be possible. Why?

First, in order to donate major organs such as a heart, lungs, kidneys or liver, you must be "brain dead." That means that death must have occurred as a result of trauma to the brain by injury, accident or disease (in the latter case such as by a stroke or cerebral hemorrhage). In cases of so-called "brain death" there is no blood flow to the brain and cryonics procedures must start as soon as legally possible. A further delay to allow for removal of tissues and organs would be unacceptable. Indeed, in most such instances a medical surrogate or medical power of attorney would have acted before "brain death" criteria (which consist of 24-hours of no blood flow to the brain or 24 hours of no brain electrical activity) were met to withdraw supportive medical care (such as a respirator) as soon as possible so that cardiac and respiratory arrest would occur as promptly after a no-flow condition to the brain was detected. In order to be pronounced brain-dead a no-flow condition would have to have existed for 24 hours at normal body temperature. For cryonics purposes this would be a disaster. It would be comparable to lying dead in a heated pool for a full day before being found!

Because of this consideration, core organs cannot be harvested in advance of cardiac and respiratory arrest in case of severe cerebral injury and a resultant condition of no blood flow to the brain.

What about skin, corneas and bone? These can be harvested long after circulation and breathing have stopped. The problem here is that we cannot delay the start of perfusion and introduction of cryoprotectants in order to allow the tissue harvesting team to collect the skin and bone. We contacted the Southern California Tissue Bank to ask if they would be willing to harvest skin and bone from a neurosuspension patient after perfusion and cephalic isolation were completed. Conditionally, they said yes. But the conditions are such that most, if not all patients would be excluded. First of all, the tissue must be collected within 24 hours of "death." This can be problematic because it may take us up to 24 hours to collect, stabilize, transport and perfuse a patient from the time legal death is pronounced. Even if this goal could be met, the tissue bank was uncertain about their ability to use skin and bone which had been subjected to a blood washout using our perfusate and technique. A break in sterile technique during our procedures could be life-threatening to a patient

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receiving the graft. The logistics get really sticky here, and liability is a major question. Since our procedures differ from the "norms," they'd just as soon avoid us altogether.

The problems with corneas are much the same, but an added set of complications is that the eyes must be completely removed, which is unacceptable from a whole host of standpoints, including delays and potential serious disruption of circulation to the brain due to leakage of perfusate from severed optic vessels.

There are also a number of other basic, excluding factors which realistically limit anyone's likelihood for being a tissue or organ donor. Those excluding factors are:

1) Sepsis (blood infection); 2) Diffuse infections or inflammation of the skin; 3) Acute respiratory infection or pneumonia; 4) Drug addiction; 5) Jaundice; 6) Toxic hepatitis; 7) Viral hepatitis; 8) Syphilis or antibody to syphilis; 9) Any cancer or malignancy; 10)

History of any cancer; 11) Collagen diseases; 12) Burns of greater than 20% of body surface area; 13) Autoimmune diseases; 14) Receiving radiation therapy; 15) Cancer chemotherapy; 16) Poisoning; 17) Controlled drug overdose; 17) Malnourishment; 18) Leprosy; 19) Meningitis or encephalitis; 20) Inflammatory diseases; 21) AIDS or antibody to the AIDS virus; 22) Other known communicable diseases; 23) Death of unknown etiology.

Additionally, donors must be between the ages of 18 and 74. As you can see from the list of excluding criteria above, only a relatively small subsets of all those dying are potential donors for any organ or tissue. At this time, it's difficult enough just to get someone properly frozen at the time of legal death without trying to worry about and factor in the tremendous logistic problems of tissue donation. For these reasons, we strongly advise against making any arrangements for tissue donation, and we will not cooperate with such arrangements where they interfere with delivering good cryonic care.

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NEW YORK SEMINAR AND TRAINING SESSION

by Mike Darwin

On Tuesday, February 25th, I flew to Gaithersberg, Maryland to meet with ALCOR Coordinator Bob Abernathy and provide some on-site instruction on use of the ALCOR rescue kit which was deployed with Bob several months ago. On Thursday the 27th, Bob and I drove up to Sayville, Long Island to meet with Curtis Henderson, former President of the now inactive Cryonics Society of New York, and to set up the training sessions and public seminar which were to held that Saturday and Sunday at the Holiday Inn at nearby MacArthur Airport.

The training session attracted a number of people from all along the Eastern seaboard. Curtis Henderson, Ruth Sears, Irving Rand, and Cindy Magellan attended from the New York area, with Glen Tupler, Andrea Hines and Jerry Cullins journeying from Florida, Virginia and North Carolina, respectively.

The training sessions were both grueling and productive. Every aspect of initial transport and stabilization of suspension patients was covered in the 16 hours or so of sessions. Both of the ALCOR Coordinators who attended, Bob Abernathy and Glen Tupler, had had some previous training or

experience in the medical/cryonics area, so the sessions for them acted primarily to polish skills and learn newly formulated ALCOR administrative and technical policy. Issues such as when not to apply CPR, how to deal with hospital personnel, coroners, and so on were among the "new" material covered.

Another very important aspect of these sessions was that they represented the first actual use of the recently completed ALCOR training manual: "Transport Protocol For Cryonic Suspension Patients." This manual was prepared to act as a document of basic standards for transport cryonic care and as a teaching manual. The New York session provided the opportunity for feedback from both

experienced and inexperienced personnel on the scope and quality of the course material. There were a lot of useful suggestions and questions from attendees, many of which will find themselves into the manual before it is released later this year.

A very gratifying aspect of the weekend was the opportunity to meet and work with people whom we have had little or no contact with before. Ruth Sears, Andrea Hines, Irving Rand, and Cynthia Magellan are all relative newcomers to cryonics who we hope will become more actively involved with

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ALCOR in the coming months. It was especially nice to get to meet ALCOR Suspension member Jerry Cullins who, until these sessions, had been just a voice on the telephone.

On Saturday evening, a slide show and lecture which was open to the public was offered. We had hoped for better attendance at this than we got: 12 attendees. However, the up side of this is that 6 of the 8 newcomers (people who are not signed up and who we've not met before) who attended the session purchased paperwork sets and began the signing-up process. Most of the "new" attendees were people who have been subscribers to CRYONICS for a year or more and who seemed excellent prospects for rapidly completing their suspension arrangements.

The dinner on Saturday night at the Bayman's Catch restaurant was something of a logistic disaster. After a hard day of training session and slide show, with only a short break for a quick-and-light lunch, everyone, despite extreme hunger, sat around and talked excitedly. In fact, we sat around so long that we did not leave the Holiday Inn where the sessions were held until well after the appointed

time for our reservations. The result was that we arrived at the Catch to find a standing room only crowd and a nearly two hour wait for a table. A group of exhausted, starving cryonicists in a restaurant full of good smells is a pitiful sight indeed, but we had no one to thank but ourselves.

However, the wait proved worthwhile; the seafood was delicious and the long wait was not wasted on a group of people anxious to share new -- and old experiences. By the end of the evening a stuffed, happy, and relaxed crowd spilled out into the cold Long Island night with warm goodbyes and promises to keep in touch.

