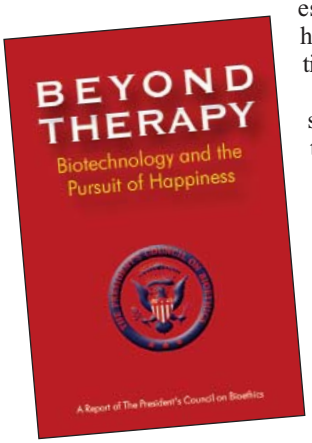
line. The researchers concluded that adrenergic activity—brain signals transmitted by members of the adrenaline family—is essential for the enhancement of emotional memories.



Problematic. The President's Council on Bioethics warns against manipulating memories.

Subsequent research has hinted that adrenergic activation plays a role in the development of PTSD. People who show greater signs of adrenergic activation, such as a racing heart rate and panicky behavior, immediately after a traumatic event are more likely to exhibit symptoms of PTSD later, says Charles Marmar, a psychiatrist at UC San Francisco.

Together with colleagues in France, Marmar recently gave propranolol to 11 people admitted to French hospitals following a motor vehicle accident or physical assault. The patients, who did not have serious physical injuries, took the drug within a few hours of the incident in most cases and continued to take it for 2 to 3 weeks. Two months later, this group had fewer symptoms of posttraumatic stress than a similar group of patients that didn't take the drug. A previous pilot study by Pitman and colleagues, published in 2002, found similar results.

Both Pitman and Marmar say the findings are encouraging but preliminary. "You can't take this to the bank," Marmar says of the combined results, "but I think it's enough to justify a large-scale trial." Indeed, both groups learned late last year that they will receive funding for larger, blinded, placebo-controlled trials. "If this is all correct, it means that PTSD, which affects close to 8% of the American population at some point in their life, might be predictable at the time of the event and may even be preventable … with a course of medication that costs $15," Marmar says.

Medicating away morality?

But that doesn't sound like a bargain to the President's Council on Bioethics. In a report* released last October, the panel opined that "the prospect of preventing (even) PTSD with beta-blockers or other memory-blunting agents seems to be, for several reasons, problematic."

Among practical problems, the report says, is knowing whom to treat. Victims don't exhibit symptoms of PTSD, by definition, at the time of the event. Accident witnesses might start demanding prescriptions, imperiling their future testimony. In the future foreseen by the council, doctors could "give beta-blockers liberally to soldiers on the eve of combat, to emergency workers en route to a disaster site, or even to individuals requesting prophylaxis against the shame or guilt they might incur from future misdeeds." The potential for misuse, they claim, abounds.

Moreover, the report continues, bearing traumatic memories is the moral obligation of those who witness atrocities. Even if individual Holocaust survivors were to benefit from treatments that weakened the memories of their experiences, the council writes, society as a whole might be badly served by having no witnesses whose memories are unadulterated. "Our memory is not merely our own; it is part of the fabric of the society in which we live."

The council's report largely misses the mark, says Arthur Caplan, a bioethicist at the University of Pennsylvania in Philadelphia. Certainly society must preserve the record of atrocities such as the Holocaust, he says, but doing so doesn't require denying individuals the benefits of therapeutic drugs: "The notion that we need to have suffering martyrs among us is cruel and exploitative."

The subtext of the council's argument, says Caplan, seems to be that using drugs to manipulate memories—whatever the content of the memories—is unnatural and therefore morally suspect. "I don't accept that at all," he says. For one, it obliterates the line between treating memory and mood disorders and using drugs for the selfish pursuit of self-improvement. And if treating an infection with antibiotics is OK, he asks rhetorically, why shouldn't it be OK to use drugs to correct a problem with memory or cognition? "It's a moral argument that, if turned in in my undergraduate bioethics class, would pull a C."

