THE QUEST FOR A SMART PILL

New drugs to improve memory and cognitive performance in impaired individuals are under intensive study. Their possible use in healthy people already triggers debate.

ON A WINTRY AFTERNOON IN APRIL, TIM TULLY AND I stood in a laboratory at Helicon Therapeutics, watching the future of human memory and cognition—or at least a plausible version of that future—take shape. Outside, a freak spring snowstorm lashed at the Long Island landscape. I mention the weather because it reminded both Tully and me of winters from our childhoods in the Midwest many years ago. The enduring power of those memories—and the biological processes that record and preserve them in the brain—lie at the heart of an incipient revolution in neuropharmacology that is unfolding in small, relatively unknown labs like this one in Farmingdale, N.Y.

Tully, a neuroscientist at Cold Spring Harbor Laboratory and founder of Helicon, has been one of the leading protagonists in the race to develop a new class of drugs that might improve memory in the memory impaired—drugs that grow out of an increasingly sophisticated molecular and mechanistic understanding of how we can remember everything from snowstorms more than 30 years ago to where we put our car keys 30 minutes ago.

It is, alas, the nature of contemporary science (and commerce and bioethics, for that matter) that we often have to conjure up the future of human cognition, and its pharmacological manipulation, while staring at the behavior of a drugged mouse meandering in a jury-rigged box. So there we stood, gazing at a video playing on Tully's laptop computer, watching a small brown rodent enter an enclosed environment and begin its scurrying explorations in an experimental scenario known as Object Recognition Training. One day earlier, Tully explained, this same mouse had been placed in this same box, which contained two odd, knoblike objects, each with its distinct olfactory, tactile and other sensory tags. A mouse that is allowed to explore this environment for 15 minutes, Tully continued, will remember it so well that the animal will immediately notice any changes the next day; a mouse allowed to explore for only three and a half minutes, however, typically does not have enough time to commit the scene to long-term memory.

The mouse we were watching had had only three and a half minutes of training. But it did have a pharmaceutical assist, and that is what Tully wanted to show me. Narrating
the action like a play-by-play announcer at a sports event, he described the scene as
the little creature immediately paid an inordinate amount of murine attention to a new
object in the room. "See, there he goes," Tully said in his earnest Midwestern locution.
"He's walking around it ....

Now he's climbing on top of it He's not even paying attention to the other object.
Indeed, the mouse sniffed at and circled and eventually clambered all over the novel
object while ignoring the second object-the one encountered the day before.

To display this degree of curiosity, the mouse needed to remember what had been in
the box the day before. That requires the formation of a longterm memory. And
although years of behavioral experiments have established that mice ordinarily do not
recall any changes in their environment after so brief a previous exposure, this one did,
because of a drug--a memory drug known as a CREB enhancer that Helicon hopes to
begin testing in humans, perhaps as soon as the end of the year. "We've shown that
several compounds will enhance the ability of a normal mouse to remember this task,"
Tully said. "And yet to make it a fact rather than a belief, we have to show it works in
humans."

These days smart mice and erudite rats are the stalking-horses for a new
pharmacology: drugs that might enhance human cognition, improving memory in
those whose memories have faltered because of neurodegenerative disease or aging,
perhaps even reengineering memory-forming circuitry in stroke victims or people
with mental retardation. The potential market for such medicines is staggeringly large.
As Tully and every other biotech and bigpharma executive know by heart, there are
four million Americans with Alzheimer's disease, another 12 million with a condition
called mild cognitive impairment (which often presages Alzheimer's), and
approximately 76 million Americans older than 50, many of whom may soon satisfy a
recent definition by the U.S. Food and Drug Administration for age associated
memory impairment (or AAMI), a form of mild forgetfulness. And judging by the
sales of the herbal medicine ginkgo biloba, consumers are not waiting for an
FDA-approved memory drug. Sales of ginkgo exceed $1 billion a year in the U.S.,
even though the scientific evidence that it improves memory is marginal at best; sales
in Germany outstrip all acetylcholinesterase-inhibiting drugs used to slow memory
loss in Alzheimer's patients, including donepezil (Kricept, marketed by Pfizer),
rivastigmine (Exelon, marketed by Novartis) and galantamine (Reminyl, marketed by
Janssen).
Despite an incessant media drumbeat about the coming revolution in what one magazine has dubbed "Viagra for the brain," smart pills are not around the corner. Cortex Pharmaceuticals in Irvine, Calif., has developed a class of memory-enhancing drugs called ampakines, which the company believes will increase the power of the neurotransmitter glutamate; the drugs have passed Phase I safety testing and are currently in Phase II tests (small-scale trials for efficacy) against Alzheimer's, mild cognitive impairment and schizophrenia. But those preliminary tests come at the end of a research odyssey that began in the mid-1980s, with no definitive end in sight.