A very gratifying and unexpected bonus (and workload) associated with trip East was the boxing and relocation of the majority of the archives and records of the Cryonics Society of New York (CSNY). The CSNY archives have been in the care of Curtis Henderson, and were in storage at Curt's home in his garage. Time and the elements were beginning to take their toll, so a decision was made by all involved (with consulting phone calls to Saul Kent and others) to transfer those archives to Southern California where more systematic archiving and care could be provided. Much of the photographic material, in particular the Polaroid photographs, were rapidly deteriorating. As an aside to would-be cryonics photochroniclers: NEVER USE Polaroid~ or other "instant" film, and if you really care about the pictures lasting, stick to black and white. The "instant developing" films, even the "new" 2nd generation material simply does not hold up. Within a decade or so all you have is ghost images -- or nothing at all.

The job of doing a preliminary inventory, boxing, and shipping this

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material was yet another demand on already short time. Bob Abernathy, Curtis Henderson, and I worked long and hard to pack and ship all 21 boxes of archival material. This material is of absolutely critical importance to any understanding of the history of cryonics. The photographs, film, letters, financial records, and other documents, much of it quite amazing and unbelievable, comprise the history of the very first cryonics society. It is an irreplaceable treasure which ALCOR is proud to act as the custodian of, and it complements the archives of the Cryonics Society of California material which came into our possession several years ago.

All in all the weekend in New York proved to be an incredibly gratifying and profitable one. Just the opportunity to meet with Curtis Henderson was reason enough to justify the trip. The added benefits of achieving real milestones in training and suspension member recruitment combine to make the sessions a stellar success. We also hope that the New York people who were brought together by this weekend will be able to stay in touch and offer some mutual support.

** TYPIST'S NOTE: THE FOLLOWING IS A COMMERCIAL **

FEELING TRAPPED

This individual grew up dreaming of the future. He's basically optimistic. He knows things are better now than they were 20 years ago, and he figures the next 20 will see even greater changes. Meanwhile, he feels trapped by death, disease, aging, gravity wells, and people that try to impede all the progress that he sees as so desirable. He knows that if

he can make it through the next fifty years, he probably won't have to worry about the following 500. He can live that future he's dreamed about.

We bring a ray of light to this person (and keep him up-to-date on that progress that's so important). CLAUSTROPHOBIA, the monthly life-expansion newsletter, covers scientific breakthroughs that will expand and enhance your life. The emphasis is on life extension, space industrialization, and related technical and medical fields. We concentrate on reporting new developments, new applications, and new ways to get around those who would restrict their use. Our news items generally appear months before the popular science magazines. Our writers include Durk Pearson, Sandy Shaw, Thomas Donaldson, Neal Wingus, Sam Konkin, John Mann, Tom Brosz, Erwin Strauss, and many others.

We're going as far as we can, as fast as we can, for as long as we can.

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** THE AD WAS FOLLOWED BY A CLIP-OUT PRESCRIPTION FORM FOR "CLAUSTROPHOBIA MAGAZINE." **

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ANTIOXIDANTS AND AGING: THIRTY YEARS OF
UNCONTROLLED EXPERIMENTS AND FIVE YEARS OF
FOOLISHNESS.

Steven B. Harris, M.D.

Note: The following article was first published in the January, 1986 issue of Claustrophobia. It is reproduced here with the permission of Claustrophobia and the author. A poll of CRYONICS readers taken several years ago indicates that a portion of our readers similar to that of the cited Claustrophobia poll are taking antioxidants.

Introduction

The August 1985 issue of Claustrophobia contains a remarkable reader survey. This survey finds the magazine's readership to be mostly young, well educated professional men (no surprise), with a passion for space, libertarianism, and what is optimistically referred to as the "life extension literature." The surprise is that 42% of these intelligent people admit to the regular ingestion of BHT, presumably with the goal of slowing the aging process. The typical Claustrophobia reader emerges as more objectivist than empiricist -- a man with something by Ayn Rand on his bookshelf, and something by Twinlab in his cupboard.

The source of the chemophilic behavior among Claustrophobia readers is not difficult to identify from the survey data, as 24% of respondents named Pearson and Shaw's Life Extension as their single favorite non-fiction book. This is about the same percentage as traditionally favor the Bible

in polls conducted among more conventional folk. Seventy-six percent of Claustrophobia readers, it turns out, are non-religious -- but one nevertheless imagines them saying a few comforting passages from Life Extension each night before going to bed, and poring by day through the scriptural concordance in The Life Extension Companion.

It is the peculiar habits of Claustrophobia readers which prompt this essay. It appears that there is some need to discuss at a bit more length the evidence (or rather the lack of evidence) for the belief that BHT, or any of the artificial antioxidants, are "life extension drugs." In order to do this, it will be helpful to review certain theories of aging, as well as some experimental work.

Certain assumptions and biases need to be reviewed as well. Anthropologists use the term amulet to denote an object whose purpose is to magically set one apart from the public to which bad things happen. An amulet can be leather bag full of sacred totems, or a Saint Christopher Medal, or (more to the point) gelatin capsules containing special powders. This essay will

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discuss a few modern amulets in current use among "life extensionists." It is hoped that the reader will eventually come to see their use as a social rather than a scientific phenomenon of our times. It is now five years since the first publication of the present generation of do-it-yourself nutritional anti-aging books, and the misconceptions generated from these have shown no signs of correction today; on the contrary, they show signs of becoming canonized into the dogma of the multi-billion dollar health food industry. Some dissent is in order, and perhaps these views will provide additional balance to the pages of Claustrophobia.

Onward, then. We begin with some historical perspective.

The Free Radical Theory of Aging

Of all the sacred cows of the longevists, the most sacred of all is the free radical theory of aging. Experimenters in the early atomic age had noted that massive doses of radiation to animals seemed in some cases to cause premature aging, with graying of hair, atherosclerosis, and earlier onset of cancer with premature death. These observations led scientist Denham Harman in 1956 to propose that the aging process itself might be due to a sort of free radical "internal radiation" generated by metabolism, and that the course of aging might therefore be modified by radiation-protective chemicals (1). Harman showed that several antioxidant

dietary supplements did indeed lengthen the average life spans of several strains of mice (2), and so the theory looked superficially promising.

On closer inspection, however, there were problems with the free radical theory from the beginning. For the viability of the theory, it was necessary to show that increased free radical activity increased the rate of aging, and unfortunately, it turned out to be more difficult than originally thought to accelerate the aging process. Numerous attempts to advance the physiologic age of animals with chemical free radical initiators failed, and have not succeeded to this day (26). Radiation turned out not to be the answer either, for it was soon found that some markers of aging were little influenced by it. These included such classic markers as cross-linking of tendon collagen and lipofuscin accumulation (3). In fact, it began to be apparent that the effects of very large doses of radiation mimicked the effects of aging only inasmuch as both caused piecemeal cell death and dysfunction in tissues (25). Smaller doses of radiation caused life shortening not by instant aging but by tumor promotion; if the animals which died early of cancer in irradiated groups were disregarded, it was found that the rest lived as long as the controls (4). And there was other

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evidence that radiation damage was different from aging damage: it was found that in male wasps of the genus *Habrobracon* (which can be either haploid or diploid), resistance to radiation is much higher for the diploid males (presumably due to the presence of a backup gene for every one damaged by free radicals). Yet it was found that diploid and haploid wasps shared the same rate of aging (5).

