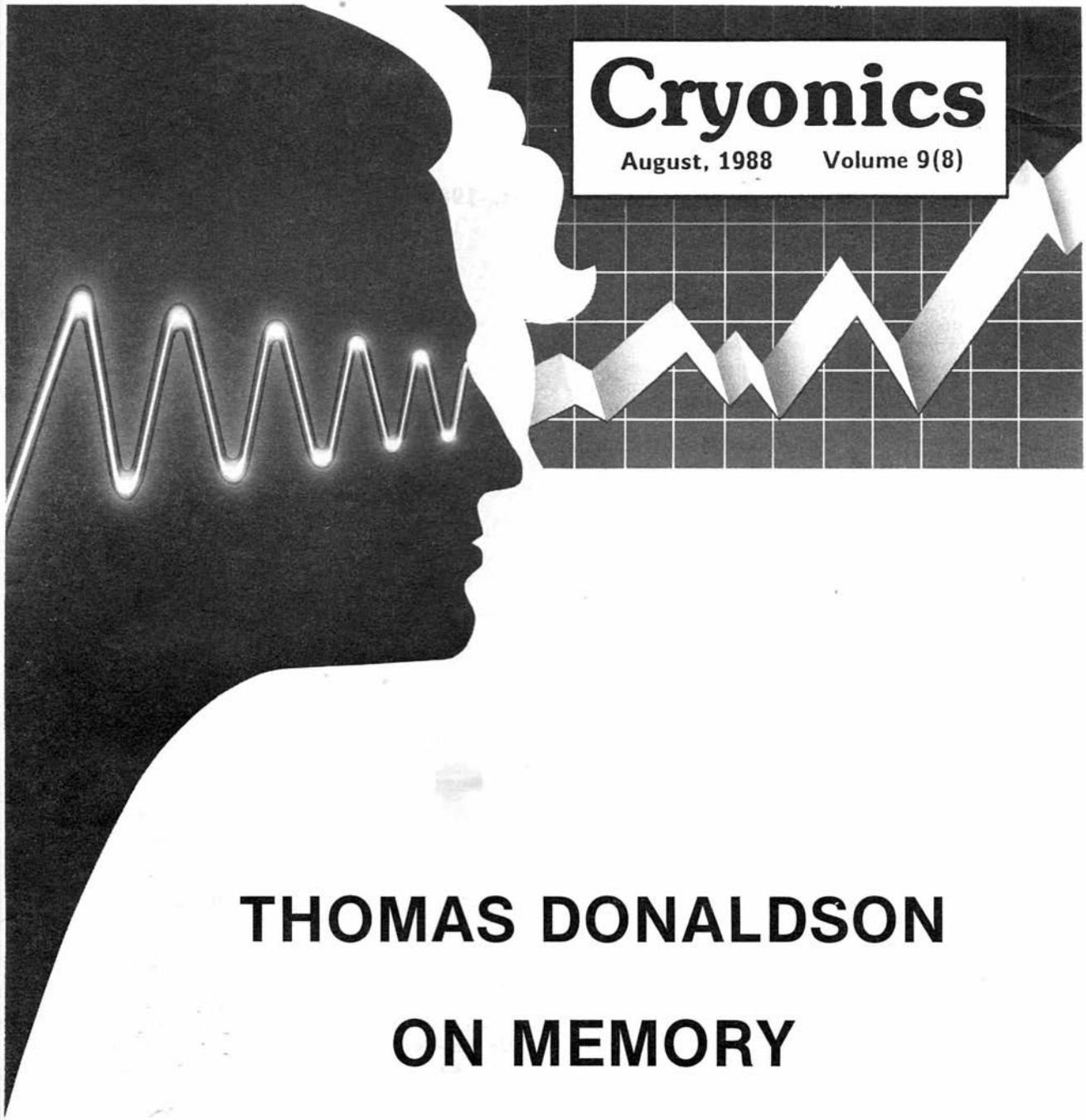

Cryonics

August, 1988 Volume 9(8)

THOMAS DONALDSON

ON MEMORY

Volume 9(8) **August, 1988** **Issue #97**

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EDITORIAL MATTERS

This month *Cryonics* tackles a tough subject: the biology of memory. While not nearly enough is known about how memories are encoded and stored in the brain, growth in our understanding of mechanisms of memory has been enormous. We have accumulated a number of articles by Thomas Donaldson that may make the welter of memory mechanism research papers flowing out of laboratories across the world comprehensible....

TERMI-NIX-MIX?

In the June, 1988 issue of *Cryonics* we published Alcor's current stabilization instructions for cryonic suspension. Some of our more technically inclined readers may have noticed the inclusion of a new anti-ischemia medication: deferroxamine HCl (Desferal). The purpose of Desferal is to chelate free iron and reduce ischemia-related free radical injury. Desferal has been shown to reduce cerebral ischemia related injury in a number of studies -- but it by no means eliminates it. The best results in preventing ischemic injury come when the animal is *pretreated* with free radical scavengers or antioxidants before the ischemic insult.

The problem with pretreatment with drugs like Desferal or the lazaroids (experimental antioxidants used to reduce ischemic injury) is that these agents either have to be administered IV, have side effects (or unknown side effects) and are available only by prescription or are not yet available at all. In short, they are not practical for use by cryonicists.

To some extent, all of us are at risk for ischemic coma. Some of us, namely those with heart disease, atherosclerosis, AIDS, and so on are at much higher risk. Is there anything that is both safe and effective which can be done to minimize the impact of ischemia for all of us?

The answer appears to be "yes". A number of recent papers have documented the extraordinary protectiveness of large doses of oral vitamin E and selenium against traumatic and ischemic injury. A recent paper by Edward Hall, et al of the Central Nervous System Diseases Research Division of the Upjohn Pharmaceutical Company has documented profound protection against ischemic injury in cats solely by supplementing

their diet with 30-40 IU per pound of vitamin E (for a total daily intake of 60-70 IU per pound.

Dr. Hall documents how he discovered that such massive levels of vitamin E supplementation could provide protection in a letter to the editor of *Free Radical Biology and Medicine* (4, 135-6 (1988)). Hall found that after a year of successfully using a feline model for subarachnoid hemorrhage (SAH) - ischemia model he was unable to re-duplicate his results. The nature and extent of the animal's injury was modest compared to what it should have been. After some detective work Hall was able to establish that the animal supplier had roughly doubled the vitamin E content of the animal's feed. Additional research was carried out to confirm this observation. Hall concludes:

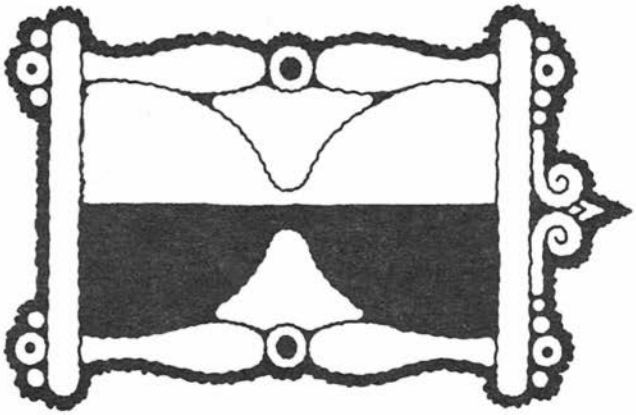
> *"In addition to the protection seen in SAH studies, we also observed a significant reduction in progressive cerebral hypoperfusion following a five minute period of near complete global brain ischemia. Moreover, in still another project in our laboratory, we discovered that the two-fold vitamin E supplemented cats were significantly more resistant to the behavioral and neurochemical (brain dopamine depletion) of the Parkinsonian neurotoxin MPTP."*

> *"While much work needs to be carried out to define the optimal level and necessary duration of vitamin E dosing to obtain a cerebroprotective effect, everyone in our Unit associated with these studies has begun their own program of vitamin E supplementation. Our results would suggest that the 3-5 fold vitamin E supplementation advocated by Dr. Diplock might confer meaningful protection against cerebral tissue damage."*

Clearly for Suspension Members at high risk of ischemic coma, supplementation with vitamin E and selenium *under their physician's supervision* would seem very prudent. For terminally ill patients with complex medical problems such supplementation would have to be carefully integrated into their medical care with due thought given to possible side effects (vitamin E in high doses can cause elevated blood pressure, anticoagulation and interfere with drug metabolism).

For well people, modest supplementation in the range of 400 units per day of vitamin E and 50 to 150 μg of selenium would seem prudent. Judicious use of other antioxidants might also be in order after a careful look at the literature. Perhaps one of Alcor's physician members could collaborate with Thomas Donaldson to come up with a mix - - and Life Extension Foundation could compound it.

What to call it? Termi-Nix Mix perhaps? Any other ideas?



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MEMBERSHIP COUNT

As of August 20, Alcor has 108 Suspension Members and 194 Associate Members.

ALCOR ACQUIRES PEDIATRIC PATIENT STORAGE UNIT

In the last two years Alcor has had no fewer than five phone calls from parents of children with life-threatening or potentially terminal illnesses. In two of these cases the parents of the ill child were well informed about cryonics and had a prior history of involvement. With growing interest in and support for cryonics we expect such cases to become more common. Additionally, our recent surge of sign-ups is bringing ever more families under the Alcor umbrella. The number of children signed up is rising.

Small dewar next to standard-sized dewar.

In fact, while the number of children directly covered by Alcor is small, that number may be misleading. A fair number of Alcor Suspension Members who have children have simply not signed them up owing to their low risk of dying -- but nevertheless *would* make arrangements to place them into suspension if the need arose. Small children could of course be stored in a standard dual patient Alcor dewar. But such storage would not be very efficient if there were an alternative.

Now, there is. On July 15, 1988 Alcor acquired a dual patient "pediatric" patient storage unit. The new unit's interior measures 22 1/2 inches in diameter by 52 inches high and could easily accommodate two children up to seven or eight years of age. The unit was not designed for this purpose, and was purchased used for a small fraction of its original price of $10,000. How much did we pay for it? Four hundred dollars!

In addition to its potential for accommodating children, the unit will be very useful in cooling neuropatients to liquid nitrogen temperature using Alcor's "nested dewar" system in which one dewar containing a patient cooled to dry ice temperature is slowly (over a period of 20 days or so) lowered inside another dewar which has been partially filled with liquid nitrogen.

The dewar was in excellent condition and had been recently reworked and rewrapped with superinsulation. We got such a good price on it because the major cryogenic repair and fabrication house in the Orange County area moved out of state and sold it for scrap prices!

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AUTOMATED PATIENT COOLING --IS IT ON THE WAY?

For a number of years now it has been known that slow and well-controlled rates of cooling result in far less disruption of complex mammalian tissues such as kidneys and hearts. For this reason Alcor has always employed slow, controlled, cooling of its suspension patients, using a liquid heat exchange bath. Several years ago we upgraded our

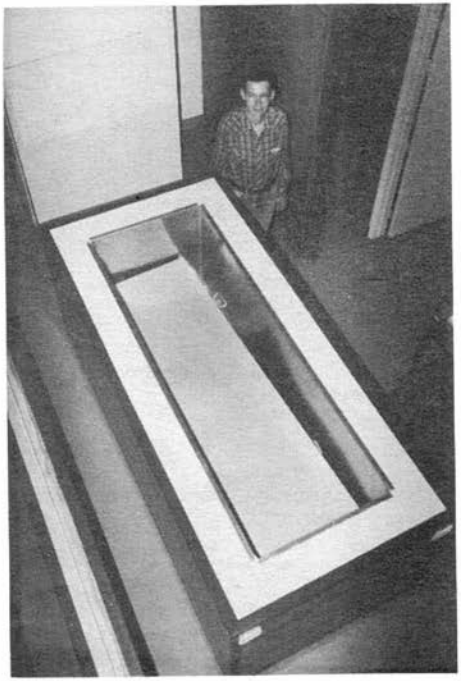
heat exchange bath and switched from flammable and potentially toxic isopropyl alcohol to silicone oil (Silcool). Per our expectations (and previous experiences with Alcor neuropatients) the Silcool bath worked well in the cooling of our recent whole body patient. But this suspension also pointed up a number of shortcomings in the cooling system as it stands.

The simplest and most apparent is that the cooling tank is not deep enough. For thin patients there is no problem, but for someone who is even a little on the heavy side, the oil level may have to be right up near the top of the tank -- resulting in splashing and handling problems. Direct addition of dry ice to the oil results in localized cold spots, contamination of the oil with particulate and chemical debris, accumulation of large amounts of water vapor, and spotty control over the cooling rate. How much dry ice do you add? What happens if you overshoot? Additionally, heat exchange rates are slower than desirable (even taking into account a slow rate of descent such as 1°C per hour) and could be accelerated if the bath were vigorously stirred.

Another problem, which is a very serious one, is the problem of active control being required every minute of the process. A person has to sit by the bath and constantly monitor the situation and add small amounts of dry ice as needed to drive the temperature descent at the right rate. Despite our best efforts at training people to do this, each individual has his or her own style and cooling curves end up deviating from the theoretical ideal.

What is needed is an automated system that can carry out controlled rate cooling, including creating plateaus and "soak periods", gather data from a number of probes at inhumanly frequent intervals (like once every 30 seconds or once every minute) and have an alarm capability to summon help if the system goes wrong (what happens if a human falls asleep at the switch?!!!).

The first steps in designing such a system have been undertaken. Dr. Mike Perry (and another Alcor researcher) have developed mathematics and programs for the purpose, a circulating pump system (capable of recirculating Silcool bath at a flow rate of nearly 3000 gallons per hour!) has been purchased, and, last but certainly not least, a cooling tank suitable for whole body patients has been constructed.



The new dry ice cooling box. A standard shipping casket inside the box and Mike Perry provide scale.

It is mostly the construction of the cooling chest that we report on here. The effort consumed nearly three weeks of Hugh Hixon's time (and about a week of Mike Darwin's) and resulted in one of the best looking (and we hope best functioning!) cooling units ever built. The refrigerator has a large inner aluminum tank (for holding cooling oil or liquid nitrogen), dual shell polyisocyanurate foam insulation (second generation urethanes which take cryogenic temperatures) and a very

rigid, sandwich panel exterior construction to eliminate the side-sagging problems which have plagued previous efforts in this area.

The unit has turned out better than we had hoped. Its appearance is spectacular -- Hugh Hixon's workmanship deserves elaborate praise. The design, which reflects Mike Darwin's considerable experience with dry ice boxes over the years, also appears to be sound. Hydrostatic testing has demonstrated the unit's mechanical strength and calculations indicate that its efficiency for both dry ice sublimation and liquid nitrogen boiloff will be within satisfactory limits for cooling of patients. From published engineering data for polyisocyanurate foam, we estimate that the dry ice box will use around 30 lbs. of dry ice per day, or around 100 liters of liquid nitrogen per day. The truth will of course be in an actual test.

The only part of the system that remains to be put in place is the purchase and adaptation of a controller/data acquisition unit. Ideally this would be a computer with the appropriate hardware and software, but less expensive (and less sophisticated) systems are also being examined. We can't say when this purchase will be made, but we hope (legal and other matters permitting) that it will be in the not too distant future. In the meantime we have a top flight "dry ice box" and a greatly improved manually controlled cooling system.