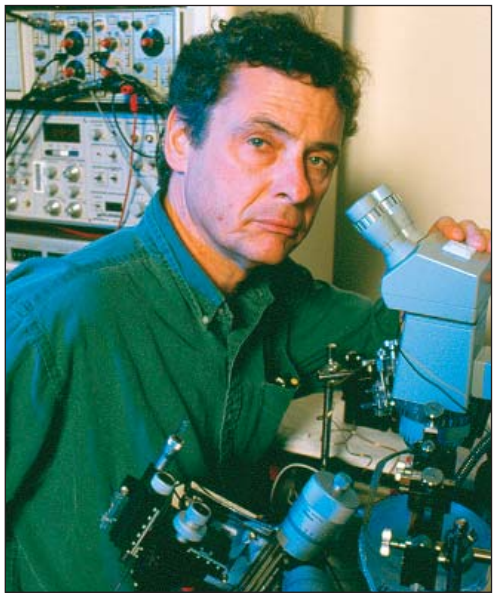
Selectively erasing memories does indeed raise ethical questions, says Joseph LeDoux, director of the Center for the Neuroscience of Fear and Anxiety in New York City. But that's always true of science that pushes the bounds, he says: "If we're successful in doing these sorts of things, it will raise a societal debate about how far we want to go." –GREG MILLER

* *Beyond Therapy: Biotechnology and the Pursuit of Happiness*

A Star-Studded Search for Memory-Enhancing Drugs

An eager market—from Alzheimer's patients to aging overachievers—awaits the first memory-enhancing drugs. High-profile neuroscientists are racing to provide the goods

Forgetfulness is a common failing of old age that patent medicines once promised to cure. But rescuing memory has now moved from snake oils and placebo effects into the scientific mainstream. There's been an explosion of new drug candidates designed to boost memory in recent years, and many are entering clinical trials. Although a few elixirs have already fallen by the wayside, observers see encouraging signs in the breadth and depth of clinical experimentation.



Early start. Gary Lynch of UC Irvine helped launch Cortex more than a decade ago; in the 1990s the firm began to develop drugs called ampakines to boost memory.

CREDIT: (BOTTOM) UNIVERSITY OF CALIFORNIA, IRVINE

Although big pharmaceutical firms are heavily involved, some of the most ambitious efforts are led by small companies, each tied to a prominent academic scientist and backed by a famous institution. And star scientists are drawing media attention and giving the enterprise a dash of glamour.

The commercial potential for memory enhancers is immense. Some drugs in development are designed to help people with Alzheimer's disease or other brain disorders, whose number is in-

creasing rapidly as the population ages. But most would equally well treat mild cognitive impairment, a subclinical condition that often progresses to Alzheimer's, or the kinds of age-related memory declines that are common even in healthy people. Some companies are planning to treat memory problems associated with mental illness and mental retardation. Even the "worried well"—and there are many among the aging baby boomers—could eventually be customers, seeking to medicate perceived memory lapses. This group overlaps with the potentially huge and ethically troublesome market for "off-label" uses—people who simply want to enhance their powers of memory rather than treat memory loss (see Editorial, p. 17).

"There's a lot of enthusiasm" about new therapies, says biochemist Tom Dietz, co-CEO of Pacific Growth Equities, an investment firm in San Francisco that follows this field. "We have an aging population, and it's growing. So these companies have a ready market" and not much competition from other approved drugs. "We're seeing the culmination of many years of work," Dietz says, adding, "that doesn't happen often." A sample of these companies reveals that they are moving toward the same goals but have different styles and strategies.

Counterpoint. Eric Kandel of Columbia (*above*) and Tim Tully of Cold Spring Harbor Laboratory are founders of competing companies, Memory Pharmaceuticals and Helicon Therapeutics, respectively, both seeking to improve memory by raising levels of CREB.

CREDITS: (TOP TO BOTTOM) SPENCER PLATT/NEWSMAKERS/GETTY IMAGES; MIRIAM CHUA

Take a memo

Gary Lynch was one of the first to explore this territory. A researcher in psychiatry and human behavior at the University of California (UC), Irvine, he helped guide a small company called Cortex Pharmaceuticals during its start-up years in Irvine in the 1980s, when it was concerned with treating stroke and neurodegenerative diseases with growth factors. At his urging, Lynch says, in the 1990s the company began to focus on molecules dubbed ampakines. They modulate so-called AMPA receptors, which respond to the neurotransmitter glutamate. Given the right kind of neural stimulation, AMPA receptors strengthen synapses, the contact points between neurons at which they exchange information. New or more sensitive synapses, according to theory, write experiences into memory.