Nevertheless, the action is beginning to heat up. Memory Pharmaceuticals in Montvale, N.J., which is commercializing the Nobel Prize-winning research of Columbia University professor Eric R. Kandel [see "The Biological Basis of Learning and Individuality," by Eric R. Kandel and Robert D. Hawkins; SCIENTIFIC AMERICAN, September 1992], began initial safety testing of its first memory-enhancing drug in humans at the beginning of 2003, and Tully estimates that Helicon's lead drug candidate should enter trials no later than early 2004. Axonyx in New York City has been looking at phenserine (a potent acetylcholinesterase inhibitor) to treat Alzheimer's; the company began advanced testing in June. Princeton University neuroscientist Joe Z. Tsien, who caused an enormous stir in 1999 with the creation of a genetically enhanced smart mouse called Doogie, has advised a San Francisco-based biotech company, Eureka! Pharmaceuticals, which is collaborating with scientists in Shanghai to look for drugs that would merge modern genetics with ancient Chinese herbal medicine. Still, Tsien has his doubts about how soon the much-ballyhooed revolution will begin. "I'd be surprised to see any of these get to the clinic and become a drug anytime soon," he predicted, "especially a drug without side effects."

Although most of these new-generation drugs are years away from government approval and clinical use, their social impact has already been profound. Bioethicists have been working overtime contemplating the social dangers of memory enhancement, especially their potential use as "lifestyle" drugs. Moral philosopher Leon R. Kass, head of the President's Council on Bioethics, recently wrote that "in those areas of human life in which excellence has until now been achieved only by discipline and effort, the attainment of those achievements by means of drugs, genetic engineering, or implanted devices looks to be 'cheating' or 'cheap.'"

In another sense, however, the use of potent drugs as cognitive enhancers has been a feature of human life ever since people began drinking coffee. About 50 years ago the practice gained a more pharmaceutical aura when normal, healthy adults discovered
that amphetamines could improve alertness. If, as some predict, the new cognitive enhancers are destined to replicate the pattern of Viagra and become lifestyle drugs, how might that happen, and how widespread might their use become? One possible answer may lie in an earlier generation of cognition-enhancing drugs that have already been approved--methylphenidate (Ritalin) for attentional focus, donepezil for Alzheimer's and modafinil for narcolepsy. These drugs are already taken by normal adults who seek to enhance mental acuity and performance. Users clearly believe that the drugs improve cognitive performance in normal people, although almost no research attests to this--and some research hints that they may be no better than a drug found on most breakfast tables.

The Caffeine Caveat COGNITIVE ENHANCEMENT has been a feature of military research for a numbers of years. At Walter Reed Army Institute of Research, Nancy Jo Wesensten works on pharmaceutical agents that might improve the alertness (and therefore battlefield performance) of soldiers suffering severe sleep deprivation. In June 1998, while attending a meeting of sleep researchers, Wesensten stopped by the booth of Cephalon, a biotechnology company based in West Chester, Pa., and began chatting with one of its marketing representatives.

At the time, Cephalon was close to gaining FDA approval of a drug with the generic name of modafinil. Marketed as Provigil, this medicine is used to treat narcolepsy, the profound daytime drowsiness that afflicts an estimated 125,000 Americans. Modafinil, it became clear, would be an obvious candidate for the U.S. Army to test as a treatment for sleep deprivation--so much so that Wesensten was whisked up to the company's hospitality suite to discuss the work further. Eventually Cephalon agreed to provide modafinil for the army's research.

[That was more than five years ago. In December 1998 the FDA approved the sale of modafinil in the U.S. to treat narcolepsy, and Cephalon is now selling about $200 million worth of the drug each year. That's a lot of narcolepsy medication--more, many observers suspect, than the U.S. population of narcoleptics can support. "There's a huge amount of off label use by psychiatrists to augment mood," said Helene Emsellem, who runs the Center for Sleep and Wake Disorders in Chevy Chase, Md. In fact, modafinil is used to treat depression, multiple sclerosis and several other clinical conditions associated with fatigue. More to the point, there have been reports that doctors "are getting barraged" (as the online magazine Slate recently put it) by healthy people requesting prescriptions for modafinil as a cognitive enhancer that allows them to sleep less, stay up longer, work harder and play more. One well-known academic sleep researcher told me off the record, "People are telling me
that they focus better on it, including some of my colleagues." Cephalon has been conducting clinical trials to test Provigil as a treatment for additional disorders of excessive sleepiness--resulting, for example, from disrupted sleep (caused by sleep apnea) or the "circadian misalignment" suffered by night-shift workers such as factory employees and truck drivers.