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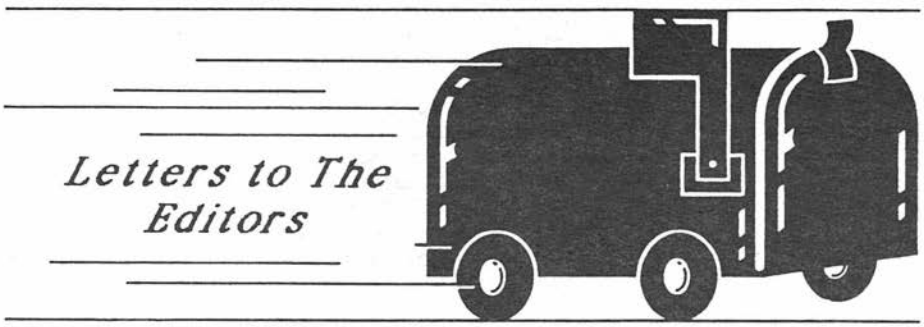
ALCOR MEMBERSHIP DIRECTORY?

Several members have requested that Alcor put out a directory of suspension members' phone numbers and addresses so that members can interact directly without having to go through us. The major obstacle to this has been a strong desire for privacy on the part of some of our members. This desire for privacy is understandable and we will not compromise it. On the other hand, the recent crisis with the Riverside County Coroner has demonstrated how important it is to have flexibility and to be able to have members "network" with each other during an emergency.

The solution to the privacy problem would seem to be to *ask* each member if he or she would like to have their phone number and address listed in a Suspension Membership Directory. The directory would be distributed only to Alcor Suspension Members.

If you would like to be listed in such a directory, please fill out and return the enclosed post card and we'll include your name and number. We will only produce the directory if there is sufficient interest. *So if you want to see this happen you need to fill out and return the card!*



To the Editors:

I wholeheartedly endorse the reasoning and recommendations in Brian Wowk's article, *The Death of Death in Cryonics*, (June, 1988). Future medicine based on assemblers and nanotechnology will be able to cure many disorders, including severe, long-term, whole-body frostbite. Today's patients with these disorders (if stabilized at low temperatures) are in *potentially perfect health.* To call such people dead is an abuse of language and sense; it is misleading, upsetting, and destructive.

When I discuss what future cell repair technologies imply for present-day biostasis, I find no reason to talk about death, except as something to be avoided. Whenever someone speaks to me of somehow returning the dead to life, I say, "What? That's impossible by definition!" I recommend this verbal practice to anyone who would like to see more accurate and and positive language used by the biostasis community. And please complain to editors until they correct their writers!

I also endorse Brian's recommendation of the term "ischemic coma" to describe the common condition for which suspension is the only medical option. If biostasis is to become widely accepted, it must be recognized as a *conservative* medical option. My dictionary defines "conservative" as conserving or tending to conserve; preservative, and as "moderate; prudent; safe." These definitions describe medical conservatism (in the technical rather than the old-fogey sense); they equally well describe biostasis, which is nothing if not safe and preservative. Which is the more conservative therapy for ischemic coma -- one which stabilizes the condition of the patient, or one of the common "therapies" which obliterate the patient's tissues? A maxim of medicine says, "First, do no harm" -- which therapy does less harm? In light of this, which is the more moderate and prudent, and hence the more conservative? I believe this conservative stance -- How do we minimize harm to the patient? -- will do more for the acceptance of biostasis than will talk about radical treatments and improbable, cosmic notions of "immortality".

Many problems would disappear (and others would arise) if suspension were recognized as a medical procedure and patients in biostasis were recognized as being in a state of (say) "suspended life". In particular, a suspension team could no longer be accused of homicide and a biostasis organization could no longer be accused of illegally storing human remains.

On the negative side, patient care in present facilities might be considered unlicensed medical practice -- but to make this accusation would entail admitting that the patients are indeed avoiding death by virtue of their continued suspension. Barring judicial madness, this would seem to preclude any legal action that would terminate

patient care -- and who else would take responsibility, and with what funds? In any event, one needs no medical license to provide a warm shelter for the homeless; why should one need a medical license to provide a cold shelter for the suspended?

More plausibly, the act of *placing* patients in suspension might be regarded as unlicensed medical practice. Here, the best course might be to use two inconsistent legal theories. First, one would note that the patient was (in accord with current, conservative medical practice) legally dead, and thus the suspension cannot have been a medical procedure. Second, one would note that, despite this legal fiction, the patient is *not* in fact dead, and this by virtue of the very suspension procedure in question. If the lack of a medical-qualified suspension team stems from the lack of an available physician willing to perform the procedure, then so much the worse for the quality of current medical practice. What persons or entities would have standing to bring charges based on the unlicensed practice of medicine, and would they in fact do so, thus admitting suspension to be a medical procedure? What would it require for a suspension team to be "medically qualified," in a legal sense? And might laws relating to emergency first aid have any bearing here?

My gut feeling is that the biostasis community needs to move from a pseudo-mortuary status to a medical or paramedical status, and the sooner the better. A large part of the battle involves the use of accurate language (which Brian Wowk has described so well), and a stance backed by appropriate legal theories (whatever those may be). But these are mere armchair observations by a theoretician stepping outside his field. I toss them out for consideration by those whose backgrounds in law and by those on the firing line of practical experience and legal responsibility.

The soundness of Brian's recommendations, I believe, stands regardless of the additional issues I have raised in this letter. His recommendations can be justified on the narrower grounds of clear, positive communication. My more tentative suggestions are aimed at longer-range goals, such as being able to bring a malpractice suit for failure to treat ischemic coma. The first creditable suit could make a world of difference.

Sincerely yours,
K. Eric Drexler

* * *

Dear Editors,

I was interested in your article, "Less Restrictive Criteria For Brain Death" (July, 1988). Please note that the originator of the concept of "brain death" was Dr. R.S. Schwab, chief of the EEG lab at Massachusetts General Hospital in boston. The criteria were as follows:

"In a patient where cardiac function is present, there should be:

1) Complete unresponsiveness and unreceptivity to external stimuli.
2) No muscle activity (except cardiac muscle).
3) No reflexes (including tendon jerks, vestibular reflexes, corneal or pupillary responses, etc.).
4) No spontaneous respiration (patient is on a respirator).
5) There should be no hypothermia (exact temperature not mentioned), and
6) No history of drug ingestion.

(Numbers 5) and 6) are included because patients with these conditions can recover from *so-called* "brain death".)

7) All these criteria should be present for at least 24 hours.
8) An EEG showing electro-cerebral silence (ECS) is confirmatory, but *not essential* for the diagnosis of "brain death".

This statement was made by a physician (the late Dr. Schwab) who was the originator of EEG's in the U.S., and who had devoted an academic lifetime to its study. I had worked with Dr. Schwab, and the findings were published in 1968.

"Flat EEGs -- Clinical and Pathological Correlation."
Drs. Aldereto, Jeri, Richardson, Sament, Schwab, and Young;
Presented at the American Academy of Neurology meeting, 1968.
Published in *Proc Amer Acad Neurology*, (1968).

Later on Dr. Schwab stated that that he did not like the term "brain death", for reasons mentioned in your own article, and he used the term "irreversible coma" instead. Some later developments in this field have been; 1) *some* neurologists have stated that 24 hours is too long to wait in the presence of all these criteria, and that twelve or six hours is enough; 2) some have stated that it is not necessary to wait until *all* the criteria are present -- for example, it is possible in some cases for the tendon reflexes in the lower limbs to persist for days or longer, even though *all* the other criteria are present. This does not alter the prognosis of brain death -- it only means that some cells in the *spinal cord* are very resistant to anoxia. Some states have included in their definition of brain death, "The total cessation of brain and brain stem function". This is not entirely satisfactory because there is no way to know if "each and every neuron" is dead. The best criteria in my belief are those advocated by Dr. Schwab (Harvard criteria), or a close modification as suggested above.

Sincerely,
Sidney Sament, M.D.
Easton, PA

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THE ALCOR SURVEY, 1988

by Max O'Connor

Introduction And Directions (The survey is inserted in the center of the magazine.)

This is the first survey of the membership in six years. The first was devised and conducted by Steve Bridge (then an editor of *Cryonics* and now an Alcor Coordinator) and revealed much interesting information about the people of Alcor as they were in 1982. In the intervening years, Alcor's membership has grown considerably, its operations have expanded and continually improved, and the environment in which it exists has changed.

Apart from an interest in seeing how things have changed, the survey may serve a practical purpose. Alcor appears to have entered a period of especially rapid growth; suspension membership recently topped 100 and looks set to reach 130 by the start of 1989, recent events have generated enormous amounts of free publicity, and there is an optimistic feeling among some of us that with the right approach we could soon have a *very* much larger membership. This survey might contribute towards that goal if it succeeds in telling us something useful about the kind of people who have been attracted to cryonics.

I'm not relying on this too much, however, since the information gained then has to be *used* effectively and, furthermore, we shouldn't assume that future cryonicists will be like us.

Please put as many of your answers as possible on the printed survey (or a copy). Please clearly label with the question number any additions which you put on separate sheets. If you decide to write out all your answers on separate sheets (which will make life harder for me) *please* ensure that it's clear which answers belong to which questions. The results will be printed in *Cryonics* by the end of the year. Please do take the small amount of time it takes to answer the questions -- the results will certainly be interesting and hopefully will be valuable if we get responses from a good proportion of our readers and members. Your answers to the survey questions are confidential. You may put your name on your answer sheets if you wish but you may prefer to be anonymous. Please send in the survey as soon as possible. Responses received ten weeks after this issue is mailed will not be used. Finally, I would like to thank Steve Bridge for producing the 1982 survey from which I have heavily borrowed. I would also like to thank everyone who suggested ideas for questions during and after the **Life** *Against* **Death** Conference.

Send your survey answers to: Max O'Connor; 1129 W. 30th St., Apt #8; Los Angeles, CA 90007. Tel: (213) 746-5571.

"THE LIVING DEAD": A Review

by Mike Darwin

A low budget horror film? A bad-joke-parody on cryonics? No, neither. "The Living Dead" is the first in-depth look at cryonics and its scientific basis. It was produced by Uden Associates (London) for for the *Equinox* series on British Television's Channel 4. The documentary represented an enormous amount of effort and was made with the full cooperation and support of Alcor. The show's producer, Valerie Kaye, came to the U.S. with a four person film crew and shot large amounts of footage at Alcor's facility and elsewhere in the Southern California area. They also traveled to San Francisco and to Bethesda, Maryland in order to get footage of some of the scientists who testified on Alcor's behalf in the recent Dora Kent case. Given the apparent professionalism and sympathy of Valerie Kaye (the show's producer), we had high hopes for the outcome of this documentary.

Were those hopes realized? Is the media finally starting to take cryonics seriously? Are we at last getting a degree of legitimacy we have been so long denied? In order to do any justice to answering these questions and reviewing the documentary, it is necessary to evaluate it from a number of different perspectives. I will try to do this -- although be advised that this is not only a thankless task; it is a nearly impossible one. (No doubt Ms. Kaye must have felt the same way about making the film in the first place!)

First let's look at "the Living Dead" from the standpoint of previous media efforts to examine cryonics. Judged from this perspective, the effort would get a rating of 80 - 90 out of a possible 100 points. Just the fact Ms. Kaye decided to examine cryonics from a "scientific evidence" perspective counts for a lot, since this has never been done before. But it doesn't merit 100 points. Far from it. In reviewing this effort I decided to pull out a tape of the late 1970's BBC documentary on cryonics entitled "The Immortals". With the exception of not having scientists of stature available to testify for the rational basis of cryonics, "The Immortals" is a better documentary in every way: organization, content, clarity, and production values.

The second and perhaps the *fairest* way to evaluate "The Living Dead" is to evaluate it as what it purports to be: straight science reporting. How does it stack up to other science documentaries? What are its production values? How well does it expose the issues and arguments and how well does it tell the story and give the viewer what he or she needs to know to form an opinion? How free is it from nonobjective slants that could cause problems in evaluating the material presented? In other words how *professionally* good is it?

The evaluation here is damning. I would give "The Living Dead" only 20 points out of a possible 100. I have seen some of the other films in the Equinox series and this is by far the absolute worst of the lot. Indeed, when evaluating

this film from the professional perspective the viewer has to rephrase the question completely and ask: "What's *right* about this film?", rather than "What's wrong with it?"

We can start with the title. It's prejudicial and sensational. It is automatically linked with images from the horror movie genre. No serious scientific evaluation of cryonics (or anything else!) belongs linked with these kinds of non-rational, blind-emotion-provoking images. Period. If you are doing a general news documentary, you can get away with almost anything. If you are doing a serious science report (which the Equinox series purports to be), even one aimed at a "popular" audience, then such prejudicial and unscientific titles are inappropriate. A better title would have been "Cryonics: A Scientic Evaluation" or even (distasteful as it would have been) something like "The Science of Cadaver Freezing?"

The lack of professionalism of the title is unfortunately *not* where the problem ends. It corrupts the effort on every level. The music, much like the title, is totally inappropriate. It can best be described as of a piece with "B" grade horror/murder mystery movie music (except this does such music a disservice!). I'd love to see a series on open heart surgery or health care issues scored with such music. Just how bad a grade of horror movie music is it? The answer is that it can't even be put on a rating scale. Listening to the score for this effort makes it infinitely more comprehensible why there are so few great British composers. I would say without hesitation that the score to "The Living Dead" is even worse than British food -- and that's what I call *very* serious criticism. It is also inexcusable, since there is so much *good* music in the public domain. Again, this is just a cheap shot, no doubt aimed at making the documentary "more compelling" or "more commercial". Unfortunately it also makes it something else; disasterously nonobjective.

Leaving aside these points of style and proceeding to matters of substance, other equally serious problems become noticeable. We are told at the outset that "Southern Californians as a people are preoccupied with physical beauty and the pursuit of immortality" and that they "torture themselves to keep fit and attractive". To illustrate this point people were shown running. What a strange statement to make! Who says running is torture? Who says exercise is torture? The person who wrote the narration for the film must have been someone who spends all of his or her time on a sofa watching British TV! What a bizzare and biased statement to make! Does London have no runners and no health clubs? Are there no cosmetics sold in Britain, no "adverts" on Channel 4 for health or beauty aids? What a contemptible attitude to have towards fitness and one's own body, that you would describe moderate exercise as "torture". When I viewed "The Living Dead" for the second time, I decided to watch carefully for expressions of pain or

discomfort on the faces of the runners and swimmers they filmed. As I expected (being a runner myself) there were none.

A little later on we are treated to a scene in a Southern California "old people's home" and told something to the effect that growing old in America is far from a happy process and is marked by disability and warehousing of the old in isolation and loneliness.

What are we to believe, that growing old in England is a benign and happy process where people survive without unsavory incident until they cheerfully wake up dead one morning? Are we to believe that England has no rest homes or ill, old people? The *fact* is that only 5% of Americans over the age of 65 end up institutionalized! And the fact is also that adult health is better overall in the United States than it is in the UK. Also, on average Americans are richer and better able to enjoy their "declining years" than are their counterparts in the UK. Once again this kind of remark is a prejudicial cheap shot and distorting view which characterizes the entire film. For instance, nowhere is it mentioned that there is a British cryonics group and that there are a number of UK people signed up with Alcor -- several of whom got the hell out of England to come to the United States and hope to avoid, at almost any cost, having to return to live there!

Then there are the problems with the very structure of the piece. The film comes across more as a collage of images and ideas rather than as any coherent effort. There is no clear and succinct articulation of the cryonics premise and the viewer is not given any framework to judge what he or she is about to see. And while two scientists speak out somewhat equivocally for cryonics being a "rational gamble" the opposing view is not presented and the hostile scientists' arguments are not made clear. Good science reporting asks questions, identifies and exposes the key issues, and then provides perspective from both sides of the controversy on those key questions and issues.