Nor were things going particularly well for the free radical theory of aging at the other end of the theoretical prediction spectrum, where it was desired to show that decreased free radical generation decreased the rate of aging. Harman's early results were in a sense deceptive, for the fact that his animals had longer average life spans was not good evidence that they were aging more slowly. The reason for this is that the average life span for a group of animals is subject to many manipulations which have nothing to do with aging (an example is the increase in average American life span seen in this century, despite no change in the rate at which Americans age). A better index of aging in a population is the maximum life span, or greatest age achieved by the oldest members. This parameter is little changed by environment as long as conditions are reasonably tolerable; maximum life span for humans, for example, has not been changed even by the application of modern technology. Maximum lifespan was not increased in Harman's antioxidant-fed mice (2,21), and therefore any effect of this treatment upon the intrinsic aging rate of the animals began to seem more unlikely.

In general, these problems did not get much play in the longevity literature, where the free radical theory of aging continued unchallenged. In popular books, circular argumentation was the rule: the free radical theory was proclaimed proven by the rat experiments, and the rat experiment results (if not examined too carefully) were explained in terms of the free radical theory. One might guess from the zeal with which this cycle was turned that economic interests in addition to scientific interests were involved. Certainly the vitamin industry was not unhappy with a theory in which oxidation caused most disease, and in which vitamins were antioxidants. Even the chelation enthusiasts and the Tijuana ozone therapists now found themselves sharing a blanket of "theoretical"

respectability.

This is not to say that even today the free radical theory of aging does not claim some supporters among orthodox, respected scientists. It is not clear, however, that these free radical enthusiasts are gaining ground against the opposition. Free radical supporters defend radiation's failure to produce instant aging by pointing out that free radicals deposited by radiation are distributed throughout cellular water, whereas free radicals generated by metabolism appear mostly in mitochondria (27). They argue that the reason why the present generation of antioxidants do not retard aging may be because they penetrate mitochondria inefficiently. But these arguments are of the ad hoc sort -- that is, they have the flavor of being modified in an arbitrary way to explain results which they did not predict. The truth of the matter is that a very great deal of fundamental molecular biology remains to be done, and hard evidence for a direct causal link between free radicals and aging remains elusive.

One may ask: If presently used antioxidants do not make animals healthier by slowing the aging process, then how do they work? And is perhaps the "how" irrelevant? The object after all is to extend life expectancy in any way one can, even if one must give up the romantic notion of prolonging youth. The

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answers to these questions are much less clear. It turns out, though, in at least one of the theories currently in vogue among biogerontologists, that the mechanism of how antioxidants work is indeed important to the question of whether they are safe to take. To see why, it is necessary to explore a certain series of gerontological experiments which have something in common.

Calorie Restriction

As the reader who is familiar with Walford's book Maximum Life Span will know, one of the few successful strategies known to gerontology for retardation of the aging process is calorie restriction. Cutting back the number of calories rodents are allowed to ingest dramatically lengthens both the animals' average and maximum life spans. Under 60% calorie restriction, for instance, the 42 month maximum life span of a long-lived strain of laboratory mouse can be increased to as much as 54 months. This is equivalent to the maximum lifespan in a small human population going from 90 to 116 years. Nearly all measurable parameters of aging are favorably influenced by calorie restriction in rodents, from age-related losses in immune function and soluble eye lens protein, to age-related increases in tumor incidence (6). Although the mechanism of action of calorie restriction is unknown (8), so powerful is its effect that calorie restriction of only 15-20% in mice can lengthen average lifespan by as much as 20% (7,9,17).

Needless to say, when caloric restriction becomes an uncontrolled (and perhaps unnoticed) variable in any life extension experiment, the results are likely to be messy. In 1971 a group of researchers at Johns Hopkins Medical School fed a group of mice a diet containing barely sub-toxic amounts of the cardiac drug digoxin. The treated mice amazingly experienced an increase in average and maximum life span over the control group which got no digoxin, and in the process had a lowered incidence of tumors and other pathologic lesions (10) (Now that this article has been

cited, perhaps the next Claustrophobia survey will find 40% of readers dosing themselves with bootlegged digoxin). What was going on in this experiment perhaps becomes understandable when it is noted that the treated group of mice weighed 15% less than the control group. Giving the mice digoxin, one of the most nausea-producing agents known to science, had simply been a fancy way of putting them on a diet. Life extension had probably been due to caloric restriction.

In 1972 it was noted (no doubt to the astonishment of the scientists involved) that vitamin restriction increased the life spans of experimental animals over control groups which got a balanced diet (11). Vitamin restriction caused marked weight loss in these animals. Protein restriction (13), and single amino acid restriction (14) in separate experiments have also been shown to have life-prolonging effects in rats; these also create calorie-restricted animals with poor appetites. Note that these results are counterintuitive given the prevailing popular view of aging. They become understandable if it is postulated that the overwhelmingly healthful effects of caloric restriction "overpower" other noxious experimental factors.

There are more examples of this effect: Recently Ooka and coworkers have shown that rats can be made mildly hypothyroid throughout life by a single injection of thyroid hormone at a critical time in development. Except for low thyroid hormone levels the rats are perfectly undamaged and healthy -- in fact they live a good deal longer than controls (15). The mechanism for this appears

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straightforward -- thyroid hormones control appetite in rats, and hypothyroid rats (unlike hypothyroid humans) are small and eat little. They are, in fact, calorie restricted. A related example: For many years it has been noted that hypophysectomy (surgical pituitary removal) has certain youth prolonging effects in rodents. These were especially interesting in light of the known pituitary "death clock" in certain species of octopi and salmon; and also Denckla's interesting but unconfirmed work suggesting a pituitary antimetabolic hormone in old rodents. Gradually, however, it has become apparent that hypophysectomy is not much more than a complicated way of making rats hypothyroid (thyroid function is controlled by a pituitary hormone), and that many of its beneficial effects are mediated by the calorie restriction which proceeds from the hypothyroidism. It can be shown, for instance, that if normal rats are fed only the same amount of food as hypophysectomized rats eat, they show some of the same effects of retarded aging (16), including the same degree of life extension. Conversely, when hypophysectomized rats are induced to eat normally (via a second surgical lesion in the appetite center), they do not experience some of the youthful effects ordinarily conferred by the hypophysectomy, and have normal life spans (17).

Uncontrolled Antioxidant Experiments

We come now to experiments with food additives. In light of what is known about life extension, one would think that longevity experiments with food additives would be controlled for the one previously proven age-retarding variable -- namely, caloric intake. No such luck. Not one longevity/food additive experiment in the 30-year history of such experiments has been controlled for food intake. The results of this are about as one would expect. Any results attributable to the food additive

are often hopelessly garbled by the powerful anti-aging effects of calorie restriction. L-DOPA, for instance, has no effect on lifespan when given in moderate doses. But when L-DOPA is given in doses large enough to make the animals sick and lose weight, then it shows life extension effects (and also causes eye lesions) (18). The result of this, curiously, is that many life extensionists are now taking small doses of L-DOPA, obtained without prescription from Central America, in hopes of living longer.

By now enough examples have been given to raise the suspicion that a successful life extension experiment can be done by putting any bad-tasting or otherwise noxious chemical into the food of a group of rodents. If such an investigatory chemical is not too poisonous, it will be found to have youth-

prolonging effects on its recipients as compared to controls who fatten on a tastier control diet. If the chemical just happens to be an antioxidant, it can be claimed on the basis of the free radical theory of aging to be a LIFE EXTENSION DRUG. Then it can be sold to Claustrophobia readers.