Lynch began this work after learning about a potential memory-boosting ampakine compound in a preprint from Isao Ito of Chugai Pharmaceuticals in Japan. Soon after that, a "fortuitous encounter," Lynch says, brought him together with medicinal chemist Gary Rogers, then at UC Santa Barbara, who quickly concluded that he could make a "more potent, more persistent" version. Rogers and Lynch teamed up to create an ampakine drug now being tested by Cortex as compound CX516. Its safety and proof of principle have been established in phase I and phase II clinical trials, according to Cortex. But it's not likely to become a prescription drug, Lynch notes, because its potency is low. Hopes are now riding on successor compounds, including CX717, which will soon enter clinical testing.

"We and everybody else who are using ampakines are trying to make it easier to encode memory," that is, create a neural trace of an experience, says Lynch. In contrast, several other new companies are emphasizing a slightly different step, targeting the protein machinery that stabilizes memory. "It's going to be entertaining" to watch the competition, says Lynch.

Nobel spinoff

Memory Pharmaceuticals Corp., a small company in Montvale, New Jersey, has been featured in journals such as *Forbes* and *Business Week*, benefiting from the celebrity of its scientific guru, Eric Kandel, a Howard Hughes neurobiologist at Columbia University in New York City. A co-recipient of the Nobel Prize in physiology or medicine in 2000 for work on the biochemistry of neuron signaling, Kandel has been showered with many awards during a long academic career devoted to the study of how memories are formed and stored at the molecular level.

Kandel says the idea for Memory Pharmaceuticals took shape over dinner one night with Walter Gilbert, the Harvard biochemist who won a Nobel Prize in chemistry in 1980. The two had been involved with another firm and were discussing memory research. Kandel recalls that his wife Denise "suggested that we start a company." They did, bringing in venture capitalist Jonathan Fleming and scientific director Axel Unterbeck from the German drug firm Bayer to found Memory Pharmaceuticals in 1998.

The company, which counted Columbia University among its first backers, has used Kandel's model of long-term memory consolidation to search for potential memory-boosting molecules in animal models. Its initial target is Alzheimer's disease, but it also aims to treat vascular dementia, schizophrenia, depression, and common age-related memory loss.

At present, Memory Pharmaceuticals has identified four drugs in development. The furthest along in testing (MEM1003) was licensed from Bayer. It's designed to protect neurons against excess calcium inflows, a common defect of the aging brain that damages neurons and eventually impairs cognitive function.

Next in the pipeline are two drugs derived from Kandel's work (MEM1414 and MEM1917). They are designed to enhance memory by sustaining levels of a critical neurotransmitter called cyclic AMP and a protein it modulates, CREB, which has the power to turn genes on and off. Fluctuations of CREB levels can reshape synapses and are thought to help cement memories. The fourth candidate (MEM3454) is an anti-schizophrenia compound aimed at a different target, the nicotinic alpha-7 receptor; nicotine eases some symptoms of the disease, and researchers suggest that this may explain the high rate of smoking among

people with schizophrenia.

Only MEM1003 has completed an initial safety trial (phase I), in 185 people. A similar trial of the cyclic AMP booster MEM1414 is under way, and phase II trials are being planned. The Swiss pharmaceutical firm Roche has invested $37 million so far and has promised $248 million if researchers achieve specified milestones. The race to be the first with a memory-enhancing product is intense.

Competition is much on the minds of folks at Memory Pharma this spring, as they prepare to convert from a private to a public company. They have filed a federal registration proposing to sell 5 million shares in the initial offering, at about $14 a share. The sale will begin after the Securities and Exchange Commission approves. But company leaders can't say much about it, a spokesperson explains. They're in a "quiet period" mandated by U.S. securities laws. This is a new experience for Kandel, an ebullient talker and teacher. He can't comment on the company's prospects, but he says he's enjoying the ride.