Why do cryonicists think that cryonics will work? What are their scenarios for repair processes and the evidence they believe supports them? What are the key objections to the procedure; scientific, social, ethical, and economic? What cryonics is all about is rooted in some very basic givens: human beings are packages of information encoded on a molecular framework, death is the irreversible transition which occurs when identity-critical information is lost..., etc. Nowhere do we see these ideas clearly presented and related to each other with an opportunity for opposing scientists to to say patently stupid things like: "It won't work because they are freezing dead people." and then being forced by the reporter to try to define death in some inadequate, circular, function-based (as opposed to structure/information-based) way.

Instead of such taut and organized reporting on the issues, we are given a lot of

mumbling and meandering and largely unsubstatiated claims. The worldview of cryonicists is presented only chaotically, and the viewer has to struggle to make sense out of the arguments.

There are also grossly inappropriate or *non sequitur* statements made in the narrative. Several times the narrator asks: "The question is, was Dora Kent legally alive when the procedure was started?" That question is never answered. It is not only never answered, there is never even an *attempt* to answer it. What are California's criteria for legal death? Why is there any reason to believe that Dora Kent may not have been legally dead when the suspension process started? Indeed, what is the background or chronology of the whole case? None of that useful and necessary information is presented which would allow the viewer to put the *question* into perspective (let alone form an opinion about what the answer might be!). This is just lousy journalism and there is no excuse for it.

Many of the visual images shown are presented without sufficient context or proper narrative to really explain what is happening and what its significance is. This is sloppy editing and reporting technique. Some of the footage is offensive and inappropriate, such as a painfully long segment of a non-Alcor suspension patient, showing a rectal probe being removed, and a poorly planned and disorganized transfer of a suspension patient from perfusion table to dry ice cooling unit. The only thing more difficult to fathom than Ms. Kaye's *use* of this degrading and disgusting footage is the rationale for its release to Ms. Kaye in the first place. (reportedly Ms. Kaye used this footage because she found it "visually compelling".)

Finally, there are is the lack of analogies or illustrations that would help to clarify or make more comprehensible the ideas being discussed. This is perhaps understandable given the modest budget and resulting low production values of the film as a whole.

The tragedy in this effort from the science documentary standpoint is that it fails to really cover or address the scientific, legal, and technical issues raised by the Dora Kent case. If suspension procedures are started within three to four minutes of cardiac arrest and they artificially restore circulation and breathing while maintaining brain viability -- and then suspension is carried out -- is that murder? What is death? Is it loss of function, or loss of information in the form of structure? What are the legal and ethical implications that result from a change in our definition of death? Was Dora Kent dead in any absolute or meaningful sense even if she did meet the legal criteria for death when this procedure was started? These are fascinating and important issues. Unfortunately, most journalists lack both the brains and the background to identify and explore these controversies at all -- let alone well.

Finally, it is possible to evaluate this effort from the perspective of how well it acts to communicate about Alcor and cryonics or educate the public about it. The rating here is a bit higher, perhaps 30 to 40 points out of 100.

Most of the reasons it doesn't get higher marks are treated in detail above but are worth briefly summarzing again: The creepy music, the inappropriate and out-of-place questions, the prejudicial statements aimed at setting the British apart from (and above) us poor Californians who "torture ourselves for youth" and who "warehouse our old people" seriously cut into the ratings. The lack of organization and coherence...

These elements allow people to "escape" from the responsibility of evaluating the idea for themselves. Getting old, suffering a horrible decline, and dying are things that happen only in California -- or at least they are things that only Californians are morbidly preoccupied with. The underlying message is: "We British, we have our heads in the right places, we know how to take death in stride" (yes, you just queue up for it). "And we don't have old people's homes" (yes, because your medical care is so bureacuratized and ineffecient that you're dead before you ever have to worry about living *long* enough to end up in an old people's home). In

short, old age and death are something that that happens to *them*, not *us*. And doesn't it make you feel superior and safe to see how those poor old Americans try to cope with it?

The film also fails to communicate key ideas that are necessary to any rational evaluation of cryonics. What is death and how is our view of death and life different than the rest of the world's? What is the cryonicist's paradigm, in other words?

Another major, and I believe inexcusable, oversight is the failure of Ms. Kaye to point out that Alcor is a mutual aid, nonprofit, membership organization. The impression that is quite deliberately given is that Alcor is a commercial business with all the misleading emotional-reaction baggage that implies. This is particularly unfair of Ms. Kaye since everyone in Alcor was at pains to emphasize that the reverse was the case.

The distasteful footage of another organization's suspension patient which Ms. Kaye chose to use greatly detracts from the the film's utility in terms of positive education of the public about cryonics. One British reviewer described the suspension process shown as "disgusting and undignified". I wholeheartedly agree. And I am not alone in that assessment: there were gasps during the showing of the film here in Southern California. Two guests who were present remarked that such footage was a total turn-off for them and would effectively prevent them from signing up with any organization that treated its patients in that fashion. And of course the B-movie title and music didn't help matters either.

So what's the final assessment? Is "The Living Dead" a plus or a minus for cryonics? I think the answer has to be that overall it is a "plus". It does articulate the core ideas of cryonics (although in a 1960's kind of way) and it does show that there are organizations which exist, which have real facilities (some of them even professional looking!) and which are carrying out suspensions. More importantly, it shows for the first time that respected scientists are taking this idea seriously. People such as Dr. Greg Fahy, the world's leading organ cryopreservationist, who spoke out at length, articulately, and well, for the rational basis for cryonics. Indeed, if there is any star in this effort it is Dr. Fahy. He is by far the most articulate and professional spokesman for cryonics in the entire production (although I imagine that was far from his intent). His mastery and organization of the facts was superb, his presentation style excellent, and his appearance very reassuring.

Of course, as usual there are lessons for Alcor in all of this. We need to be more careful about footage that is released by Alcor. Tape with staff members using inappropriate language and engaging in unprofessional behavior such as gum-chewing were released by mistake -- this will *not* be allowed to happen again. We also need to be more circumspect about remarks we make on technical and ethical issues which are "red buttons" for the community, such as the use of anencephalic infants for organ transplantation.

Nevertheless, despite its many and serious defects, the Equinox effort represents a turning point for cryonics -- credible scientists stating publically that cryonics is a rational undertaking with a solid basis in fact and science.

Right now, that is about all we can hope to get.

Thomas Donaldson On Memory

The following articles and book reviews were gleaned from the scientific literature by Thomas Donaldson, and written up by him for his *Science Updates* section in *Cryonics*. Between Thomas's productivity (which we encourage), a good supply of articles from other sources, and a desire on the part of the Editors of *Cryonics* to keep its page count to a managable size, Thomas's articles have accumulated. One of the topics that is of burning interest to Thomas (and the rest of us) is the *nature of memory*. In particular, what is its physical basis?

This question is of interest because successful revival from cryonic suspension depends on whether or not our suspension techniques preserve memory. Obviously, the question cannot be conclusively answered until the first people are revived from cryonic suspension, but we *can* engage in informed speculation, and modify our techniques to meet our needs.

These articles are not intended to be comprehensive. They are synopses of recent and

ongoing work on the leading edge of science, and are as they are found. Still, given enough of them, you can get a picture of recent work and thought in the field....

Read on.

* * *

Explorers Of The Black Box: The Search For The Cellular Basis Of Memory
Susan Allport; W.W. Morton & Co., New York, 1986.

Learning and Memory: A Biological View
Joe L. Martinez and Raymond P. Kesner (Eds.); Academic Press Inc., Orlando, FL, 1986.

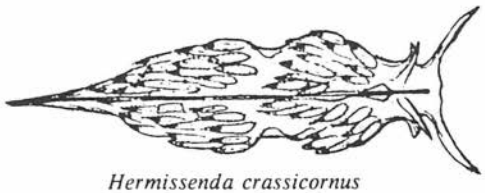
Both of these books are expositions of the current status of work on the biology of memory. Allport's book is a popular account, in fact the only popular account I know of. The book by Martinez and Kesner is a joint effort of several neurophysiologists, each of whom contributes a chapter. It is intended to serve as a text for a university course on the biology of memory. It is therefore written at a much higher level, assuming that the students already know a good deal of general biology and biochemistry, and giving an exposition of memory in a biological way.

Our understanding of memory is currently progressing very rapidly. We have a serious hope of understanding the main features of memory storage and processing, in a direct biochemical way, well before we'll be able to show direct survival of memory in suspension. This means, of course, that we'll be able to describe the biochemical processes involved, and show that they are extremely likely to survive freezing (or, perhaps not), well before we actually revive an animal or a human.

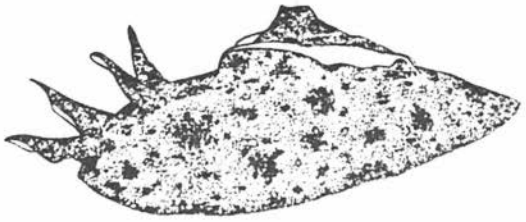
I think this possibility deserves serious thought right now about how we can take advantage of it. Survival of memory is now the only major gap in cryonics theory. Serious reading of the biological literature on memory, even though it gives no actual *proof*, leaves us with an impression of survival which is much more than mere faith (though still less than proof). We will be faced with the need to explain the biology of memory to a general audience, draw the conclusions about cryonics, and show that personality survives suspension not directly but rather by showing the survival of its *biological substrate.*

Susan Allport organized her book about the work of two major scientists in the study of memory, Eric Kandel and Daniel Alkon. For basically "tempest in a teapot" sorts of reasons, these two scientists have been at odds for a long time. Perhaps the reason is that both of them are studying very similar phenomena in basically similar animals; *Hermissenda* (the snail) in Alkon's case, and *Aplysia* (the sea hare) in Kandel's case. Both scientists are trying to work out how memory works by studying very simple invertebrate preparations. Both scientists have achieved very important insights into memory by this approach.

Condensed into a paragraph, the major insights have been that *Hermissenda* and *Aplysia* can learn simple associations between touch and a subsequent shock, or a smell and a subsequent shock. The neural circuits involved in this learning have been traced. Learning acquired by an individual animal



Hermissenda crassicornus
Length up to about 5 cm.



Aplysia californica
Length up to about 45 cm.

will survive in a neural preparation made from that animal. We can study this preparation isolated from its original body. The immediate biochemistry of this learning involves attachment of a phosphate group to a membrane protein which controls entrance of calcium into the nerve cell. Finally, there are tantalizing suggestions that this learning results in activation of particular genes, similar to what happens during development.

Susan Allport's book, perhaps because it is aimed at a popular audience, spends at least half its attention on personalities. She writes as if she is much more interested in the personal relationships of scientists than in the science itself. For someone who is interested only in the science, this can get annoying. We would like to have a clean summary of just what is known about the biology of memory.

For someone with this orientation, the book by Martinez and Kesner is much more to the point. It contains much more detail, not just about the lower-level learning of invertebrates but also about many other avenues of research. These include the studies of brain injuries and what they tell us about memory, the distinction between declarative and procedural memory, studies of long-term potentiation (Slices of hippocampus given repeated electrical stimulation will show a long-lasting propensity to respond to electrical stimulation). The book has a good discussion on this work, in which Gary Lynch is a major figure. The book also has a good discussion of Richard Thompson's work on a possible location of one kind of conditioned reflex. Finally, it has a discussion of what we now know about the biology and biochemistry of Alzheimer's disease and other amnesias.

Most current studies of memory don't directly address the issue of most importance to us: that is, how *long-term* memory is stored. The connection between memory and development could potentially become very important: it could tell us to look at the nucleus, rather than the synapses, for the chemistry of *long-term* memory. Unfortunately, neither of these books really addresses these issues directly. E.R. Kandel and P. Goelet have given an overview of their own special theory of memory, together with their thoughts about memory shutting off or turning on particular genes, in *Nature* (**322** 419-422 (1986)). As yet, however, that is a story not yet fully told. We'll have to wait patiently for its answer.

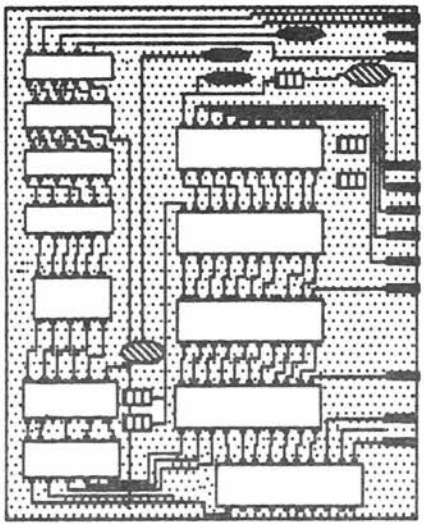
I would like to be able to state definitive conclusions from this work on memory, but we can't do that yet, however much we'd like to. both of these books suffer the inevitable defect that they are only Act I of the play. The major characters and their setting are now introduced. The major problems are set out. But where is the play going? We'll have to wait and see.

* * *

AN OLD WAY OF THINKING

It's been clear for a long time that our brains don't work like the "traditional" computers we see around us. There is no "CPU neuron", and brains still work after injuries that would stop ordinary computers completely. It's clear that we are chemical computers, but our principles of operation just don't match ordinary sequential computers.

But over the last several years both neurologists and computer scientists, working

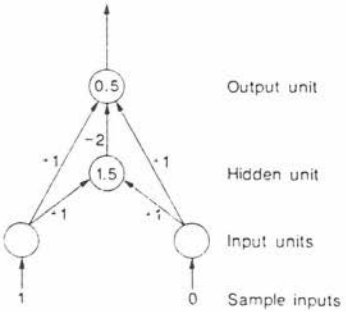


together, have begun to piece out how our brains actually process information and acquire new learning. This work isn't yet complete, but it's begun to succeed. Using these new principles, engineers have built devices able to carry out computational tasks very difficult, even impossible, for "ordinary" computers, including recognition of scenes, faces, and lettering. These devices are *neural nets.*

In the 1960s computer scientists made some of the first attempts to construct a network able to do computation. Marvin Minsky and Seymour Papert, at MIT (perhaps you have heard of them) constructed a device they called a perceptron (M. Minsky, S. Papert, *Perceptrons*, 1969). The perceptron was just two layers of "neurons", linked together. The aim was to imitate a nervous system. But Minsky and Papert discovered that perceptrons couldn't do some simple recognitions, such as seeing that something was square or blue but not both (an exclusive or). So for many years both computer scientists and neurologists forgot about perceptrons.

But only about two years ago, D.E. Rumelhart, G.E. Hinton, and R.J. Williams showed that by introducing a third layer in between the other two, and using a simple algorithm, they could obtain a network (of the kind now called a neural net) which could not only learn "exclusive or's" but also carry out complex recognition. Since that time many people have put a lot of work into neural nets.

Neural nets show behavior very reminiscent of animal and human learning. For instance, neural nets trained to translate written English into spoken English pass through a period in which they babble, just like babies learning to speak. This correspondence is close but not exact. In particular, human beings do seem to formulate high-level principles. But these principles come somehow from a compilation of the lower-level behavior of a neural net: they are not Rules in the sense of an AI inference machine (*Nature*, **330**, 12-13 (1987)).



Simple neural network with hidden unit.

Neural nets learn by adjusting the strength of connections of all their "neurons" to one another. They converge upon a solution. One of the most successful algorithms for neural net learning, simulated annealing, uses randomness to help this process. Connections aren't changed according to a fixed rule, but always have a "penumbra" of randomness about them. This randomness is very important because it prevents the neural net from getting "stuck" on a wrong idea. The algorithm can achieve learning which completely deterministic algorithms cannot.

In these systems, and very probably in our brains too, randomness plays a very important role. It makes possible a kind of natural selection for rules and ideas. Many organisms use random variation to achieve effects which look very intelligent. For instance, the bacteria *Escherichia coli* will randomly tumble about when food concentration is low, and suppress their tumbling when it is high. This causes them to congregate near

food (J.E. Segall et al., *Proc Nat Acad Sci*, **83**, 8987-8991 (1986)).