Centrophenoxine causes weight loss in animals at

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"life extension" doses (19). So does ethoxyquin (20). A number of antioxidants, including BHT and 2-MEA, cause reductions of 10-20 percent in food intake in mice during longevity experiments (2,21,24) and this amount of calorie restriction is in the range shown to be effective at prolonging life span (9,17). In one of Harman's experiments, reduced doses of these chemicals which produced less weight loss also produced less life extension (21). In fact, there appears to be only a single report of life extension via food additives in a naturally long-lived rodent strain where weights are comparable for control and treatment groups. This is Hochschild's report of the life extending effects of DMAE in already old mice (22). (Unfortunately, this drug appears to shorten the life span of old quail (23).) There is irony in all of this. It is just the experiments cited above which the popular longevity literature uses as evidence that it does not matter what or how much you eat as long as you ingest the proper food additives. Pearson and Shaw, to cite one example, go so far at one point as to publish a grocery list illustrating their own high fat lifestyle (28). Yet there are exceedingly few longevity experiments in which food additives are the only variable, and the evidence from most food additive experiments highlights the supreme importance of caloric intake.

Conclusion and Recommendations

The experimental gerontology literature contains many strategies for prolonging the lives of rodents. Among these are judicious irradiation (12), vitamin restriction, and feeding of artificial antioxidants. The popular longevity literature advocates only the last strategy, possibly because that is where the money is (the public would hardly buy a book which advised mild radiation exposure, or vitamin restriction). Probably, however, all these strategies are unhealthy, and none of them should be followed. They undoubtedly produce some if not all of their benefits by caloric restriction, and people in search of longevity would be better advised to restrict their calories in other ways.

The free radical theory of aging, as we have seen, is at present not well enough supported by evidence to be able to lend much weight to arguments involving it, and this includes the argument that antioxidants are beneficial. The best that can be said of food additive experiments is that, due to uniformly poor design, none have proven what they set out to prove.

Hope of an age retarding effect is not the only reason why enthusiasts take BHT and BHA. These substances do have interesting anticarcinogenic properties in some systems. They have tumor promoting properties in others. In any case, the major anticarcinogenic success of these agents has been in animal systems where cancer occurs with unnatural frequency and precocity, or in which life span has been shortened by an adverse diet (21). In animal systems where cancer incidence corresponds more closely to that in humans, the results are less

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impressive, and again might very well be secondary to the known significant antineoplastic effect of even modest caloric restriction (9). The would-be longevist whose ancestors have all died of cancer in their 30's and 40's might with some rationality consider a desperate translation of the animal data to himself. The longevist looking to prevent cancer in his 60's and 70's -- closer to the average human lifespan -- has much less support from the experimental literature, and so runs a far greater chance of doing himself harm.

Again, enthusiasts might be tempted to hypothesize that if antioxidants cause weight loss in animals, then they might be good as diet aids in humans (the reader may guess what sort of diet books are now in the "life extension" pipeline). Most food additive experiments, however, have been done with high concentrations of the chemical of interest mixed directly with the animals' food. If humans were forced to eat all foods mixed with unpleasant BHT or evil-smelling 2-MEA, it is probable that rapid weight loss would occur. Ingestion of smaller quantities in tasteless capsules would presumably be ineffective, and no calorie restriction benefit would result. Furthermore, there is the question of toxicity of these substances. If calorie restriction reliably causes extension of maximum life span, and yet artificial antioxidant supplementation, which usually results in calorie restriction, does not -- then one wonders why not. Antioxidant-fed animals, while living longer, are still not living as long as they ought to on the basis of food intake, and one might speculate that some toxicity of the antioxidants is being masked by the physiologic benefits of calorie restriction so that things come out nearly even. If that is so, then the unsuspecting longevist who takes capsules of

artificial antioxidants might be missing out on the main benefit of these agents (their bad taste), but might still be in for the full impact of any toxicity they have in store.

Perhaps the point can best be summed up in a piece of whimsy. In the anecdotal appendix of Pearson and Shaw's "Life Extension" there appears the case history of one "Mr. Smith," a famous movie actor who takes L-DOPA and DMAE, and whose age and description calls strongly to mind Clint Eastwood. Eastwood, as the character Dirty Harry, is famous for getting the drop on a bad guy, and then explaining that he can't remember whether he has fired five rounds from his revolver, or six. "The question," says Dirty Harry, "is: DO YOU FEEL LUCKY??" Perhaps Eastwood would agree to do some endorsement labels for some of the L-DOPA and DMAE products intended for the health food crowd, since the caption "DO YOU FEEL LUCKY?" is also most appropriate for these items.

A Closing Note

The ideas summarized in this essay have been current in the field of gerontology for some time. If some of them seem new to the reader that is undoubtedly due to the fact that they are not covered well in the tertiary (popular) literature. Most such literature

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has some particular axe to grind, and is not particularly interested in presenting an unbiased account of research. The reader who wishes to keep truly informed will need to read some primary or secondary sources. A place to start, which is wholeheartedly recommended, is the Handbook of the Biology of Aging, 2nd Ed., edited by Caleb E. Finch and Edward L. Schneider, Van Nostrand Reinhold, New York, 1985 (ISBN 0-442-22529-6). This is a comprehensive, up to date review of much of the field of biogerontology, and is well worth the asking price of \$75.

At the beginning of this essay, the average Claustrophobia reader's devotion to the popular longevity literature was characterized as a sort of techno-religious faith. When 25% of Claustrophobia readers name the "Handbook of the Biology of Aging" as their favorite non-fiction book, then (to continue the metaphor) the preventative medicine millennium will have truly come.

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INTERVIEW WITH MIKE DARWIN

Part I

by Luigi A. Warren

Mike Darwin (nee Federowicz) is President of the ALCOR Life Extension Foundation. Now aged 30, his involvement with cryonics stretches back to his high school years in Indianapolis, Indiana. Few cryonicists can claim such a long history of participation at the "sharp end" of this idea.

It was Mike's "What You Can Do" article in CRYONICS which brought me to the United States from England, a year ago. That, and the fierce dedication which he communicated in all his writing, was enough to convince me that cryonics, ALCOR-style, was for me.

I am happy to report that Mike fully lived up to my expectations. He's smart and very articulate, of course. More importantly, he is utterly focused on the task of achieving physical immortality through cryonic suspension. He has no time for armchair dreamers who effervesce with proposals, good or bad, but never do anything to turn them into reality. Mike's a doer. He also has the valuable faculty of being able to fire others with some of his sense of urgency and enthusiasm concerning cryonics. That's vital in an enterprise which offers few short-term social and monetary rewards.

Mike's extraordinary range and depth of experience in every aspect of cryonics -- medical-procedural, theoretical, organizational, financial and promotional -- is perhaps his most irreplaceable asset. He's seen the rise and fall of public interest in cryonics, the vicissitudes of organizations, the projects that never materialized, the setbacks and the out-and-out disasters, as well as the years of slow, steady progress, to which he has

contributed much. As a realist, his refusal to view the world through rose-tinted glasses has often generated friction with other cryonicists, who prefer to take the more optimistic view, but I have seen his judgment vindicated often enough to prefer the Mike Darwin approach. And it is doubly encouraging, therefore, that he speaks in this interview of real prospects for major technical advances and growth in the public acceptance of cryonics.