Selected Memory Drug Companies

	Academic leader	Founded	Staff	Memory enhancer in development
Cortex Pharmaceuticals	Gary Lynch	1987	22	One in phase I, one in phase II
Helicon Therapeutics	Tim Tully	1997	20	One preclinical
Memory Pharmaceuticals	Eric Kandel	1998	75	Two in phase I
Sention Inc.	Mark Bear	1999	28	One in phase I, one in phase II

Rivalry

Similar targets are being pursued by a smaller company built around the research of Timothy Tully and Jerry Yin of Cold Spring Harbor Laboratory, called Helicon Therapeutics, in Farmingdale, New York. Like Kandel, Tully has specialized in studies of the molecular basis of memory, also focusing on the role of cyclic AMP and CREB. Tully achieved fame when he published reports in 1994 and 1995 on fruit flies genetically engineered to express high levels of CREB. The insects performed astonishing memory feats, learning a new path to food in a single pass, much faster than normal flies.

Tully's company, like Memory Pharma, is investigating molecules that can sustain or boost CREB levels in neurons, in the hope that doing so will improve memory function in aging patients. A key element in both cases is to identify specific enzymes (called phosphodiesterases) that degrade CREB and block their action. Helicon and Memory Pharma have patents and interests that could clash.

Stealth flier. With colleagues at Brown, MIT's Mark Bear founded Sention, a quiet memory drug company that has tried to stay below the media radar.

Tully says he was spurred to start Helicon by a report on CREB unrelated to his work, published in *Nature* in 1995. The study identified a defect in a human CREB-binding protein associated with a type of mental retardation, Rubinstein-Taybi syndrome. The only way to test the possibility that this condition might be treatable, he argued to Cold Spring Harbor Lab president James Watson, would be to start a company and make drugs that influence CREB. Watson was persuaded, Tully says, and the lab became a prime investor in Helicon.

Seven years later, says CEO John Tallman, Helicon has one candidate drug ready for human trials, a phosphodiesterase inhibitor. It might be used to treat early Alzheimer's disease and mild cognitive impairment. Animal testing has gone well so far, Tallman reports, and a phase I clinical trial is set to start "in the second half of 2004." It is "too early" to talk about other projects, he says. Unlike its rival, Memory Pharma, Helicon isn't selling public stock. "We're happy to be private," Tallman says; the lack of big company partnership is fine, too, because it gives the company founders "more control."

Dark horses

Less attention has been paid to Sention Inc., a spinoff from Brown University in Providence, Rhode Island. It is the "stealth bomber" of memory-enhancement firms, says Harry M. Tracy, editor of *NeuroInvestment*, a newsletter in Rye, New Hampshire, that follows the business. He says the company is "very circumspect," although it has put two candidate compounds through phase I clinical trials and one through phase II. Company co-founder Mark Bear, a Howard Hughes investigator in neuroscience now at the Massachusetts Institute of Technology, admits that he wants to keep it low-key: "We try to be quiet … and let Helicon and Memory have the limelight." Bear formed the company in 1999 with two colleagues at Brown: Leon Cooper, a theoretical neuroscientist who won a Nobel Prize in physics in 1972, and Mel Epstein, then head of clinical neuroscience at Brown. A distinct aspect of Sention's approach, Bear says, is a broader focus—one that centers on functions "that are well upstream of CREB that regulate the strength of memory consolidation." But he isn't ready to disclose details.

Asked about the rumor that they are specifically focusing on glutamate receptors, CEO Randall Carpenter says: "We're receptor agnostic. … We're trying to turn up the gene expression" of proteins that are used as "the universal building blocks for memory storage." Results should be available "by the end of the year," Bear promises.

Many other small firms are contending for a profitable niche, with varying results. Daniel Alkon, a neuroscientist at West Virginia University in Morgantown, has patents on another string of neural receptors. The company he was once allied with, NeuroLogic in Rockville, Maryland, sponsored phase I and II clinical trials, but recently, Alkon says, it "has become less active." A company official says they and Alkon have parted ways. Meanwhile, other companies are advancing rapidly—most with less direct academic ties—such as AGY Therapeutics in South San Francisco and Saegis Pharmaceuticals in Half Moon Bay, California.

These are just a handful of the biotech ventures that may have a shot at delivering a first generation of memory-enhancement drugs. Each is trying to chart its own path through the science; each holds a set of patents; and each is trying to pull together funds needed to commercialize its discoveries. It's shaping up to be a memorable race.

–ELIOT MARSHALL

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