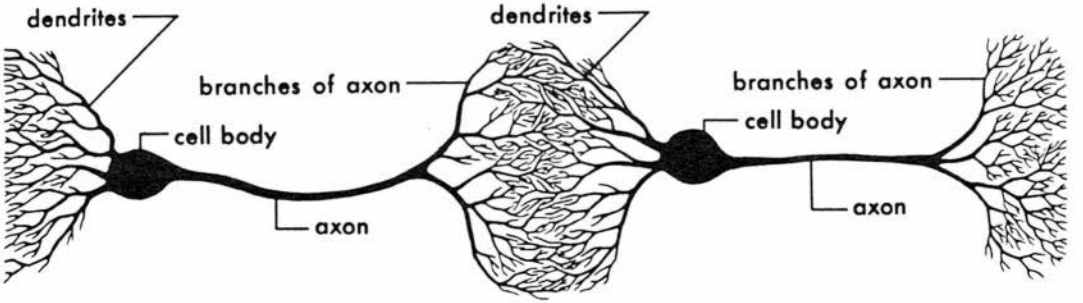
Neural nets are important for both computing and cryonics. One very old and difficult problem in AI is the "frame problem". This is the problem of constructing a machine able to change its frame of reference, rework its own rules, or go outside a codified body of knowledge fed into it from outside. Neural nets show one way to solve the frame problem. (It's not a way which normal sequential computers could emulate. These algorithms perform very poorly on sequential computers). Since neural nets have a random character to their learning, they can abandon even long-held principles when faced with new facts. Furthermore, neural net learning is highly parallel, and therefore can achieve goals taking sequential computers far too long. In fact, neural nets embody a serious criticism of the Turing test and Turing machines: simply that the time taken to do a computation is very important. Doing some kinds of recognition as fast as human brains but with a sequential computer, even a Cray, is quite out of the question.

For cryonics the lessons are different. First, when a neural net learns, what it has learned isn't encoded into any single neuron. We can't even find out *what* is learned without knowing the content of many neurons and the connections between them. But once learned, this knowledge is very distributed. Outright erasure of many neurons leaves the neural net quite unaffected: it behaves as if it still remembers. Neural nets therefore give us an example of how memory can be very robust. For years some neurologists have talked of memory as "holographic". That was a metaphor, rather than a theory, and now we have a theory. Secondly, and almost as important, neural nets show us that memory does not require explicit growth of new connections between neurons. All the neural nets studied by computer scientists and neurologists to date have an "anatomy" which remains fixed. What changes is the strength of connections, not their existence.

Computer scientists have implemented neural nets as parallel computing systems. At the IEEE Conference on Neural Systems (Nov, 1987) at least two scientists have programmed the Connection Machine (an experimental highly parallel system) to emulate a neural net. J. Alspector of Bell Labs has designed a specialized chip which will act like a neural net. Others are also working on similar chips.

The significance of neural nets isn't lost on neurologists either. At the 50th Dahlem Conference (*Neurobiology of the Neocortex*, reported in *Nature*, **328** 572-573 (1987)) Richard Andersen of MIT and David Zipser of UCSD reported their work with a neural net model of an area of the brain which locates objects in relation to the position of the head in space. The intermediate "neurons" in their model develop responses to their inputs which closely resemble the intermediate neurons in the actual visual cortex.

At this same conference many scientists reported results locating different processing functions within our brains. These indirectly support a "neural net" theory of brain function, even though few of the scientists spoke directly about neural nets. The



neural organization was exactly that we would expect if our brains were neural net computers.

For instance, visual processing in the monkey involves many different channels, some dealing with size, others with shape, color, position, and others (Semir Zeki, London). These channels are all interconnected. For instance, neurons in two separate brain areas respond to the length of bars in a way which depends on their interaction. Long range lateral connections within brain areas modulate and select responses. Charles Gross, at Princeton, reported his work with visual neurons in monkeys. He found that no single neuron gives a complete account of the stimulus; recognition requires response of a collection of these neurons (cf. also C.G. Gross et al., *J Neurophysiol*, **35**, 96-111 (1972)).

Even more recently, in *Nature* (**332**, 357-360 (1988)) C. Lee, D.L. Sparks, and others at the University of Alabama have reported an elegant experiment on control of eye saccades in monkeys. When we (and monkeys) look at a scene, our eyes jump about. Neurologists have traced the control of this motion to a particular brain area, the *superior colliculus*. Stimulating this brain area will cause eye motion, just exactly as if a button had been pressed on a machine. By reversibly anesthetizing some of the neurons involved, Sparks, Lee, and their coworkers could show that the direction of the saccade depended on the vector sum of directions coded by each neuron individually. This gives us another example of a kind of "neural net" behavior, in that mass effects of many neurons, rather than the computations of only a few, control behavior.

Neural nets use three fundamental principles to control their computing. These are the use of mass effects (many neurons, rather than only one, involved in a function), the use of randomness and natural selection to converge on the right response, and the use of specialized interconnection schemes for specialized processing. I believe that these principles not only underlie brains, but also underlie biological systems at a much lower level. Cells just do not operate like "machines" in the traditional sense. Instead they are bags of interacting chemicals. Enzymes do actually perform OR or AND operations on their chemical inputs, but they aren't physically connected to on another. They communicate through the mass effect of chemical reactions between many molecules. Often cells also use random effects such as diffusion to converge on a solution. Just as in neural nets, this use of randomness makes the cell very robust. Destruction of single components has no effect on cell metabolism, while destruction of even one part of a traditional machine can cause complete failure.

When we construct such machines ourselves, we will have learned many of these lessons. Conceivably such machines can be miniaturized still further. Alternatively, we may devise nanomachines which are much less robust, protecting them with elaborate shields against perturbation. Miniaturized computers operating exactly like those of today would have many uses outside of biology, even if they could not work for cell repair or seriously compete with cells in the cell's own milieu. Traditional computing will have its uses, into the indefinite future. But neural nets, and life forms generally, tell us very loudly that even our current engineering *architecture* isn't the last word in sophistication and advance.

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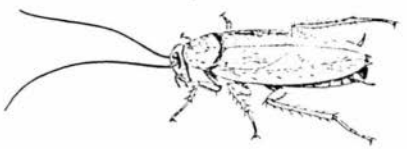
Thomas Donaldson On Memory

CELLULAR LOCATION OF MEMORIES

Over the last 10 years neurophysiologists have made striking advances in understanding how memories are stored. Unfortunately they still haven't come to a fully proven theory. But they've worked out the *right questions*. With the right questions, answers are only a matter of time.

The major advances made over the last 10 years have come because of studying several *model systems*. Some of these are invertebrates which can learn simple things, such as *Aplysia* and *Hermissenda*, two varieties of sea mollusk. But neurologists have also used other systems, such as cockroaches and mammalian brain slices. They have also used some simple conditioned responses in mammals. By reducing the problem to these models, we can study learning in simple cases without becoming sidetracked by all the complexity of normal learning. Invertebrate systems such as *Aplysia, Hermissenda*, or cockroaches are particularly interesting because the nervous systems of several such animals have now been mapped out *in detail*. On this basis we can say, for instance, that connections in the nervous system of *Aplysia* are the same for all individuals. Among other consequences, this means that learning in these animals *cannot* proceed by the formation of new connections.



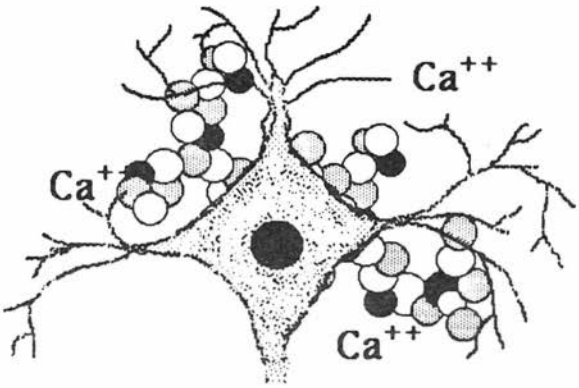
Recently in both *Science* and *Nature* several scientists involved in the study of memory published two separate reviews of their work. In *Nature* (322, 419-422 (1986)) E.R. Kandel and his colleagues, who have intensively studied learning in the marine snail *Aplysia*, published a review of their work with general discussion of what it means for long-term and short-term memory. Not long after that, Richard Thompson, who has studied learning of conditioned responses in *rabbits*, published his own separate review in *Science* (233, 941-947 (1986)).

Kandel and his coworkers have studied the basic cellular neurobiology of learning in *Aplysia*. They distinguish four different forms of memory on the basis of their experiments. First, short-term memory may come from a modification of local proteins. These proteins are somehow involved in the nerve transmission process at synapses. Second, a longer-term memory may come from feedback processes set up among these proteins. One theory, for instance, proposes the existence of an enzyme which increases its own activity, coupled with a second enzyme which damps down the activity of the first. If activity is increased enough by some stimulus, a positive feedback loop starts off. This loop persists for much longer than before it existed. The enzyme may modify itself by causing attachment of a phosphate group.

All of these mechanisms can explain short-term memories. For longer-term memory, protein synthesis seems necessary. For instance, several authors have shown that using drugs to prevent synthesis of new proteins will block the formation of long-term memories. In mammals scientists have known this for a long time. In *Aplysia*, however, these experiments were only performed recently (E.R. Kandel *et al*, *Soc Neurosci Abstr*, 11 795 (1985)). This work draws a link between memories in human beings and the simple model systems. What it says about memory in general is that long-term memory must somehow involve proteins. But these authors propose at least two *different* mechanisms of long-term memory. The key point is that *most brain cell proteins only last for at most two weeks*. We can't explain truly long-term memory by protein synthesis alone.

These authors propose that true long-term memory comes about because of a change in expression of *genes*, very similar to the process of development. It's clear that the normal changes of development, that is, how cells of one kind differentiate into specific

functions (i.e., kidney cells), are among the few very long term processes in biology. They are certainly good candidates for explaining the long-lasting change of long-term memory. Kandel and his colleagues are proposing that long-term memory is like cellular development, in fact *is* one form of development.



The persistence of memory is only one piece of evidence. Kandel *et al* also point out other evidence. Long-term memory causes growth of synapses. This is very close to a developmental change. The same drugs preventing protein synthesis and memory at critical times will also prevent development. Among the chemicals which may be involved are specific protein products which, for instance, cause cell transformation to a cancerous type. (Kandel and his colleagues aren't proposing a relation between cancer and learning, but instead saying that the chemical behavior may be similar). These proteins are all made by specific genes (*oncogenes*) which transmit a susceptibility to cancer. Higher levels of Ca^{++} (positive calcium ions) and cAMP (cyclic AMP, a cell messenger chemical) happen in neurons with learning. These same chemicals cause the oncogenes to switch on.

This is a theory about the cellular basis of memory, rather than established fact. However it is easy to see how we can test it, especially on model systems.

Richard Thompson in *Science* (**233**, 941 (1986)) approaches memory much more from the top than the bottom. Thompson has engaged in careful studies of one particular kind of conditioned response in rabbits, blinking in response to a tone. Thompson's experiments have involved systematic damage to his rabbits' brains, trying to elucidate the circuitry involved in this one learned response. He has also used chemical means to temporarily cut off operation of specific brain regions. He believes that he has found a small (but that is many thousands of cells!) brain region both necessary and sufficient for learning the eyeblink response.

By this Thompson means that an injury to this small region will prevent learning the eyeblink response, even though it seems to have no other effects. Furthermore, this injury does *not* prevent the normal response of blinking to a stimulus such as an air puff. He suggests that this location actually contains memory for the eyeblink conditioning. In his article in *Science*, Thompson reviews his own work and that of others on circuits involved in memory for specific conditioned responses. His work includes studies of the complete circuit for eyeblink response. Others have studied the *vestibulo-ocular reflex* (or VOR, the system by which our eyes adjust their focus whenever our head moves, M. Ito, *The Cerebellum and Neural Control*, 1984) and conditioned fear response (M. Davis *et al*, *J Neurosci*, **2**, 791 (1982)).

Detailed study of simple conditioned responses in mammals may well tell us how our own memories work, particularly in terms of the anatomical connections needed. That sort of mapping of course can't come from studying *Aplysia*. It seems that studies of this kind may help us locate simple memories to particular groups of cells. Even so, these cells aren't the end of the matter. Thompson himself points out in his article that these conditioned responses leave traces in other parts of the brain. Even though our brains

could not naturally recover the memory if the crucial brain region is destroyed, it may still leave traces. Furthermore, the region to which Thompson has "localized" a memory contains thousands of cells. For normal cases of brain damage, however, I believe the strongest point is simply that most memories are not nearly so simple as Thompson's test cases. They will therefore necessarily leave widespread traces in our brain.

Kandel and his coworkers give some serious attention to the hypothesis that our long-term memories derive from developmental changes in the nuclei of our neurons. Thompson also, although his review concentrates much more on the anatomy of particular memories in mammals, does mention the possibility that nerve cell DNA (meaning *genes*) are essentially involved in long-term memory. He says that memory traces "very likely involve DNA".

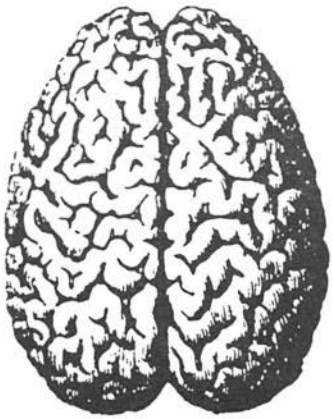
There is an alternative viewpoint held by several prominent cryonicists. This is that the memory traces reside *essentially* in the anatomical connection of our neurons. It would follow that if this were destroyed, the memories will disappear.

This viewpoint could be true. However it is still an *assumption* which should be flagged as such. For the sake of balance, I shall argue the opposite viewpoint here.

First, it is not hard to imagine how the entire connectivity of our neurons could be coded in our DNA. We have about 100,000,000,000 neurons. This seems a large number. However it requires about 40 bits to specify that many numbers. If each neuron connects on the average to eight others, then we need 43 bits to code each neuron, plus the neurons to which it is connected. Even twice this amount of information wouldn't overload our genome. *Aplysia* has a nervous system with hard-coded connections. It's not impossible that we do also. It's also important that we don't need strict identity here. It's true that twins aren't identical, and hence won't have identical nervous systems. But this need not mean that their differences would lead to differences in memory.

If connectivity is inborn, *and* if every single connection were lost, recovering us might still be done simply by consulting an atlas of the human nervous system.

Even leaving DNA to one side, it seems to me unlikely that the anatomical connection of dendrites will be the *sole* mark of a long-term memory. First, memory does not cause a totally new connection of two neurons. It causes a strengthening of an old connection. This involves such things as an increase in the number of synapses between the two neurons and changes in the synapses themselves. This connection must be controlled and *actively maintained* by some process independent of the connection itself. Nerves are active living things, constantly tearing themselves down and rebuilding. Despite this, memories are maintained. C. Otelo and S.L. Palay have reported (*Lab Invest*, **25(6)**, 653 (1971)) that nerve cell connections constantly form and reform in living animals. Furthermore, developing neurons will grow toward the proper connections even when displaced (*Nature*, 320 266-271 (1986)). Transplanted embryonic neurons will grow connections to their proper areas (F.H. Gage *et al*, *Science*, 221, 966-969 (1983)).



The suggestion here is that nerve cells know to what other cells they must connect, and how strongly, because of cues other than the simple existence of a connection. This cue may well lie in developmental expression of genes in their DNA, exactly as Kandel and his coworkers suggest.