Which brings us back to Wesensten's study at Walter Reed's sleep center. "We were specifically interested in whether modafinil has any advantages over caffeine, which we find very good for reversing the effects of sleep deprivation on cognitive performance. Plus it's widely available, nonprescription and has a low side-effect profile," she said. "So was there any benefit to modafinil over caffeine?" Wesenken and her colleagues organized a randomized, double-blind, placebo study in which 50 volunteers were kept awake for 54 continuous hours. After about 40 hours, the subjects received either a placebo, 600 milligrams of caffeine (a stiff dose equal to about six cups of coffee) or one of three doses of modafinil (100 milligrams, 200 milligrams or 400 milligrams). Then they were subjected to a battery of tests to assess cognitive function and side effects.

The bottom line? The highest dose of modafinil, 400 milligrams, cut through fatigue and restored cognitive performance to normal levels--but so did caffeine. The reported side effects of modafinil were quite low--but so were those of caffeine. "What we concluded," Wesensten said, "was that there didn't appear to be any benefit to using modafinil over caffeine. It just wasn't there. Both drugs looked very similar."

The U.S. Air Force has also conducted extensive experimentation with drugs that increase alertness in fatigued military personnel, a particular concern for pilots in an operational setting. The air force al- lowed use of amphetamines as "go pills" by pilots as early as World War II, according to John A. Caldwell, a sleep disorders expert with the air force who has conducted such experiments over the past 10 years. "My primary objective is not to enhance cognitive performance," he said in an interview, "but to maintain the already excellent performance levels of our military."

Beginning in 1993, Caldwell carried out randomized, double-blind experiments showing that dextroamphetamine eliminates virtually all the decrements of performance in both male and female pilots who have not slept for 40 hours. Some of the studies took place in a helicopter flight simulator but have been replicated in real aircraft. More recently, he tested modafinil head-to-head against dextroamphetamine in sleep-deprived pilots, showing that the narcolepsy drug overcame fatigue and maintained cognitive performance, although some of the subjects developed nausea
akin to motion sickness inside the simulator. "Ultimately, I think there will be a place for modafinil," Caldwell said. "It wouldn't surprise me if it would be approved for use within a year. But I don't think it will be a replacement for our current 'go pill.' We have 50 years of operational experience, and tons of laboratory research, with dextroamphetamine. We're not there yet with modafinil."

**A Halo of Powder**

RESEARCH ON MODAFINIL, nonetheless, highlights a paradox in the ethical debate about cognitive enhancement. The Defense Advanced Research Projects Agency (DARPA) has funded considerable basic and chemical research looking at ways for its personnel to increase cognitive performance. Its Continuous Assisted Performance (CAP) program has funded preclinical research with Cortex's ampakine drugs, for example. So whereas members of one government body, President George W. Bush's bioethics panel, have characterized the use of drugs by healthy people to enhance cognitive performance as a form of cheating, another branch of the government, the military, has aggressively explored the capacity of new pharmaceutical agents to increase cognitive alertness and performance in fatigued but essentially normal individuals--a short hop, skip and a jump to cognitive enhancement for civilians.

Modafinil is merely the latest cognitive enhancer to develop a following among healthy individuals. There is a mini literature (not to say mythology) surrounding the use of Ritalin as a study aid by high school and college students. Ritalin, marketed by Novartis, is typically prescribed for children with attention-deficit hyperactivity disorder (ADHD) but has reportedly found favor with students and even business executives. Several students at a prestigious East Coast preparatory school told me that Ritalin use as a study aid was so common that students occasionally sported a halo of powder around their nostrils after snorting the drug. The practice has spread to college campuses. "It's here," confirmed Eric Heiligenstein, clinical director of psychiatry at the University of Wisconsin Health Services. "It's fairly well established, if you want to use it." Although the amount of Ritalin consumed by college students is almost impossible to quantify, Heiligenstein said that the number of hard-core users is "very small" yet more extensive than those who take modafinil because Ritalin is "available, relatively cheap and has a pretty good safety profile."

Among the sparse findings about the effects of these drugs on healthy individuals, at least one study suggests that a long-standing dementia treatment improves cognitive functioning in normal people. In July 2002 Jerome A. Yesavage of Stanford
University, Peter J. Whitehouse of Case Western Reserve University and their colleagues published a study in Neurology assessing the impact of donepezil on the performance of pilots. Donepezil, marketed as Aricept, is one of many drugs approved by the FDA to slow the progressive memory loss experienced by patients with Alzheimer's disease. The researchers trained two groups of pilots in a Cessna 172 flight simulator; one group then received a placebo while the other group took five milligrams of donepezil, less than the routine dose for Alzheimer's, for 30 days. Then they tested both groups again in the simulator.

Yesavage and his colleagues threw several curves at the pilots--they were asked to perform some complicated air-traffic maneuvers and had to react to inflight emergencies, including a drop in oil pressure as indicated by cockpit instrumentation. A month after their initial training, the pilots on donepezil performed significantly better than the control group, with especially enhanced performance on the landing approach and in handling emergencies. Yesavage, who hopes to conduct an expanded study sometime soon, noted in the Neurology article that "if cognitive enhancement becomes possible in intellectually intact individuals, significant legal, regulatory, and ethical questions will emerge."