This interview was conducted at the end of a long day at Cryovita Laboratories (the early hours of the morning, actually: Mike's a creature of the night). As we sat down in the reception area of the ALCOR office, I wasn't hopeful for a productive session. It had been one of those too-frequent days when more problems came up than were resolved, and Mike seemed down. But his demeanor changed as soon as I started quizzing him on his favorite topic: cryonics. We spoke for three hours.

Part I of this interview deals with the results of ALCOR's research into the effects of cryonic suspension. Some serious deficiencies in current preservation techniques are described. Mike then outlines two radical new technologies, vitrification, and vapor cooling, which may open the door to true suspended animation.

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LW: ALCOR has conducted extensive research into the effects of cryonic suspension. What have you learned, and how has it affected your confidence in the technology?

MD: That's a lot of ground to cover; we've done a great deal of research in the last few years. I'm still confident that cryonic suspension is a workable technology; that it is going to allow us to get to the other end. However, today's suspension techniques cause damage, which implies a loss of information and a reduction in the fidelity with which identity may be reconstituted. It doesn't have to be that way. I think the damage we're seeing is due largely to technical problems which could be solved given a relatively modest amount of money.

LW: What kinds of injury have you identified?

MD: Briefly, there is damage at the fine level (the cell ultrastructure) arising directly from the freezing process and as a result of ischemic periods (without blood flow) prior to the procedure, while, on a gross scale, we are seeing serious tissue fracturing on cooling to liquid nitrogen temperature.

LW: What's happening at the "fine" level?

MD: The research we conducted in this area involved examination of tissue samples from a Northern California suspension patient, who was converted from whole body to neuro, and from cats which we perfused and froze using the best techniques available, some immediately after death and some after 24 hours of cold ischemia. Our initial light microscopy work gave us a lot

of confidence that we were preserving essential structure. The cell-to-cell relationships looked well preserved.

We proceeded to do electron microscopy on the cat samples, to evaluate preservation on the level of the individual cells. I'm much less happy about the results of this work. Preservation of cell ultrastructure in the kidney and heart were very good. Liver preservation was very poor; there was almost complete loss of structure, as if the sample had been ground up in a blender. The condition of the brain was intermediate between that of the liver and the heart and kidneys.

There are a number of caveats here. Because we have a limited number of animals to work with and because electron microscopy, in particular, is very costly, we have to make some decisions about experimental technique which are based on limited information and which are to some extent arbitrary. Some of the things we are seeing may be artifacts of our experimental procedure.

LW: What kinds of artifacts?

MD: One is the phenomenon of osmotic dehydration. Before you can look at

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biological specimens with an electron microscope, they have to be fixed. (Fixatives, such as glutaraldehyde, lock molecules together with crosslinking bonds.) The cells in thawed tissue contain a solution of water and cryoprotectant -- glycerol in our experiments. If the fixative isn't prepared in a solution with the same concentration of cryoprotectant, then water will pass through the cell membrane by osmosis, until the concentrations are the same on both sides (this is called equilibration). If the concentration in the cell is lower than that in the fixative the cell becomes dehydrated.

Unfortunately, it's very difficult to estimate the concentration of glycerol in a particular piece of brain tissue accurately and reliably. The approach we took was to assume a value equal to the last recorded concentration of the effluent during the original perfusion with cryoprotectant.

In retrospect this may have been a poor choice. The brain does not equilibrate well with cryoprotectant, so the actual concentration of glycerol in the brain cells was probably lower than we assumed. Introducing fixative with this concentration of glycerol probably caused significant osmotic dehydration of the brain cells. This would have caused them to undergo partial collapse, which could have been responsible for some of the appearance of disruption we observed. The kidney and heart equilibrate with glycerol better than the brain, so the estimate of glycerol concentration we used in preparing the fixative was probably a better match for those tissues, and they showed up well under the electron microscope.

Another problem is that tissue which has been cooled to liquid nitrogen temperature fractures -- the gross level problem I mentioned -- making it impossible to use the circulatory system to introduce fixative evenly, as would normally be the case when preparing such samples. That's going to have some impact on the results you get from electron microscopy.

LW: What can be done to improve the quality of ultrastructural

preservation in the brain?

MD: It may well be possible to eliminate most of the damage we are seeing at this level by vitrifying instead of freezing. Vitrification involves introducing relatively high concentrations of antifreeze compounds during perfusion. Instead of freezing, the water-cryoprotectant solution gets thicker and thicker until it forms a solid, without any crystalline structure -- a glass. Vitrification occurs gradually, over a temperature range of several degrees. There's no sudden phase change, as with freezing. This is advantageous because we believe that the damage we're seeing comes about largely through mechanical disruption when ice crystals are formed, and from the increased concentration of chemicals which were formerly dissolved in the water and are "frozen out" in the phase change.

On the other hand, very high concentrations of antifreeze compounds are toxic. But a number of researchers, including Fahy, Takahashi, and Rall, have shown that a wide range of tissues can be vitrified without significant injury. Embryos can now be vitrified and recovered. A certain type of white cell, which has proven to be highly resistant to freezing, can now be vitrified. Fahy has shown that kidney slices can be loaded and unloaded with the requisite concentrations of cryoprotectant with only a slight reduction in viability. I understand that, in unpublished work, liver slices have been treated similarly,

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with virtually no diminution of viability.

There are many technical problems that must be solved before we can apply vitrification successfully. The biggest is getting high enough concentrations of cryoprotectant to penetrate the fatty myelin which covers the white matter in the brain. I think that answers could be had with the application of relatively little money. Preliminary experiments which we have conducted with propylene glycol and DMSO indicate that this cryoprotectant combination will penetrate the brain, and do so rapidly.

LW: However, you also mentioned that there is ultrastructural injury due to ischemia. Vitrification won't help there. What are you finding, and what can we do about it?

MD: We know that a tremendous amount of damage is occurring due to ischemic periods, when the brain is deprived of oxygen and nutrients. There were large areas in the brains of the animals that had been subjected to ischemia where it was obvious that cryoprotectant had not penetrated well. There were blood filled capillaries where clotting had occurred that had sequestered tissue from flow. There was extensive interstitial edema and breakdown of structure, and much debris and loss of structure and ground substance (the basic molecular framework which comprises the tissue).

LW: Are you saying that ischemia, in addition to causing damage prior to freezing, also impairs the permeation of cryoprotectant into the brain?

MD: It's probably worse than that. That is certainly a fair statement, but ischemia may also cause the cryoprotectant perfusion to do a lot of additional injury. If you look at ischemic tissue without having restarted circulation, it looks very good. It's only when you restart circulation that everything falls apart. You're then supplying oxygen, which generates a lot of free radicals, and metabolites, which restart metabolism in

fashions which are inappropriate or awry. A tremendous amount of injury that we see in animals or people who are revived after ischemia is what we call "reperfusion injury," due to the restarting of normal circulation. I think that what we may be seeing in our frozen ischemic animals is also reperfusion injury, due to the attempt to introduce cryoprotective agents.