Unfortunately, at this time we don't really know the answer. I am only presenting some evidence against a "connectionist" view. As cryonicists we're in fact very lucky that we probably won't have to test this issue of the exact cellular substrate for memories on ourselves. When we're frozen under good conditions, with suspension preparations in place, destruction of this degree probably won't happen at all. But we can't be complacent about memory either. Even with the best preparations, we all know how easily things can go wrong.

* * *

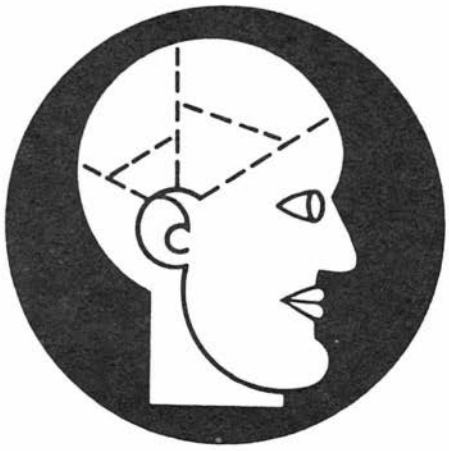
WHERE IS THE COLOR BLUE?

It's a commonplace not only among cryonicists, but even among neurologists seriously interested in memory and brain processing, that our individual memories depend on interactions of very many neurons. We can easily see how we can someday reach a full understanding of memory at the level of individual neurons. True, we don't have it yet, but biochemical and cellular techniques should lead to understanding. In fact, work on a cellular level with *Aplysia. Hermissenda*, and other mollusks looks like it will soon tell us in detail what happens when our individual neurons form a permanent memory.

Yet what about memory and personality on the level of the whole brain? Clearly we can't get far by recording electrical signals from particular neurons, since what we seek comes from many neurons interacting rather than any single one.

Several new techniques may give us entry into this problem. The first consists of developments in models of neural systems. For many years now, scientists have studied abstract neural networks. These are systems of interconnecting nodes which individually turn on or off depending on their inputs from other nodes. Such models may resemble brains in suggestive ways. First, their behavior should depend on the network as a whole. Second, a fragment of a network pattern should force the rest of the network to recover the whole: rather like our memories seem to do. Of course, when the idea of neural networks first arose, nobody knew that these properties would in fact hold true.

In 1982, J.J. Hopfield at Caltech showed that such networks did in fact resemble memory in one such crucial way: connections between nodes can be set up so that the network will show a large number of *stable* configurations. That is, neural networks could have memories which would not be disrupted by noise (*Proc Nat Acad Sci*, 79, 2554 (1982)). But in itself, that is not sufficient. We need to know if neural networks can in fact produce a particular memory in response to stimulation. Recently, however, in *Physical Review Letters*, (57, 2861 (1986)), H. Sompolinsky and I. Kanter, two physicists at Bar-Ilan University in Israel, point out that by modifying the properties of the "neurons" slightly (they must have time-dependent properties) they can produce neural networks which will run through a set of configurations whenever stimulated, exactly as if the network will play a "movie" in response.



Objectively seen, neural networks are rather far from explaining nervous systems and how they

work. However, the hypothesis has merit. It's very clear that our brains do not work, in detail, like computers. Some form of neural network seems the most likely explanation, even if it needs still more modification to model brains better.

But even if we are organized in neural networks, we'd need more than abstract models to convince us of that. We'd need actual studies of the workings of animal brains showing that they behave like these models. At this point, an interesting series of recent techniques for studying global processing in brains becomes more important. In the next article we will report on one such idea. This is to use chemical dyes which are *sensitive to voltage* to monitor neuron activity. The dye is given to the animal. Watching brain areas change color as the animal responds then tells us what brain areas are involved and what they are doing (cf. G.G. Blasdel and G. Salama, *Nature*, **321**, 579 (1986)).

However, known dyes can cause side effects which disturb the experiment. Recently in *Nature* (**324**, 361 (1986)), A. Grinvald and others from Rockefeller University and the IBM Research Center describe a new technique which works only from changes in the color and optical properties of normal brain neurons. Grinvald and his coworkers point out that changes in reflected light from active neurons were known for years. They use them to measure the activity of a cat's brain. They also report changes in the *arterioles* in brain regions when stimulated.

These workers used this technique to make a map of the visual system of their cats. It does not replace use of voltage-sensitive dyes. The dyes show electrical activity, while the normal changes without dyes show changes in metabolic activity. The dyes also change much faster than metabolic activity. But what is most important is that both techniques give us a way to actually study the workings of networks of real neurons. This should materially help to provide a true account of how our memories and thoughts happen.

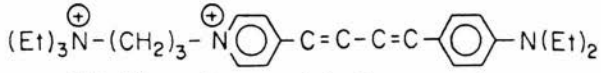
* * *

I CAN SEE YOU'RE THINKING

Only about two years ago, neuroscientists worked out how to use nontoxic voltage-sensitive dyes to study brain activity. These dyes are chemicals which change color depending on the voltage applied to them. While they may not be nontoxic enough to use in human beings, they are enough so for use in animals, and over the last two years many laboratories have used these dyes to watch brains in action.

Up to now, this technique forced us to make a choice between high spatial resolution and high temporal resolution. If we wanted to watch the pattern of activity during thinking, we'd have to give up on one of these parameters. Since thinking is a dynamic activity involving many brain centers, some of them quite small, this isn't a good choice to have to make.

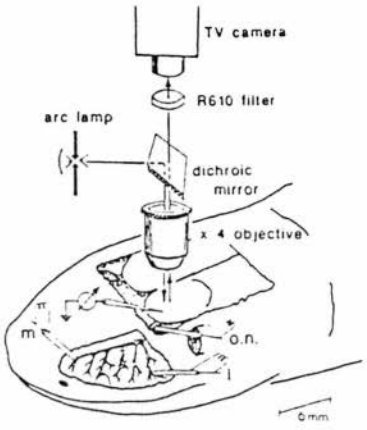
However quite recently in *Nature* (**331**, 166-168 (1988)) John Kauer at the New England Medical Center and Tufts (both) reports a method which significantly improves combined space and time resolution of these pictures. His method (unlike any used to date) allows accurate imaging in real time.



RH-414, a voltage-sensitive fluorescent dye.

The method isn't perfect. The animals he used (salamanders) have the largest change in fluorescence of any vertebrates studied. But Kauer could produce some fascinat-

ing pictures showing how a smell stimulates the olfactory centers of the salamander's brain. Furthermore, salamanders have brains which must resemble ours in many respects, so that knowledge of salamander brains should tell us a lot about our own processing.



Very active work goes on to improve this technique, since it ought to tell us a lot about how brains work. Among the approaches are systematic attempts to reduce the noise in the signal (some people are working on devices which will use as many as 2500 detectors for the signal, specifically to reduce noise). Movement by the animal also causes noise; one method to reduce movement noise is to subtract the fluorescent image from another taken at a different wavelength which will not show the dye. One approach so far relatively little worked on consists of making new and much more sensitive voltage-sensitive dyes. Of course, such work will come.

Up until only a few years ago, the only way we could tell that particular neurons were active in a brain consisted of sticking an electrode into that neuron and measuring its electrical activity. Voltage-sensitive dyes give us, potentially, a way to study mass excitation of neurons throughout the brain. Since our brains very likely work by mass action, this is an important technique from which we may expect many insights in future, eventually even in human beings.

* * *

METABOLIC MAPS OF MEMORY

Lashley's work on memory was among the very first attempts to study its neurophysiology. He tried to locate a memory in some particular brain region and consistently failed. No amount of brain damage compatible with the ability to function at all seemed to extirpate from rats their memory for a maze. This must tell us that most memories in the ordinary global sense are distributed throughout our brains.

Recently however some scientists have developed very simple models of simple memory in which they can specify the exact circuitry involved (for instance, the work of E.R. Kandel and R. Thompson described elsewhere in this issue). Their work necessarily attempts to look at small units of memory. We can almost certainly localize a small enough unit of the right kind. But most memories are global and must involve many neurons.

Some recent experiments by a group centered in New York (E.R. John, *et al*, *Science*, **233**, 1167-1176 (1986)) give us a much more detailed picture of the kind of distribution Lashley's experiments have shown. Their final results were very simple, though to attain them they needed very ingenious and involved experimental apparatus. They used this technical apparatus to obtain a detailed mapping of exactly which regions in the brains of cats were activated when these cats performed a discrimination task. They could actually make a good estimate of the locations and number of neurons involved in remembering this task. It turned out that between 5,000,000 and 100,000,000 neurons were involved. They were spread throughout the cat's brain. This is a very large number. It makes clear why it is normally so hard to destroy a memory by surgical removal of brain regions. It also

gives us good reason to think that many of our own memories will be resistant to widespread brain destruction.

The technique of John and his colleagues worked as follows. They needed to find some way to distinguish areas of brain activation which had nothing to do with the memory from other areas of brain activation which depended directly upon it. There is a chemical technique to map out activated brain regions. It consists of giving radioactively labeled *deoxyglucose* to the animal. Brain cells take this up as if it were glucose, but can't metabolize it. It therefore stays in the activated cells. If the animal is killed and its brain examined, we can map exactly which cells were activated.

John *et al* used cats whose brains were split into two hemispheres, using each hemisphere successively as experimental and control. Because these scientists had surgically separated the two hemispheres, each hemisphere remembered independently of the other. They used two *different* radioactive labels on their deoxyglucose, so that they could feed it to their animals *twice* and distinguish the trace left by the first feeding and the second. After two successive experiments in which one hemisphere, then the other, recalled and performed a task, they killed the animal and made radiographs of its brain. Because the two radioactive labels decayed at different rates, they could use very sophisticated image processing techniques to distinguish labeling due to one label from that due to another. This let them find exactly those cells activated by the memory rather than background noise.

These experiments give us a far more specific idea than do the old experiments of Lashley about just which brain regions are involved in a memory. We ought to be able to map out specific regions for several memories. We can find out just how brain cells activate in learning.

The authors of this study claim that it disproves theories of memory based upon changes in a small number of cells. They refer to some papers of Kandel as examples of such theories. I believe that they are engaging in an argument over words rather than substance. There is no visible conflict between their experiments and those of Kandel or Thompson. The trick in seeing this is to reflect that after all memory must involve *some* changes on the level of individual neurons. Kandel is studying how *neurons* remember. John *et al* are studying how our *brain* remembers. These are not the same thing and it is trivially wrong to identify changes in any particular neurons with a memory achieved by the *brain*. That would be like confusing the physiology of the rods and cones with the much more global question of how our eyes and brains see. But of course, without memory in neurons brains can't remember either.

* * *

BEE VENOM AND MEMORY

Long term potentiation, or LTP, is one of the phenomena in brain tissue which may underlie learning. Slices of hippocampus tissue from the brain, if stimulated by pulses of high frequency electricity, will develop a long lasting increase in the ability of their synapses to transmit signals. Hippocampus slices treated in this way do not become any more excitable. Instead, the same incoming stimulation produces a larger output signal. The long-lasting character of this change is one major reason why some scientists think that LTP may underlie learning itself (T.V.P. Bliss and T. Lomo, *J Physiology*

(London), **232** 331-356 (1973); P. Andersen *et al*, *J Physiology*, **302** 463-482 (1980); E.R. Kandel and J.H. Schwartz, *Science*, **218**, 433-443 (1982)).

As yet, however, we don't have a good handle on the physiological reasons for this long term potentiation. We need to know the biochemistry and cell physiology involved in this response. Until we do, its connection with memory won't be completely established. And if it is connected to memory, we won't know how memory itself works without such information.

A recent paper in *Nature* by E. Cherubini and others at INSERM in France presents a very interesting clue about the biochemistry of long term potentiation (E. Cherubini *et al*, *Nature*, **328**, 70-73 (1987)). Cherubini and his coworkers have shown that a chemical normally occurring in *bee venom* will mimic the effects of LTP after only one application to slices of hippocampus. They call the chemical MCD.

The responses of neurons after application of MCD were virtually identical to those after application of the high frequency electrical pulses which cause LTP. Furthermore, Cherubini and his coworkers could not obtain any greater effect by applying electrical pulses to MCD-treated neurons. A chemical treatment known to prevent LTP also prevented the effects of MCD.

As final evidence that their chemical has similar effects to electrical pulses, these researchers showed that a very similar chemical already exists in normal hippocampus tissue. Many animal and plant poisons work because they mimic the effect of other natural substances occurring in our tissues (opium comes to mind!). Cherubini and his coworkers showed that such a substance, resembling MCD, occurs naturally in our brains.

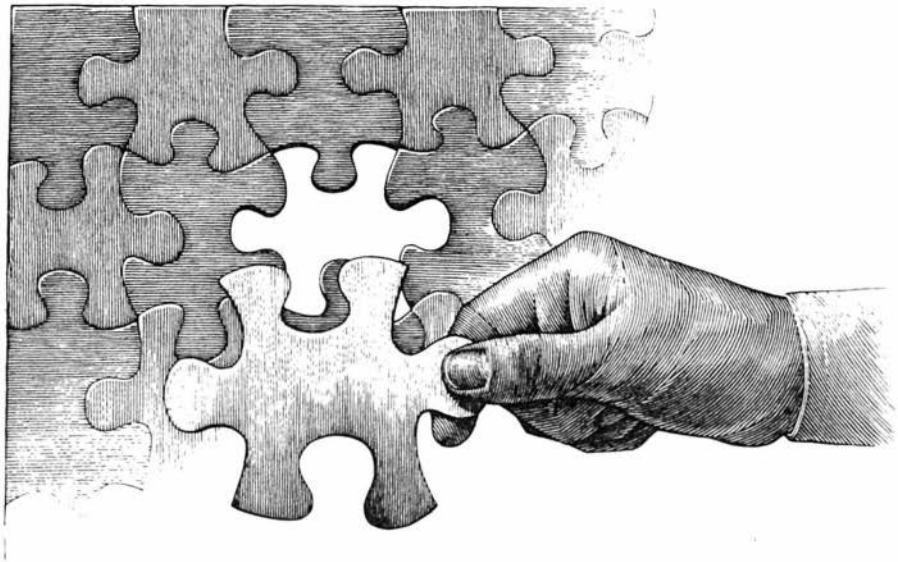
This discovery is not a full explanation of the biochemistry of LTP but rather a step along the way. Once we know a chemical involved, however, we can work on the problem of how it has its effects. This second stage with LTP is still not done. The discovery is important because it is a first stage, which must precede the second.

* * *

NEW FACTS AND SPECULATIONS ON MEMORY

We still have no firm knowledge of how our brains store memories. Yet over the last several years a large number of new facts and ideas have entered the field. It's quite possible that some decisive experiments are imminent, even though they haven't yet occurred.

One major recent experiment published in *Nature* (**319**, 774-776 (1986)) by R.G.M. Morris, M. Baudry, *et al* connects one recent experimental hypothesis directly with memory. Over the last several years many scientists have explored *long-term potentiation* (LTP) as a possible explanation for memory. LTP refers to a characteristic response of nerve cells of the hippocampus to high frequency electrical stimulation. A brief period of such stimulation will cause these nerve cells to transmit impulses more easily for more than a month thereafter. LTP, in fact, is one of the few forms of electrical brain stimulation known to cause a relatively long-term change. The first report of LTP occurred in 1973 (T.V.P. Bliss and T. Lomo, *J Physiology (London)*, **232**, 331-356 (1973)). R.G.M. Morris, M. Baudry, G.L. Collingridge and others have since studied this phenomenon quite closely (G.L. Collingridge, *et al*, *J Physiology (London)*, **334**, 19-31 (1983); E.W. Harris *et al*, *Brain Research*, **323**, 132-137 (1984)).



However, up to now this connection with memory had consisted of theory only. No one had shown that LTP actually played any real role in real memory. The *Nature* paper by Morris, Baudry, and their coworkers mends this deficiency. These workers noted that one of the neurotransmitters in the hippocampus, glutamate, attached to one special class of receptors which respond markedly to LTP. Furthermore, they noted that the drug *aminophosphovaleric acid* (AP5) would also block these receptors. This means that they could test if stopping LTP would also stop memory.

They performed this experiment in male rats. They implanted a pump in these rats which continually bathed their hippocampus with the drug AP5 and then tested their memories in a place-learning task. The task consisted of tests of the ability of these rats to swim to a hidden platform.

The drug AP5 did in fact block the ability of the test rats to learn the location of the hidden platform. AP5 also blocks LTP. This gives us very strong evidence that LTP is involved in place learning.

Baudry, Morris, and their co-workers also studied another kind of memory, visual discrimination. This time, test rats had to distinguish between a "fake" platform (it sank if the rat tried to get on) and a "true" one. The two platforms differed in the pattern painted on them. Their results weren't so good on this task. The animals did not show any significant impairment of discrimination.

It's true that we could try to argue that these experiments don't *prove* that relates to memory. However, such arguments seem strained to me. We now have strong evidence that a particular biochemical event in neurons relates to memory.

These experiments aren't the only recent experiments to illuminate memory. Another recent experiment in *Science* (232, 85-87 (1986)) by S.R. Kelso and T.H. Brown brings out another connection between older "physiological" ideas of memory and actual observed memory. One of the oldest ideas about memory goes back as far as Pavlov, the idea of conditioned responses. Pavlov's classic experiment was to obtain a dog which would

salivate at the sound of a bell by giving the dog its food shortly after ringing a bell. This is in fact a kind of memory, and ever since Pavlov, neurologists have supposed that this association might explain *all* memory.

What Kelso and Brown have done is to actually obtain a conditioned response from slices of rat hippocampus. They obtained an enhanced response from one nerve pathway in the hippocampus by consistently stimulating it shortly before stimulating another pathway.

Although this model doesn't directly tell us anything about the biochemistry of memory, it's still very important. Normal memory is too complicated. We need a simple model to study it. Up to now we had little direct evidence for any kind of simple event in the brain which relates to memory. Kelso and Brown have shown that the old idea of conditioned response may actually explain learning through elementary brain responses. Furthermore, studies of slices of the hippocampus have recently become a major model of memory. The work of Baudry and Morris, of course, was done on hippocampus slices.

Several other highly suggestive experiments were reported at the 10th Annual Meeting of the International Society for Neurochemistry. Proteins linked to sugars (*glycoproteins*) may play a special role in memory. This work distinguishes itself from earlier work on proteins in memory because it involves quite specific proteins rather than some general impairment of "protein synthesis".

M.E. Gibbs and others at La Trobe University in Australia presented their work with antibodies against one such protein, THY-1, in chicks. These antibodies would inhibit memory formation in the chicks. This work therefore shows that THY-1 must play some critical role in memory (Abstr. S21C). As yet we don't know what role this may be.

Several authors studied another glycoprotein, *ependymin*. Studies of ependymin began with V. Shashoua at Harvard Medical School, who discovered that turnover of this protein increased markedly during learning in goldfish. Shashoua has continued these studies to look closely at the involvement of ependymins with calcium levels in the brain cells. Changes in calcium ion levels may occur as an essential stage to the initial learning process. Shashoua reports (Abstr. S14A) that ependymin is very soluble in the presence of calcium ions. If these ions are removed, they will form very insoluble fibers. He speculates that ependymins may be involved in permanent storage. R. Schmidt, from J.W. Goethe University in Frankfurt, Germany, also reported studies of ependymins. Schmidt used immunological methods to study how levels of ependymin changed when goldfish learned two different tasks. Antibodies to ependymins would also prevent goldfish from learning these tasks (Abstr. S21D).

Relations of ependymins with calcium are very interesting since Baudry, Morris, and others have detected a link between calcium metabolism and the process of laying down a memory. The fact that ependymins could form insoluble fibers *might* become very important. For many years neurologists have supposed that some kind of structural change to the neurons encodes our memories. This change must persist for a long time. A relatively durable, insoluble protein which is at the same time involved in memory therefore deserves close scrutiny.

Finally, at the Dahlem Conference (8-13 December, 1986, West Berlin) reported in *Science* (**231**, 1246-1249 (1986)) several of these researchers, and others, presented further work on these and other experimental models of memory. One common theme of this conference was that of calcium ions and their role in memory and nerve transmission. Several researchers, among whom were R. Nicol and others at UCSF and D. Johnson and W. Hopkins at Baylor College of Medicine, presented evidence for several varieties of involvement between nerve transmitter chemicals, LTP (that is, long term potentiation) and

calcium ions within nerve cells.

A second theme of this conference consisted of *attachment of phosphate groups to proteins.* A wide variety of models for memory, including invertebrate models such as *Aplysia* (a marine snail) and rat hippocampus slices, will all show signs that phosphate groups are attached to proteins as an essential part of learning. In all of these systems, enzymes which attach phosphate to protein become active whenever learning happens (J. Farley and S. Auerbach, *Nature* **319**, 220 (1986); E. Kandel, *et al*, *Cold Spring Harbor Symp Quant Biol*, **47**, 821 (1983)).

However, the Dahlem Conference seems most distinguished by the speculations and generalizations put forth. Thomas Carew of Yale presented several of these. It seems now well established that whatever changes occur with memory occur at *existing* connections between nerve cells. New connections are not made whenever a new memory forms. These changes depend on activation of enzyme systems within the nerve cells. These enzyme systems involve calcium and attachment of phosphate to proteins. They also must involve a change in the ability of potassium to pass through nerve cell membranes.

J.P. Changeux and A. Klarsfeld at the Pasteur Institute raised another possibility important for stability of memory. Formation of a permanent memory may involve activation of *genes* within the nerve cell.

None of these changes are likely to encode our *memory* (as we ordinarily think of it) on a cellular level. Changes in nerve cells probably produce memory in much the same way that flecks of paint produce a painting. The number of colors a painter uses is small. The painting resides in the location of these colors on the canvas, not in the color of any particular cell.

Even though this work still hasn't given us a picture of how memory is stored, for cryonics it does have one highly significant suggestion. Memory on a cellular level must be *complex*. This therefore ought to mean that our memories will leave many traces in our brains, *other than* the ones we ourselves use to remember. Any process used to reconstruct us will therefore have many clues available to tell it just what our memories and personality were.

* * *

THE FIRST STAGE OF MEMORY

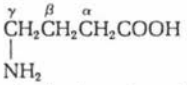
For several years now, scientists have studied a phenomenon called long-term potentiation is cells from the hippocampus of rats and other animals. The name long-term potentiation (LTP) describes a special phenomenon which happens in these cells. A sufficiently strong stimulus makes nerve cells of the hippocampus abnormally ready to respond to later, milder stimuli. Just this property resembles at least the first stage

of memory: initial stimuli cause the nerve cells to "learn" how they should respond. It's the idea that LTP related to memory that caused so much interest in it.

Like most effects within our cells, LTP depends upon particular chemical transmitters and chemical receptors. For LTP, this has turned out to be the chemical NMDA (N-methyl-D-aspartate) and its corresponding receptors. These receptors have chemical properties which make them suitable for explaining LTP. In particular, they can take two different forms, the "potentiated" form and the "nonpotentiated". They can flip between these two states (G.L. Collingridge and T.V.P. Bliss, *Trends Neuroscience*, **10**, 288-293 (1987)).

For a long time one major problem with interpreting LTP as a stage in memory remained in the background. This was that no one had found signs of LTP in cells *other* than those of the hippocampus. Since all our other brain cells undoubtedly participate in memory, that's an awkward problem.

However in *Nature* (**330**, 649-652 (1987)) Alain Artola and Wolf Singer at the Max Planck Institute in Frankfurt have shown that LTP does indeed happen in regions other than the hippocampus. They were able to find LTP in the visual cortex of rats. This must mean that LTP occurs in many other brain regions too.



γ-Aminobutyric acid

Specifically, they found that previous attempts to get LTP from visual cortex had not accounted for a new fact. This is, that another nerve transmitter, GABA (gamma-aminobutyric acid), was controlling LTP. Nerve cells in the visual cortex wouldn't show LTP unless inhibition by GABA was removed. (Of course, visual cortex cells must learn. What this discovery means is simply that normally they are "turned off" by GABA. Learning happens when GABA is reduced). Artola and Singer showed this very simply, by using another chemical to reduce the effect of the GABA. Nerve cells from the visual cortex, treated in this way, easily showed LTP.

LTP is only one stage in formation of a permanent memory. Its importance comes not because this is a likely way in which our long-term memories are directly stored, but because once we understand how the process begins, we're well on the way to understanding how it ends. That is, by finding one end of the rope we can follow it to see where it leads.

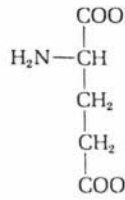
* * *

MORE BRICKS FROM WHICH TO BUILD MEMORY

Anyone who seriously reads the articles on memory appearing (almost monthly) in *Nature*, *Science*, and elsewhere, will soon realize that we are close to finding out how our brains learn. Certainly, even if we know how memory works at the lowest level, we'll still be far from knowing how it works at higher levels. But understanding of how individual neurons handle memory is extremely close.

Nevertheless it's still not here yet, and besides, science doesn't work that way. However, two recent papers do cast more light on how memory works and deserve reporting, even if they don't provide anything like a Complete Story.

In *Science* (**240**, 649-653 (1988)) a team of scientists headed by John A. O'Connor, working at Bell Laboratories in New Jersey, report some of the effects of nerve stimulation in the hippocampus on calcium ion levels and gradients within single dendrites (dendrites are the projections from a nerve cell where the nerve receives impulses from



Glutamic acid

other nerves).

The hippocampus is most important because of LTP: long-term potentiation, which was first discovered in slices of hippocampus tissue. This is a phenomenon by which repeated stimulation causes the neurons to respond much more readily, and for a prolonged period, to another episode of stimulation. Almost certainly LTP is not a form of long-term memory. But LTP is very likely to be a stage in the formation of memory.

What O'Connor and his colleagues have found is that stimulation by some nerve transmitters (glutamate and NMDA) would cause a persistent gradient of calcium for the length of the dendrite. Persistence here is measured in hours. Calcium levels are highest at the tip of the dendrite, growing lower as we approach the actual body of the nerve cell. O'Connor and his coworkers could show that this gradient occurred because calcium was entering the cell at the dendrite tip.

Nerve cells will go through a brief change in calcium levels when stimulated. But this is different. The same brief change happens, but the later calcium gradient comes later and persists for very much longer. This gradient change also needs a priming stimulus to the nerve: one stimulus alone won't usually work.

O'Connor and his coworkers suggest that this long-lasting change happens because of a change in the ability of the dendrite surface to admit calcium. One chemical, sphingosine, which inhibits addition of phosphate to proteins, will stop a long-term calcium gradient from happening. The suggestion is that the long-term change happens because of phosphate attaching to a protein on the cell surface. Which protein, of course, nobody yet knows.

In another paper, in *Nature* (**333**, 171-174 (1988)) E.R. Kandel and several scientists at the Howard Hughes Medical Institute have shown the existence of long-term *inhibition* of one synapse by another in the nervous systems of *Aplysia*, the sea hare. Kandel, of course, has done a great deal of work on memory in Aplysia. He discovered the original *facilitation*, which may represent one form of memory.

In this case, Kandel and his coworkers found that a different set of neurotransmitter chemicals could cause inhibition rather than facilitation. Serotonin will cause facilitation. The new information is that a small protein molecule (which Kandel and his coworkers call FMRFamide, Phe-Met-Arg-Phe-amide) will cause inhibition under similar circumstances. The phenomenon resembles LTP very closely. Five short applications of the neurotransmitter will cause a facilitation (or inhibition) which can last for over 24 hours.

This inhibition resembles facilitation in many ways. For instance, drugs which prevent synthesis of protein (like anisomycin) will prevent inhibition just like they prevent facilitation. It lasts just as long, and only happens after several repeated short applications of the neurotransmitter chemical.

Since learning involves not just learning what we must pay attention to, but also what we need not pay attention to, inhibition is at least as important as facilitation. These experiments, individually, of course mean very little. But a nerve mechanism explaining learning must handle both facilitation and inhibition. They were therefore very necessary.

PHOSPHORYLATION AND MEMORY

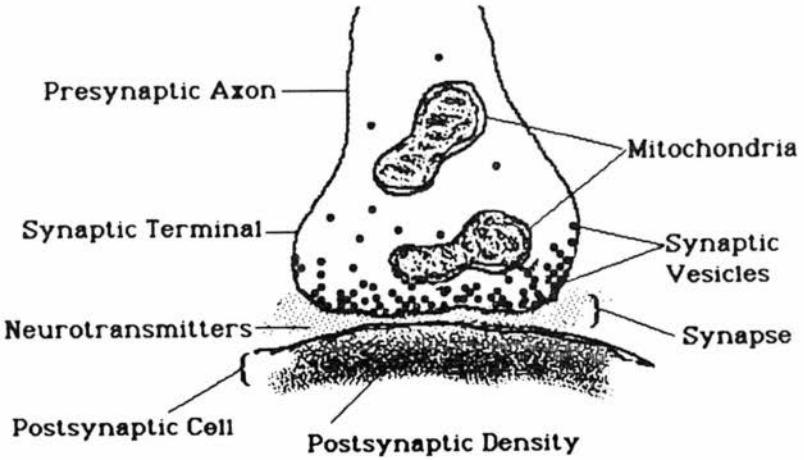
By now it's a commonplace that we have several different kinds of memory. First, there is "knowing how" and "knowing that", each of which involves quite different brain regions. Alzheimer's patients and others can learn a new skill but never remember the circumstances in which they learned it. That is a dramatic example of how "knowing how" and "knowing that" can differ. Our memories also pass through at least two, and probably more, *stages*. That is, the memory begins as a short-term memory and only later becomes a long-term, permanent memory.

One recent set of ideas of how these stages of memory may work involves a nerve cell phenomenon called *long-term potentiation*. Slices of rat hippocampus, if electrically stimulated repeatedly, will become much more likely to respond to further stimulation. In some ways this change resembles memory. It lasts for hours or days. Memory also must involve a change in likelihood that our nerve cells will respond.

What *chemical* mechanism is involved? One hypothesis is that these long-term changes occur because phosphate is attached to some (unknown) protein at the synapse, where the nerve cell connects to another. Such a change is called *phosphorylation*. The advantage of phosphorylation is that it can cause a long-lasting change in a cell protein even without making new protein.

A recent paper by a team from the University of Oslo and Rockefeller University in New York, G.Y. Hu and others, has just provided some strong proof that protein phosphorylation is really involved in memory (*Nature*, **328**, 426-429 (1987)). Their method was simple. They injected small amounts of an enzyme known to phosphorylate proteins, *protein kinase C* (PKC for short), into individual nerve cells in a slice of hippocampus. They then measured the electrical response of these cells to stimulation.

Prior injection with PKC mimicked most effects of long-term potentiation. These authors give plots of electrical response of their test cells to stimulation, both after long-term potentiation and after injecting PKC. These were quite similar. Just as happens with long-term potentiation, electrical responses only happen when the synapses are stimulated. Electrical stimulation of the cell body has no effect.



Synaptic junction.

It's very likely that long-term potentiation, and the phosphorylation of some membrane protein(s), is only one stage in the process of memory. Among other differences, long-term potentiation does eventually fade. We know that some long-term memories do not fade for years. The membrane proteins involved are probably broken down and replaced in a few weeks. Some other process must carry true long-term memory.