One highly speculative conclusion that might be drawn is that it might be better to simply proceed with straight freezing, without cryoprotectants, when presented with ischemic patients. This needs to be evaluated. In fact, we have tissue from animals that have been straight frozen, with and without ischemia, sitting in storage now, but we don't have the money to evaluate them. The answer to the question is probably sitting in the back of Cryovita Laboratories right now, but we need \$3000-\$5000 to do the research that could give us some definitive answers. That infuriates me.

LW: Do all suspension patients undergo significant ischemia?

MD: No. In fact I can think of suspensions I have participated in where that wasn't the case. In one case the patient had a total of only about 60 seconds of ischemia. That's trivial, especially when you can provide good metabolic support by getting the patient on a Heart Lung Resuscitator quickly, and then on to a blood pump within fifteen or twenty minutes from the time of cardiac arrest.

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There will always be ischemic episodes for some patients, when death occurs suddenly and there is no cardiopulmonary support, or when the ability to provide effective gas exchange or cardiac output is minimized due to the dying process. If you have someone whose lungs are 80% malignant tissue, or who has pulmonary edema so that the lungs are filled with fluid, then there's very little gas exchange area -- the patient essentially dies from suffocation -- and CPR is not going to be very effective. There are also cases of elderly patients with extensive arteriosclerosis, where a fairly high perfusion pressure is needed to get adequate circulation -- and CPR isn't going to give you that kind of pressure. An issue which will have to be addressed sooner or later is: do we want to wait around for these kinds of terrible injuries to be imposed on us as a result of the dying process, or do we want to proceed with suspension before we're subjected to that kind of injury?

Many other people, however, die from failure of a single organ system, for example a myocardial infarction. In these cases death can be fairly abrupt and yet take place in a situation where good stabilization and metabolic support are available.

LW: Hasn't Dr. Blaine White of Detroit Receiving Hospital demonstrated that it's possible to recover people without brain damage after an hour of ischemia?

MD: He claims to have done that, and I think that there is certainly some merit to his claims. We have tried to recover one animal, a dog, after thirty minutes of warm ischemia. We succeeded in recovering every organ system to good functioning -- with the exception of the brain. A number of studies have demonstrated recovery of animals after fifteen to thirty minutes of ischemia at normal body temperature, with little neurological injury. But I don't think that applying these techniques to human beings is going to be as straightforward as the popular medical press, or the

cryonics press, has made out. We have probably been guilty of hyping that research to some extent, and this should stop.

LW: So we can say that ischemia is a serious problem, which greatly amplifies the damage attendant to cryonic suspension?

MD: There is no question but that this is the case. Anyone who thinks otherwise is being sadly misled.

When patients living a distance from us can see deanimation coming, or become at increased risk due to poor health or advanced age, they ought to make every effort to minimize the chances of ischemic episodes at their end, or relocate closer to one of our facilities. It may be painful economically and personally to become separated from a familiar environment at a time when one needs support, physically and emotionally, but those are the brutal realities.

Unfortunately, dying people are rarely blessed with tremendous emotional or financial resources. It's often not clear that it is time to resign yourself to the fact that you are going to die. Waiting until you're dying before moving sounds fine in principal, but in practice it's almost never done.

Some of us have made that decision already -- I'm a long way from my friends and family in Indiana. You yourself have come a long distance from your own country to a completely new kind of life. People have had to deal with hard realities in the past, and make tough decisions in order to survive. Many

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people have to pursue medical help in unfamiliar cities, away from friends and family. This is something people are simply going to have to face -- or they're going to have to face a more difficult alternative, which is to create the kind of facilities and support structure to provide quality cryonic care on a local level. Those are really the only alternatives.

LW: Let's move to the problem of cracking. What causes this phenomenon?

MD: Cracking occurs because the various tissues that make up the human body -- skin, bone, muscle, brain tissue -- contract at different rates as they are cooled. The different tissues are bonded together in a solid matrix formed by the mixture of water and cryoprotectant, which vitrifies (becomes a glass) at around -135°C. Stresses build up as the tissues attempt to slide by one another, leading to fractures. The problem is less serious in fiber-reinforced tissues, such as the skeletal muscles and skin. It is worst in soft tissues like the brain, kidney, liver, and lungs.

LW: If the stresses occur where different tissue types adjoin, couldn't you solve this problem for neuropatients by removing the brain from the skull, prior to cooling to liquid nitrogen temperature?

MD: You could do that, and it might be a solution to the problem. However, the brain is very fragile. Left on a counter top, an unsupported brain quickly develops tears under its own weight. That's a formidable technical problem. Also, if the brain is in contact with its container during freezing, you have the same problem; it will be bonded to the container walls.

There's probably a better way to solve the problem: find a safe temperature for long term storage which is higher than the temperature at which cracking occurs. We have cooled dogs to -112°C and rewarmed them, and have established that there is no cracking at that temperature. I think that the only safe temperatures for long term storage are in the range -135 to -140°C -- the range in which water and most cryoprotectant solutions vitrify.

You have to realize that from a biological standpoint, there simply isn't any need to go to liquid nitrogen temperature. Safe storage can be carried out on the basis of immobilizing the system -- locking up the reactive molecules in a matrix of solid material. When you lock up the position of potential reactants, the Arrhenius equation (which predicts rates of reaction versus temperature) ceases to apply. Dry ice temperature, or room temperature for that matter, would be safe from this standpoint, if only they solidified the system. But they don't. What a lot of people fail to realize is that even though there is a lot of solidification of the system at dry ice temperature (-79°C) in the form of water frozen out as ice, the inside of the cells are not frozen.

LW: Why are the cell interiors unfrozen?

MD: That's a rather complicated issue which I won't go into in detail. Suffice it to say that ice always forms first outside of cells and as the ice grows it removes water from the cell. This concentrates the cryoprotective and salt mixture present inside the cell until you get a very high concentration of antifreeze cryoprotective agent and salts present intracellularly. At -79°C this solution is liquid and diffusion and chemical reactions can proceed apace, per the Arrhenius equation. If you look at the Arrhenius equation and its predictions for the rate of reactions at -79°C the numbers are not very

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reassuring.

I think it's also worth pointing out that when you cool the typical frozen, cryoprotective treated biological system described above to below the glass transition point or to liquid nitrogen temperature, what in reality happens is that the intracellular milieu vitrifies. The rate at which you have to cool and rewarm to achieve intracellular vitrification will be determined by the concentration of protective agent in the tissue. The higher the concentration, the slower you can afford to go without getting lethal intracellular freezing. This is why, when you use low concentrations of agent such as 10% or 15% glycerol or DMSO you have to freeze at rates of at least $1^{\circ}\text{C}/\text{min}$ or more and rewarm at rates of $100^{\circ}\text{C}/\text{min}$ or more.

I mention all of this to point out that even with so-called freezing of cells or tissues, the cells survive only by virtue of the fact that they vitrify, even though most or all of the extracellular fluid is frozen.

LW: So patients may have to be stored in a fairly narrow temperature range indefinitely?

MD: That's right. And in a range that doesn't include the boiling point of liquid nitrogen.

LW: Or any other economical cooling medium?

MD: There are things which boil in the right range, but they are prohibitively

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expensive, and in some cases present serious handling problems. We have to come up with an alternative approach to maintaining stable temperatures in the range we're interested in.