Still, it's important to understand all the stages of memory because each stage is a clue about the one before it. Furthermore, in any future process by which we'd try to *deduce* the personality and memory of someone suspended under damaging conditions, we'll need to know *all* the processes involved in memory, even if they aren't directly involved. Every event can give clues about the others.

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A GLIMPSE OF THE CHEMICAL MECHANISM OF MEMORY

One fundamental fact about memory, already known ten years ago, consists of the distinction between short-term memory and long-term (i.e., permanent) memory. Even ten years ago, of course, no one claimed that this dichotomy was complete. That is, perhaps there were still other forms of memory yet to be found. But the fundamental distinction remained.

This distinction remains today. However more recent studies on animal preparations suggest that indeed there are more than two stages in progress of a memory from short-term to long-term. Studies of *Aplysia* in particular, for instance, have shown a need for at least one more form of memory, intermediate-term memory. This acts as a bridge between short-term and long-term.

If stimulated by electric shock, the mollusk *Aplysia* will withdraw its siphon. Much more important, a series of such shocks will make the animal much more ready to withdraw its siphon. The effect is called *short-term sensitization.* Short-term memory only lasts for a few minutes, while short term sensitization persists for an hour. It acts as a bridge between short- and long-term memory. For long-term memory, the nerve cells must make new protein. But they need no new protein for this short-term sensitization. Nevertheless, both long-term memory and short-term sensitization act on the same synapses, with the same ultimate chemical effects. How can this happen?

Recently in *Nature*, (329, 62-65 (1987)), Steven M. Greenberg, Vincent Castelluci, and others at Columbia University in New York presented their work on a likely mechanism by which short term sensitization can occur.

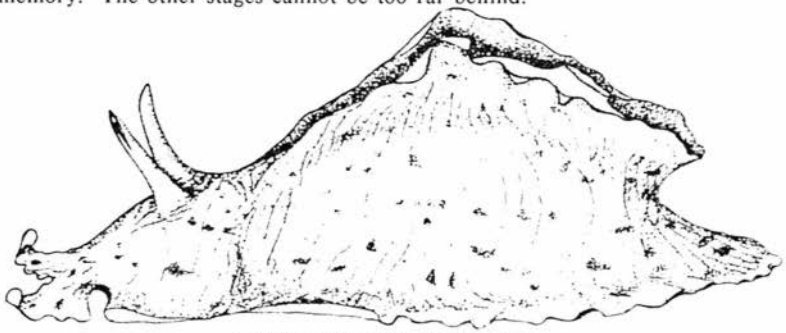
The first chemical event in memory consists of *phosphorylation* (adding a phosphate group to) a protein at the synapse. This change affects how easily a synapse will receive an impulse. Special enzymes (called *kinases*) promote this phosphorylation. Because it is a beautiful example of how nanomachinery works, I'll describe the mechanism which Greenberg, Castelluci, and their coworkers found, in detail.

There are really two different nanomachines directly involved. One of them is the kinase. The second is another machine (the regulator) which attaches to the first whenever the level of one cell chemical, cAMP, is low. When it attaches to the kinase, the regulator prevents this kinase from acting. But the regulator itself has another spot to which cAMP can attach. If there is lots of cAMP, the regulator is turned off. It releases the kinase, which can then go off attaching phosphate to proteins in the synapse.

And what role does cAMP play in this process? cAMP is a chemical which floats freely about in the cell. In other cell types, it acts as a messenger substance: attachment of a hormone to the outer cell wall causes cAMP levels to increase. This increased cAMP level then causes a change in the cell nucleus, to make more protein. Much the same thing happens in memory for nerve cells. Nerve impulses at the synapse cause cAMP levels in the whole cell to go up.

This is exactly the interesting point. Because cAMP levels have increased, the kinases are released to do their work. They proceed to change the synapses, so that later impulses act even more easily. That means that cAMP levels inside the neuron will stay high much longer than otherwise. A single nerve impulse creates a condition in which the nerve will respond much more readily to later impulses. Once touched, the cell rings like a bell for an hour or more.

This process, of course, will only preserve memory for hours, not for days or weeks. We still need to know about the earlier stages (that is, exactly how the synapses are altered) and the later stages (how proteins are synthesized for a long-term memory). What is important about this work is that it uncovers quite fully one entire stage in the process of memory. The other stages cannot be too far behind.



Aplysia californica (sea hare)
Brownish-green with dark brown blotches

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C-FOS AND MEMORY

Recently, as neuroscientists have found out much more information about memory several have suggested that long-term memory results from masking or unmasking of specific genes in the cell nuclei of neurons (cf. E.R. Kandel *et al*, *Nature*, **322**, 419-422 (1986)). Such changes underlie development, itself a very long-lasting change. They would be particularly important for cryonics, since such changes are also likely to survive major damage to brain cells. Some memories might very well survive treatments such as desiccation or burial in peat bogs.

Up to now, unfortunately, these suggestions have remained suggestions only. However a recent paper in *Nature* (S.P. Hunt *et al*, *Nature*, **328**, 632-634 (1987)) may start to put substance into this suggestion.

Hunt and his coworkers looked for evidence that one special gene, *c-fos*, was induced

by stimulation of nerves in the spinal cord. The gene c-fos is important because it seems to act as a controller of other genes, similar to that which happens in development. Hunt and his coworkers used an immune-labeling technique to detect this protein.

They stimulated one set of test rats with an irritant (mustard oil) and another set with heat. These two treatments both caused many neurons in the spinal cord of these rats to start making c-fos. The exact distribution of c-fos depended on the exact stimulus. The important fact about these stimuli, of course, is that they are known to cause reflex withdrawal and therefore may be involved in primitive learning.

As yet this does not make a proof of the suggestion. What this experiment does is to raise its likelihood. The exact role of c-fos, even when it is involved in differentiation, isn't yet known (M.E. Greenberg and E.B. Ziff, *Nature*, **311**, 433-437 (1984)). Furthermore, the relation between a noxious stimulus and memory isn't as close as we'd like. What is true is that until now, no one had shown that neurons even *made* c-fos. As for the crime of memory, c-fos has now been found near the scene of the crime. Whether it is actually implicated still remains to be shown.

* * *

FOS GENES AND THEIR ROLE IN GROWTH (AND MEMORY?)

In *Nature* (**322**, 419 (1986)), E.R. Kandel, P. Goelet, and others made an important suggestion about long-term memory. They had noticed that one gene, *c-fos*, was activated when hippocampus nerve cells were stimulated. This gene is one of a group of genes controlling other genes. Cancer cells also show stimulation of these genes.

Their suggestion was important because it may provide a clue to long-term memory. Since that time, several papers have studied the phenomenon. It turns out that other brain regions also respond to stimulation by activating this gene. As yet we have no direct, smoking-gun proof that c-fos and other related genes are involved in memory. But the suggestion has got stronger with time.

Recently in *Science*, (**239**, 1147-1150 (1988)) Thomas Sutula and others at the University of Wisconsin reported one more experiment implicating *fos* genes with memory. Like the others, it's not yet proof. But it provides a great deal more circumstantial evidence of a connection. Perhaps much more important, it introduces some new techniques and observations about exactly what happens during this stimulation.

Sutula and his coworkers studied epilepsy. They implanted electrodes into rats and then stimulated their brains until the rats had an epileptic seizure. After several seizures, they looked at the brains of these rats compared to controls.

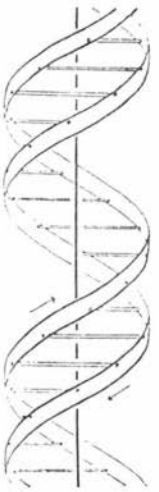
Their most significant innovation in technique consisted of using a special stain for zinc. It turns out that the nerve fibers of the nerves they studied (the mossy fibers) normally contain much more zinc than normal nerve fibers. Because of this fact, they could use stains for zinc to detect growth or change in them after electrical stimulation. The zinc itself isn't abnormal. But by tracing out pathways high in zinc, we can see changes in these fibers which in other nerve fibers would be hard to see.

It turns out that electrical seizures definitely caused a reorganization of synapses for the mossy fibers. It may have caused actual growth of axons. These authors show several micrographs of the hippocampus of these rats, both controls and electrically

stimulated. Their stains for zinc are deposited much more strongly in stimulated rats. In seizured rats, one whole region which would be clear of stain in normals is dotted with specks from the zinc found in the cells. On an electron micrograph, some (but not all) synapses of cells are stained with zinc. These stains did not go away with time. Seizured rats, kept alive for weeks afterwards and then killed for examination, showed the same changes had persisted for that long.

These stains definitely show a reorganization of the synapses and sprouting of nerve terminals. What do they have to do with c-fos? The authors point out that c-fos activation definitely occurs in the same cells after electrical stimulation to seizure in rats. After repeated electrical stimulation, these animals become more and more susceptible to seizures. The changes which make them so resemble, in this respect, changes occurring with memory.

Given that we know the genes involved, it's possible to trace out the chemical stages involved in permanent learning. That is the importance of this work on c-fos. In itself, c-fos affects many other events besides learning. But we already have techniques to detect it in animals after learning, find out which genes it is activating, and trace out the proteins which these genes make.



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BIOCHEMISTRY OF THE *FOS* COMPLEX

Because long-term memory may somehow be involved with the *c-fos* gene, work on how this gene acts within cells becomes important to us, even if that work has no direct relation to memory. A recent paper in *Science* (**239**, 1150-1153 (1988)) by Robert Franza, Tom Curran, and others at Cold Spring Harbor Laboratory in New York presents some interesting facts about c-fos and its related genes -- even though none of it bears directly on memory.

The proteins made by c-fos attach to particular sites in our DNA. From this location, they control whether or not their target site makes protein. What Franza, Curran, and their coworkers have done is to identify some of these sites, working out what proteins they make. Memory isn't mentioned in their paper.

A great deal of the paper consists of a description of the actual techniques by which they identified some of the sites to which c-fos binds. That isn't the principal breakthrough, though, so any readers interested in these techniques, perhaps wanting to apply them too, will read the original paper.

It turns out that c-fos contains a special sequence in common with several other proteins controlling gene activation. These proteins include AP-1, a binding site for cell activator protein in a strain of cancer cells. The same sequence occurs in a special gene in fat cells called AP-2, in another gene from an ape leukemia virus which increases the rate of protein radiate from genes, and in part of the AIDS virus.

These authors don't say, and it's unlikely to be true, that they have found a complete list of genes related to c-fos. Their work means, of course, that we can now use this sequence as a marker for genes involved in controlling development. We can also use the sequence to hunt for genes involved in long-term memory.

* * *

VARIETIES OF MEMORY LOSS

Memory loss is a very important question for cryonicists. It's clear that many of us will experience some brain damage before suspension. What we'd like to know is just how

much this damage will destroy our stored memories. It's also clear that the exact type of damage might make a big difference to survival of our memories. One brain condition might leave our stored memories themselves completely unimpaired while severely damaging our ability to read them out of store. Another condition might eat away at the stored memories themselves while leaving the read-out machinery untouched. Memory loss won't be a single disorder but a whole series of different disorders ranging from trivial to very serious for our survival.

For our own thinking we need one very important conceptual distinction. However hard it may be to tell them apart, "loss of memory" can mean two different things: either the loss of actual stored memories, or the loss of the ability to acquire new memories. The second can be clearly reversible. In fact, one valuable clue to Alzheimer's disease itself came from the fact that the drug scopolamine will partly mimic Alzheimer's disease in young volunteers. Unfortunately this fact only suggests but doesn't prove that memory loss in Alzheimer's disease is potentially reversible.

Two recent papers present some interesting comparative data on four different kinds of memory loss. In *Archives of Neurology* (**43**, 239-246 (1986)) M.B. Moss *et al* present a comparative study of memory loss in three different conditions: Alzheimer's disease, Huntington's disease (an inherited brain disease), and Korsakoff's syndrome (a kind of loss of memory caused by alcoholism). In their terms, when these authors study "memory loss" they mean not the loss of already stored memories but the loss of the ability to learn new information. Purely from the pattern of memory loss Moss *et al* could describe three very different kinds of defect in the three conditions they studied.

They studied their patients using a special recognition memory task. They presented their subjects with brown plastic disks on a white target background, with recognition testing for spatial, verbal, color, pattern, and facial stimuli. For instance, for color recognition they glued standard colors onto the top of their disks; for verbal recognition they glued written words to the disks. Spatial memory was tested simply by testing memory for location of the disk. Finally, in a different series, they tested their patients on their ability to recall words presented to them after a delay.

They got striking differences between the three different diseases. Huntington's disease patients were nearly normal in verbal recognition in the disk test. Furthermore, even more than normals they would tend to remember previously presented words which at first they had forgotten. Their total performance did not equal normals, however. They behaved as if they had unimpaired ability to put memories into store, but very impaired ability to recall them back from store when needed. On other tasks such as color or spatial recognition, however, these patients did not perform as well. Unimpaired storage with impaired retrieval ability therefore can't tell the whole story.

Korsakoff's syndrome patients showed a different pattern. They had difficulties learning words for recall. On the other hand, once they learned these words they would forget them at the same rate as normal subjects. They were uniformly impaired on all of the disk tests for recognition memory. The authors speculate that Korsakoff's syndrome may come from a loss of the ability to immediately register a memory.

Finally for Alzheimer's disease, one of the more striking differences lay in the much more drastic loss of memory it involved. The most striking difference of Alzheimer's disease patients came from their very rapid loss of information on the recall tests. When tested successively (15 seconds after learning, and two minutes after learning) Alzheimer's disease patients lost over 70% of the information presented. Patients with the other two brain diseases lost only 10% to 15%. Alzheimer's disease patients could register new information but they could not retain it for long. It was as if they had short-term memory but no long-term memory.

A second paper by B.T. Volpe and others in *Neurology* (**36**, 408-411 (1986)) presents some studies of memory in patients who had survived a cardiac arrest. Volpe and his coworkers may have discovered a quite new kind of memory loss. Patients with brains damaged by cardiac arrest show a loss of the ability to *recall* facts combined with *no* loss of the ability to recognize facts which they had previously met. Tests for both recall and recognition were tests not for preserved memory laid down before their illness but

instead for their ability to learn new facts.

The test for recall memory consisted of presenting these patients with a list of words. Then, after a delay, they were asked to recall as many of these words as they could. The test for recognition memory consisted again of presenting a list of words. This time, however, after a delay they were shown another list of words. They were asked to state which of these words had appeared on the previous list. Both tests, therefore, were tests of ability to acquire new facts rather than of the ability to remember facts learned long before illness.

As a kind of memory defect, loss of recall memory combined with preserved recognition memory is quite new. It also tells us something of the kind of brain damage we might expect from loss of blood flow to our brains. The authors promise further studies to find out which brain structures were involved.

For cryonics, one interesting incidental fact comes out of these studies. Volpe et al *did* do one test of memory in the sense which really interests us. As part of their general assessment, they applied the Boston Remote Memory Battery to their patients. This test involves presenting patients with pictures of leading figures from the past, starting in the 1920s and following up to the present. Subjects are then asked to identify who these people are. Of the many tests of memory applied, this is the only test which characterizes preservation of stored memories laid down before illness. Volpe and his coworkers report that their patients could correctly identify 81% of pictures from all decades *except* the one in which their cardiac arrest had occurred. Their success rate dropped to 61% in this last decade. Controls could get 94% right. Although this test suggests that there may be some loss of memory, it also predicts a substantial preservation.