LW: How might that be achieved?

MD: A mechanical refrigeration system is one possibility. There are systems available off the shelf today which can maintain temperatures of -130°C or so. Unfortunately, they are fraught with problems. For one thing, they need electrical power to operate. So you're sharply dependent on a continuous power supply. Contrast that with our present liquid nitrogen storage system. If something goes wrong, a vacuum failure for instance, then there is a tremendous heat-sink, in the form of a reservoir of liquid nitrogen which has to boil off before patient temperature is affected.

Another problem with existing mechanical refrigeration systems is their lack of heat moving or "pull down" capacity. These systems are basically capable only of maintaining a low temperature on a precooled sample. This may not sound like a serious limitation, but in reality, when the unit needs to be entered on a regular basis, it is. Every time you enter the system you introduce the possibility of serious warming. Also, the durability and maintenance requirements of these systems are pretty bad.

An alternative approach, which I see as more promising, would be to develop a system in which patients are maintained in vapor boiling off from a reservoir of liquid nitrogen.

LW: You would need some form of active temperature control, unlike the present system in which the temperature is naturally fixed at the boiling point of liquid nitrogen?

MD: Yes, that's true. However, the system I envision would be mechanically very simple. It would use the pressure generated by the boiloff from a liquid nitrogen reservoir to pump vapor into the cooling chamber: temperature control could be achieved through a thermostat controlling the vapor flow rate. It may be possible to eliminate any requirement for blowers to circulate the vapor, by allowing liquid nitrogen to passively cool the system.

LW: How would you protect against failure of the system?

MD: You'd need a heat sink of some kind. The heat sink would maintain cryogenic temperatures for a few hours, or even a day or two, in the event of a problem with the primary cooling system. The ideal candidate would probably be dry ice.

LW: Won't tissue devitrify if it's rewarmed to dry ice temperature?

MD: The word you're looking for is liquefy. Devitrification means to freeze during rewarming. Depending upon the concentration of agent present, patients stored in the vitreous state would be at risk for either

freezing during rewarming (devitrification) or liquefaction. The former would be a very serious matter, since it would wipe out any advantage gained from vitrification in the first place (the purpose of which is to avoid freezing injury). The latter might not be so serious, since the worst that would be expected would be resumption of biochemical activity at a very reduced level, until

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resolidification of the system by cooling was reimposed.

LW: Will cycling between the vitrified and unvitrified states cause tissue damage?

MD: Once again, that depends on whether or not enough cryoprotective agent was introduced to allow for vitrification at 1 atmosphere of pressure. Many of the schemes currently under evaluation involve use of lower concentrations of agent, which are "coerced" into vitrifying by the application of 20,000 to 30,000 pounds of pressure and relatively high rates of cooling. I think it unlikely that such approaches will be used in the vitrification of suspension patients -- the costs and logistics would be staggering. Nevertheless, if a reversible technique of cryopreservation for the brain hinges on such a strategy, then it may well be pursued, in which case very, very careful control of storage temperature will be essential to avoid ice formation. Accidental warm-ups of the system will be intolerable.

LW: What form will ALCOR's future storage systems take if vapor storage is adopted?

MD: It's probably not economical to build a system like this for one or two patients, so it's going to be a big system. A unit would probably hold five or ten whole body patients, and have the ability to accommodate neuro patients as well. That would, incidentally, eliminate the wide differential in the standard of security provided for the two different classes of patient that we have today. Both kinds of patients would be stored in the same unit.

The operating temperature would be high enough that we could probably get away from vacuum technology and use high-quality foam insulation instead. We've looked at the numbers and it appears that foam will be economical in a system that works at around -135°C.

I foresee a system contained within a large, probably room sized, concrete utility vault, which is a relatively inexpensive off-the-shelf item. It must be a rugged structure that can take earthquake and fire. The interior would be lined with perhaps a foot of foam insulation and held at about -140°C by a cooling system of the kind I've described. There would be massive amounts of dry ice to act as a heat sink. The patients might be in individual insulated cassettes -- foam-lined metal or wood boxes. The cassettes might have heat exchangers in them as well, for active cooling during transport.

LW: Why go for such a large system if it will be feasible and even necessary to have individual cooling systems for each patient?

MD: The cooling systems in each cassette, if we go that route, would be inefficient for long-term storage. It wouldn't be practical to have each patient contained within a foot of insulation: boiloff of liquid nitrogen

would be very high. Cassettes would only be useful as a stopgap, for times when the patient has to be moved, for example for transfer to another facility.

Another feature we might include in the cassette design would be a removable foam plug, to permit viewing of the patient's face. That may be important for psychological, legal and logistical reasons.

LW: Will it be possible for personnel to enter the vault?

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MD: It's conceivable, but I think there will be very little dead space in the early versions of this system. I imagine that the vault will be almost completely filled with dry ice, except for the cassettes. Access to patients would be via a hatch in the side of the vault.

LW: ALCOR has already been criticized in THE IMMORTALIST for pursuing the best technology without regard to the affordability of cryonics to the average person. Won't this drive up costs even more?

MD: I don't know. This would be a radically different system from any that has been employed before in cryonics. I think the capital costs are going to be higher. On the other hand, the amortization schedules are going to be a lot longer than with the short-lived high vacuum systems we're using now. The unit I've described should last almost indefinitely, especially if the concrete vault is protected from the weather.

The components of the system will be generally low technology, simple and rugged. Even the cooling system should be very simple with the right design. The only part of the system which may require relatively sophisticated technology will be the monitoring equipment used to evaluate the system's performance and alert us to problems. Ideally I would like a computer display showing temperature readings throughout the vault, to pinpoint hot spots or other unexpected effects.

LW: How will liquid nitrogen requirements be affected?

MD: At this point I can't estimate that precisely. I emphasize that what I've described is very preliminary. We haven't yet looked at this problem in much detail. A completely different approach may turn out to be superior.

I do feel reasonably confident that I've identified some of the major features any vapor system is going to have. Some kind of heat sink material, whether it's dry ice or something else, is going to be necessary. If we can get away from high-vacuum insulation, which should be possible in the temperature range we're talking about, that has to be very desirable, because vacuum-based systems are troublesome, they're expensive, they don't last very long, and they're not very safe.

LW: Is the development of a vapor storage system within ALCOR's capabilities?

MD: Not today, no. We would have to shift our priorities considerably to undertake the project. The first step would be to establish a safe storage temperature, through research. We've been very slow to do this, because there's been no money for that kind of work. The construction of a vapor storage system will be challenging, technically and financially. But until

we do it, patients are going to continue to suffer fracturing injuries.

LW: What would be the upshot of solving the technical difficulties you have described?

MD: Techniques which are either close to, or actually do represent viable preservation of the central nervous system.

LW: In other words, reversible suspended animation for the brain?

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MD: Yes, and probably for other organs too. I think that both the heart and the liver may be the objects of reversible vitrification in the near future -- in 5 to 10 years if there's any significant application of resources.

LW: What about whole bodies?

MD: Vitrification is less likely to give us a practical technique for whole body suspended animation in the near term because of problems with non-vascular water that is inaccessible through the circulation -- in the gut and in the eyes for example. Also, there is probably going to be wide variation in the sensitivity of different tissues to the toxicity of the cryoprotective agents.

LW: Is there any prospect that vitrification can be developed into a technique which could be applied before legal death?

MD: Yes.

LW: Even if the technique is only reversible when applied to the brain, and not the whole body?

MD: I think that you could plausibly argue that brain death could be prevented by suspension of the brain with a reversible technique. The first cases where it might be applied would be those in which the patient's brain is being destroyed by disease -- severe multiple sclerosis, Alzheimer's disease, or Huntington's chorea for example -- and the patient faces inevitable personality loss followed by death. Under such circumstances, I think that many medical authorities would agree that the patient has nothing to lose by opting for reversible cryopreservation of the brain.

Perceptions may change radically if Dr. Robert White, or someone following in his footsteps, ever performs a head transfer -- whole body transplant -- on a human patient. White has conducted the procedure on animals on numerous occasions. At present it is not possible to rejoin the spinal cord after the procedure. However, there are many cases of patients who are already paralyzed and suffer terminal illnesses, such as cancer, which are restricted to the body. Some of these patients might find the option attractive.

LW: How soon could a reversible suspension technique for the brain become available?

MD: I think that there's every reason for optimism that it can be achieved in ten to fifteen years, if the money is there. And I didn't feel that in the past. Our work, and the work of Fahy and others on vitrification,

makes me feel that this is now a real possibility.

The problems we face, if we move to vitrification, are basically technical problems, as opposed to the fundamental theoretical problems we face with freezing. We still don't have a good understanding of the mechanisms of freezing injury, and even if we did that doesn't necessarily mean that there are ways of overcoming them. Because freezing causes injury by several quite different mechanisms -- mechanical damage from ice, precipitation of solutes that are forced out of solution, and so on -- it may be that freezing of organs like the brain or the lung or the heart will never be possible without major tissue damage.

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All the problems associated with vitrification arise through one mechanism: the toxicity of the cryoprotective agent. We are in a much better position to focus on that problem than we are to deal with the multiple difficulties of freezing. The message should go out to people with money, who want to stay alive and see cryonics or suspended animation as a means to that end: we're now very close to perfecting a technique which can provide a much better shot at indefinitely long life, and your \$10,000 or \$100,000 can have tremendous leverage in allowing that technology to be developed soon, rather than in the distant future.

On the other hand, I want to go to great lengths to point out that we are not talking about vitrifying people tomorrow. There are tremendous technical and logistic problems which would have to be overcome before this would be possible, and an immense amount of research needs to be done. I think the important message here is the tremendous potential of the technique. What's done with it, how much money is spent and so on, will really determine what will happen and whether it will ever see application to humans.

TO BE CONCLUDED NEXT MONTH

SCIENCE UPDATES
BY Thomas Donaldson

GENETICALLY ENGINEERED MICE

Unfortunately, the experiments I'm about to describe involved engineering the genes of fertilized eggs, rather than the body cells of a living adult animal. However, they are interesting despite this as an indication of just how advanced our genetic technology has become. By now, in fact, changing the genetics of mice by implanting foreign genes has become a common laboratory technique.

Recently NATURE (316, 14 (4 July, 1985)) published the news that three independent teams of researchers had used genetic engineering techniques to restore a deficient immune response in one strain of mice. Their purpose was to study the genetics of our immune response generally. They see their techniques as contributing to that goal. However, their technique reaches a milestone in genetic engineering also.

The researchers were Marianne LeMeur et al (at the Faculty of Medicine, University of Strasbourg, France), K. Yamamura et al at the University of Osaka, and L. A. Pinkert et al (unstated affiliation). The particular

defect cured was of an arcane kind. One particular gene, the E-alpha gene, controls the ability of the immune system to attack some (but not all) antigens harmful foreign substances). These researchers began with a strain of mouse deficient in this gene. These mice produced all the molecular machinery needed to attack antigens of this class except for one chemical (made by the E-alpha gene). By inserting this gene into fertilized or unfertilized eggs of the mice, these scientists could produce mice capable of a full immune response.

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The interesting points in genetic engineering are that these injected genes did incorporate themselves into the DNA of the host animals and properly express themselves. It's relatively trivial to inject genes into cells. The really important point is that the new gene functioned appropriately. Not all genes injected into cells will do that. Foreign genes can cause mutations (cf. SCIENCE, 228, 1516 (1985)) or simply fail to integrate. It's quite significant that some genes controlling the immune response are usable in genetic engineering techniques.

Success on this question suggests that some of the human diseases due to lack of inherited immune function might soon become repairable. And, of course, this work presents a much more efficient technique for studying the genetics of the immune system, the purpose for which these researchers did their experiments.

BRAIN ISCHEMIA: ITS EFFECTS AND REPAIR

Work still continues on piecing out the effects of brain ischemia and methods of repairing those effects. Brain injury through cessation of blood flow has very complex effects. We can't sum them up in any single

event such as constriction of the arteries or brain swelling.

Recently, two further papers put some interesting light on the complex events involved in brain injury through ischemia.

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One kind of destructive event which happens with ischemia is a release of neurotransmitter chemicals. The neurons become overstimulated. In JOUR NEUROCHEMISTRY (45, 145-151 (1985)), J. Drejer and others from the University of Copenhagen present some studies of how and why brain tissues release glutamate in ischemia.

Glutamate is an amino acid of the sort proteins are made of. Glutamate is also a neurotransmitter. It transmits impulses from one nerve cell to another. In ischemia, glutamate levels increase greatly. This increase may explain some of the damage from ischemia. In fact, some scientists have mimicked the brain damage of ischemia by giving animals doses of kainate, a drug which greatly increases stimulation from glutamate. Brain regions such as the hippocampus, which contains many neurons using glutamate as a transmitter chemical, will show patterns of injury very similar to that from ischemia after kainate treatment. The problem at issue is why.

Drejer et al used experiments to consider several possible explanations. It may be that ischemia causes massive release of glutamate from within the neurons. It may also be that normal chemical processes which remove glutamate will shut down during and after ischemia. Finally, glutamate could diffuse out of the neurons because of breakdown of cell membranes.

The experiments consisted of studying glutamate release both in the test tube and in whole animals under ischemia. Drejer et al duplicated ischemia in cell cultures by depriving the cells simultaneously of both oxygen and glucose. If blood flow to the brain stops, lack of both oxygen and glucose is the main event involved.

While we won't give a full analysis here, the authors feel that their experiments are clear. The main event is a massive release of glutamate from pools within the neurons. It is not a slow diffusion due to membrane properties. Subsequent to this, and worsening the damage, the chemical processes which inactivate this glutamate have also shut down.

This release of glutamate depends on calcium levels outside the cells. They could abolish this release by incubating their cells in a medium containing magnesium ions. This reduces the release of neurotransmitter chemicals such as glutamate. Media containing cobalt ions also reduce glutamate release (although they are less practical from a therapeutic standpoint).

The metabolic processes which deal with glutamate once it is released seem to depend on potassium ion levels in the medium. Drejer et al could show that if potassium levels remained constant (not normal in ischemia) then the neurons disposed of the glutamate normally.

Drejer et al have no firm suggestions about therapy, but their work does give us valuable ideas in that direction. The relations with magnesium, potassium, and calcium are very suggestive. They also mention that a drug antagonist of glutamate (that is, a drug which acts against the

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