Other than outright cures of these memory defects we don't have good ways of finding out just how many memories still exist in the brains of damaged patients, unable to show themselves because of defects in retrieval rather than outright destruction. One hopeful sign is that many memory defects involve damage to brain structures important in the *recall* process, combined with relative preservation of other brain parts. If recall mechanisms are impaired, we wouldn't expect any ability to remember. Preservation of other brain structures suggests that memories may still exist. However as yet this is only a hope, not a promise, from research into brain disease and damage.

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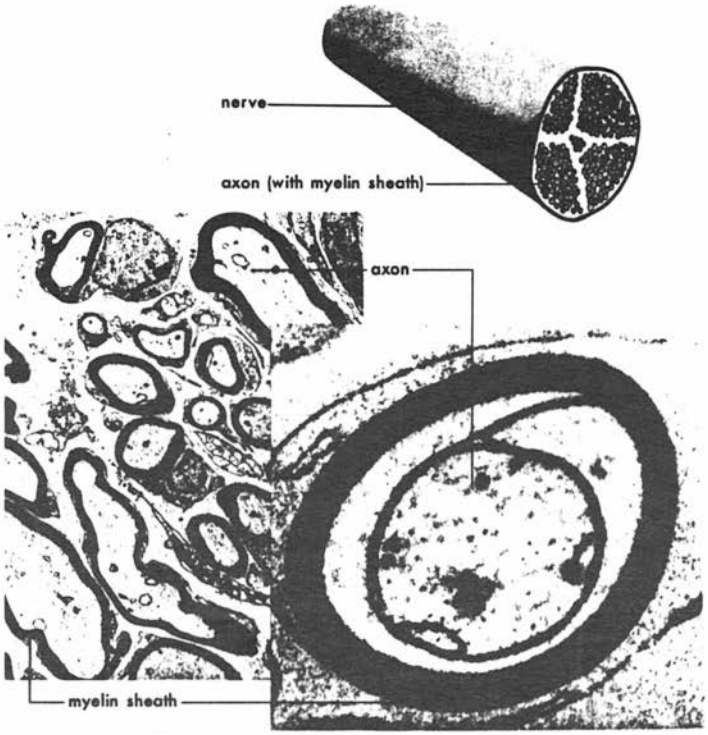
CHEMISTRY AND PATHOLOGY OF TWO MEMORY SYSTEMS

One commonplace fact about amnesia may provide a very important clue to how our memories work. Everyone knows of how people stricken with amnesia somehow still remember their language (instead of babbling incoherently, they ask "Where am I?" "Who am I?) and many other normal everyday skills. This fact, everywhere taken for granted, is really quite interesting and surprising. Recently, neurological experimenters have taken notice of it (cf. N.J. Cohen, in N. Butters and L.R. Squires (Eds.), *Neurophysiology of Memory*, 1984, pp 83-103). Although names for the different memory systems haven't stabilized yet, current ideas say that there are al least two *different* memory systems, *procedural* and *declarative* memory.

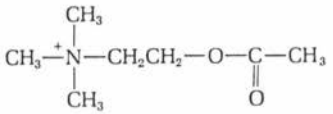
N.J. Cohen, for instance, could train amnesiacs with injuries to their hippocampus so they could solve the Tower of Hanoi puzzle (a *procedural* memory). These same amnesiacs, though, could not remember how or when they had learned to solve the puzzle (a *declarative* memory). We all know this distinction, too, from our own memory. we have all learned many skills, some quite intellectual, while we've completely forgotten how or when we learned them.

Given these two memory systems, it's very much of interest to work out how they work



out *chemically*. It's also of interest to find out more about how people with different kinds of amnesia deal with these two memory systems. Two recent papers by Mary J. Nissen and D.R. Knopman in *Neurology* (37, 784-8 (1987); 37, 789-94 (1987)) give us some answers to these questions. In particular, they help clarify the mechanism of declarative memory and the loss of it in Alzheimer's disease.

One major chemical involved in declarative memory is *acetylcholine*. Acetylcholine was the earliest nerve transmitter chemical discovered. Nerves which transmit impulses from one to another by acetylcholine play an important role in the hippocampus. The hippocampus, in turn, seems to work as a brain module which reads memories in and out of long-term store.



Acetylcholine

Drugs which block the action of acetylcholine correspondingly interfere with declarative memory in normal subjects. One of the more striking and interesting experiments on Alzheimer's disease, in fact, was D.A. Drachman and J. Leavitt's discovery that scopolamine will cause symptoms similar to those of Alzheimer's disease in normal human subjects (*Arch Neurology*, 30, 113-121 (1974)).

Nissen and Knopman therefore sought to study both scopolamine and Alzheimer's disease in *procedural* memory. In their first paper, they report studies of normal human volunteers given injections of scopolamine. They then presented their subjects with opportunities for declarative (a recognition test) and procedural (pressing a button appropriately) memory. Scopolamine caused dramatic differences between declarative and procedural memory. On ability to remember or recognize lists of numbers, the people who received scopolamine did only half as well as controls. On the procedural task, though, the scopolamine people did nearly as well as controls.

This experiment shows that acetylcholine is probably not closely involved in procedural memory. It therefore tells us something about the neurochemistry involved in

memory of both kinds.

Their second experiment consisted of trying the same tasks with control subjects and subjects with Alzheimer's disease. Their control subjects were chosen of the same ages as subjects with Alzheimer's disease. Once more, the subjects with Alzheimer's showed a nearly unimpaired ability to learn a new procedural task. At the same time, just as in other experiments on procedural memory in brain-damaged people, the Alzheimer's patients had no continuing memory of how they had acquired their new skill.

The authors point out that one brain region does play an important part in procedural memory. Injuries in the *basal ganglia* seem to disrupt procedural learning. We may hope for a much more complete understanding of memory in the near future. Both these papers present new and interesting facts about the two memories.

* * *

BRAIN DEVELOPMENT: HOW DOES IT HAPPEN?

One long-standing issue in cryonics is that of how much information about ourselves and our memories resides in the actual physical linkage of our neurons. What if injury disrupts this physical linkage? Of course we can use this physical linkage to infer conclusions about how our memories. But physical wiring diagrams of neurons may be the expression of other information held in our genes.

In *Brain Research Reviews*, (13, 1-23 (1988)) Susan McConnell, at the Salk Institute for Biological Studies, has just written an interesting review of brain development. She aims to piece out what we know about how growth works in mammalian brains. We need much more information to really answer these questions. Still, scientists know a substantial amount even now.

The main idea of this work has been that of commitment. We want to know when a cell becomes committed to grow into a cell of a particular type. The embryonic cell is committed to becoming a neuron, for instance, if it will grow into a neuron more or less independently of its environment. We discover this by transplanting brain cells to new places within the embryo. Usually cells will migrate within the embryo. They don't form in the same place they will remain in life. Instead, they start out from one special layer of cells (the ventricular zone) and move to their final location. The ventricular zone is in the anatomy of all mammalian embryos. When they start out in the ventricular zone, brain cells usually show no obvious signs of their fate. They may have become committed as early as this. Then again not.

Fundamentally, we don't even know how early in development glial cells and neurons become committed to their fates. However even in this case, some evidence exists that it is very early. Cells in the ventricular zone make proteins characteristic of neurons or glia well before they migrate.

McConnell reviews many experiments on brain development. A number of facts emerge. First, the fate of brain cells correlates to their final position in the brain. Second, final position depends on the generation of the cells. Recall that all these cells come from a single original, so that we can draw a genealogical chart of their history. It turns out that their position on this genealogical chart, how many divisions they are from the parent cell, correlates very much with their final position in the brain.

Neurons differ among themselves not just in their position and connections to other neurons, but also in the transmitters they use to pass messages. For instance, cholinergic neurons use acetylcholine. Serotonergic neurons use serotonin. Generation time may not control the neuron's fate completely. Neurons very close to one another in generations will differ considerably in details such as transmitter type and exact connections.

A variety of experiments using transplants, chemical treatment of brains of mice, and mice with inherited defects in development, suggest that neurons become committed very early. That commitment happens before they migrate out of the ventricular zone. It primarily depends on the cell generation of the neurons. For instance, we can transplant very young brain cells

into much older, fully developed brains. These cells don't stay where they're put. They move within the host brain, toward the same kinds of places in which they would normally grow. Once there, they try to form connections of the same kind as those they would normally form. Such experiments strongly suggest that commitment happens very early.

After reviewing all these experiments, McConnell offers some conclusions. Brain cell development involves very early commitment of neurons to a general fate and location. Even the neurons to which a given neuron will connect are determined by this early commitment. However local chemical cues felt by the cell after its commitment, and after it has migrated to its final position, do determine the exact path of these connections and sometimes whether or not they exist.

For our purposes, time of commitment isn't the primary issue. Mode of commitment is. By this I mean, that even if commitment happened very late in the development of neurons, this could still mean that neuron interconnections were stored in some way other than their actual physical connections. But if commitment happens very early on, then neuron interconnections must be stored in some way other than actual physical connections.

Transplant experiments are very suggestive here. They don't just tell us that commitment often happens early on. Since neurons transplanted into an adult brain try to form appropriate connections, it follows that whatever chemicals control these connections must still exist in adult brains. These chemicals (whatever they may be) therefore provide another way information about neuron interconnections is stored.

No one should think this issue is settled. Most experiments McConnell reviews aren't nearly as conclusive as we would like. Just as in the question of memory survival itself, we'll have to live with some uncertainty for a while.

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Synapses, Circuits And The Beginnings of Memory
Gary Lynch et al, MIT Press, 1986

Although *Cryonics* has covered work on biochemical theories of memory, we haven't yet discussed in detail any work on memory at levels higher than the neurons. We know that ultimately our memories must come about from mass action of many neurons rather than changes in any single one. Certainly this will require that individual neurons have a memory of their own. We can study this individual memory and make progress unraveling its workings. But the memory of individual neurons isn't the same as the memory we experience daily.

We've also had a very good reason for not discussing this higher order memory in detail. The reason is that there just hasn't been a lot of work on the subject; nonexistent news is hard to report.

Of course there are connection theories of memory. There are some very interesting models which show how a network of "neuron-like" transistors can show some characteristics of memory. The earliest attempt at connection theories was the idea of the *perceptron* (M.L. Minsky and S. Papert, *Perceptrons*, MIT 1969). When it became clear that perceptrons could not emulate some very simple kinds of learning, the idea collapsed in ignominy. But over the last few years, model makers have learned how to make networks of "neurons" which do much better. The key idea to such progress has been to introduce a layer of "intermediate neurons", which sum up the effects of perceptual neurons and pass these summed results on to "effector neurons". The best statement of these models and theories to date is in the two-volume set by D.E. Rumelhart and J.L. McClelland, *Parallel Distributed Processing: Explorations in the Microstructure of Cognition.* Unfortunately, however, the theories of Rumelhart and McClelland, just like earlier connection models, are only *models.* They don't attempt to link, in detail, anything about structure of our brains with the kind of learning we do.

The problem with such models is that we can only go so far with the mathematics of networks and a bit of human behavior. We want *anatomy* and *chemistry*.

The book under review constitutes the first attempt I know of to work out how actual real connections in a real animal brain might relate to connectionist theories of memory. Gary Lynch has worked extensively on the memory of individual neurons. The first part of the book presents his theories on how neuron memory works. It is valuable for that alone, since he sums up this work in a way which would be hard to get from individual papers. But the most important part of the book consists of Lynch's speculations (which he carefully labels as such) about how learning of these individual neurons comes together into learning of the whole animal. Lynch looks at the detailed anatomy of our brain, and animal experiments, and tries to see how a connectionist theory could explain our learning from this anatomy.

Lynch's theory about neuron memory is that long-term memory occurs because nervous impulses uncover extra receptors in the synapses receiving them. The process of uncovering these receptors involves an enzyme, *calpain*, activated in the presence of calcium ions in the local cell substance. Calpain degrades one membrane protein, *fodrin*. This degradation exposes new receptors for transmitter chemicals. These receptors then increase the propensity of these local synapses to receive new impulses.

To find out how individual neuron learning may relate to whole-brain learning, Lynch proposes to examine *olfactory* learning and the hippocampus. Most of his article consists of detailed consideration of the anatomy of nervous connections within the hippocampus and to and from olfactory brain centers. The reason for emphasis on olfactory learning is first, that phylogenetically the hippocampus is closely related to smell, and secondly that unlike (say) vision, the anatomy takes us directly into nets of neurons which may very well resemble a connectionist network. (Visual brain centers have extensive wiring for recognition of particular inputs such as edges. These are very interesting but confuse the analysis of memory).

As a result of his speculations, Lynch has several predictions about how animals will learn olfactory stimuli. For instance, he suggests that mice and rats will learn combinations of odors (ABC, for instance) as single perceptual entities, that if they have learned to associate an individual odor (say A) with a stimulus, then they will afterwards find it hard to learn that a combination AB is different, and so on. He also suggests that the hippocampus *does* contain some particular memories: one interesting point he brings up is that patients with hippocampal injuries can't remember associations between odors and other objects, even those learned before their injury.

Hopefully Lynch's predictions, and his anatomically based theories, will get much more experimental attention in future. Attempts to link connection theories to brain anatomy deserve a lot of attention. This is the only way we will show that connection models *actually* represent memory, rather than just showing that they *could* represent memory.

Although I feel that this point does not detract from the value of Lynch's discussion, I would like to point out that his particular theory of neuron memory doesn't confront one problem, the long-lasting nature of memory. His work makes it very likely that degradation of fodrin by calpain explains one stage in formation of a memory. But we also need to know why this change at a synapse does not disappear with time. The change does persist for hours and days. We need changes to persist for months.

This book is valuable. Anyone who wants to find out the state of current thinking on memory should read it. Anyone who wants to advance the state of current thinking on memory needs to study it.

Meeting Schedules

Alcor business meetings are usually held on the first Sunday of the month. Guests are welcome. Unless otherwise noted, meetings start at 1 PM. For meeting directions, or if you get lost, call Alcor at (714) 736-1703 and page the technician on call.

ALCOR

The SEPTEMBER meeting will be held at the home of:

(SUN, 11 SEP 1988) Paul Genteman
(SECOND SUNDAY) 535 S. Alexandria, #325
(PLEASE BRING CHAIRS) Los Angeles, CA

The OCTOBER meeting will be held at the home of:

(SUN, 9 OCT 1988) Allen Lopp
(SECOND SUNDAY) 13354 Veracruz St.
Cerritos, CA

The NOVEMBER meeting will be held at the home of:

(SUN, 6 NOV, 1988) Brenda Peters
8150 Rhea
Reseda, CA

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The Alcor Cryonics Supper Club is an informal dinner get-together in the Greater Los Angeles area. These meetings are for newcomers and old-timers alike -- just an opportunity to get together and talk over what's happening in cryonics -- and the world!

If you've wanted an opportunity to ask lots of questions about cryonics, or if you just want a chance to spend some time with some interesting and nice people, pick a date and come! All dinners are scheduled for Sundays at 6:00 PM.

Sunday, September 25

94th Aero Squadron Restaurant
(Van Nuys Municipal Airport)
16320 Raymer Ave.
Van Nuys, CA Tel:(818) 994-7437

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The New York Cryonics Discussion Group of Alcor has recently formed.

The group meets on the the third Saturday of each month at 5:30 PM. The meeting place has been established at the *Omnia Cafe* (Greek), 32-20 Broadway, Astoria, New York (phone #: (718) 274-6650). This is near 31st Street and Broadway, off the elevated train line. There is a train stop from Manhattan on the B and N trains. It is also very close to the Grand Central Parkway and Brooklyn Queens Expressway.

If you live in the New York, Philadelphia, New Jersey, or Boston areas and would like to participate in the rebirth of New York cryonics please contact one or more of the following people:

Gerard Arthus	(516) 273-3201
Al Roca	(201) 352-5268
Curtis Henderson	(516) 589-4256

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