If those questions are true of donepezil, modafinil and other existing drugs, they will be especially true for the new generation of smart drugs, precisely because they are based on a mechanistic approach to memory that could be particularly powerful--unlike the accidental discoveries we have often had up to now. And although every biotech executive decries the notion of a lifestyle drug, everyone is aware of the precedent. "Typically industry wanted to avoid enhancement drugs in the 1990s," said one neuroscientist. "But I think Viagra changed a lot of people's opinion."

**Improving Memory**

As he guided me through some 32,000 square feet of drug-discovery real estate at Memory Pharmaceuticals in northern New Jersey, Axel Unterbeck punctuated every stop on the tour with the phrase "very sophisticated." Unterbeck, the company's tall, charming, elegantly dressed president and chief scientific officer, invoked the words again and again in the electrophysiology lab where half a dozen biologists record the effect of potential memory-enhancing drugs on individual neurons and slices of animal brain, in the vivarium where the company tests those candidate drugs in elderly rodents, and in the pharmacokinetics room, where the disembodied whines and clicks of robotic machinery accompany the analysis of blood samples from
animals and humans. "They're doing the job as we speak," Unterbeck said, proudly pointing out a $250,000 machine that speedily determines the concentration of drug metabolites in blood. "Very sophisticated."

Everything about Memory Pharmaceuticals bespeaks state-of-the-art science and high-end ambition-its intellectual godfathers and founders (Columbia Nobel laureate Eric R. Kandel and Harvard Nobel laureate Walter Gilbert), its beautifully landscaped headquarters with birch trees and daffodils flanking the entryway, even its tony neighbors (the North American headquarters of Mercedes-Benz is just up the road). Founded in 1998, the company is betting a lot of money--$41.5 million from a recent round of financing, plus a co-development deal potentially worth $150 million with the Swiss drug giant Roche--that it can navigate the shoals of drug discovery more efficiently by identifying toxicological and pharmacokinetic (drug metabolism) problems in cognition-enhancing drugs early in the process. "That's the future," Unterbeck said, "and we are very well positioned for translating the science into smart drugs."

Early in 2003 Memory Pharmaceuticals began initial safety testing of its first smart drug, a compound called MEM 1003, in healthy volunteers in London. The compound regulates the flow of calcium ions into neurons and is designed to restore the equilibrium of calcium in brains cells that have been disrupted by Alzheimer's, mild cognitive impairment or a condition called vascular dementia. "So far this program looks exceptionally good in terms of pharmacokinetics and toxicology," Unterbeck said. "The compound looks exceptionally safe." But perhaps the most closely watched of Memory's potential smart drugs is a compound called MEM 1414, because this drug would tweak a molecular pathway identified by Kandel's and Tully's labs as crucial to converting short-term experience and learning into long-term memory. It involves a powerful protein known as CREB.

In the mid-1990s Tully and Jerry Yin of Cold Spring Harbor Laboratory genetically engineered a fruit fly that displayed the insect equivalent of a photographic memory--these flies learned and memorized a task after one training exercise, whereas normal flies took 10 practice sessions. They managed this stunning enhancement of memory by goosing the output of a single gene called CREB. Both Tully's and Kandel's labs have shown that when simple animals learn a task and commit it to memory, the synapses used to form the memory are remodeled and strengthened in a process that requires the activation of genes. As it turns out, memory formation unleashes a messenger molecule inside the cell known as cyclic AMP. This
molecule in turn triggers the formation of a protein that binds to the DNA of a nerve cell, thus activating an entire suite of genes that add the mortar and brick at synapses to consolidate memory formation. This instigating protein is called cyclic AMP response element binding protein, or CREB. The more CREB swimming around in a neuron, the faster long-term memory is consolidated. That at least has been the case with sea mollusks, fruit flies and mice. Now the question is: Will it be true of humans, too?

Normally, another chemical--phosphodiesterase (PDE)--breaks down cyclic AMP in the cell. Pharmacologically inhibiting phosphodiesterase makes more CREB available for a longer period--thus, in theory, strengthening and speeding the process of memory formation. Phosphodiesterase inhibitors have a spotty reputation in pharmaceutical circles, however; one version was approved in Japan to treat depression, but the molecules have a history of causing nausea. Nevertheless, PDE inhibitors have performed exceedingly well as memory enhancers in preclinical testing, according to researchers in the field, because they allow more CREB to hang around in the cell during learning, which promotes memory consolidation. Hence, both Memory Pharmaceuticals and Helicon Therapeutics are developing drugs based on a class of molecules known as PDE-4. Helicon is also working on a drug that suppresses memories, something that might be used to block or erase disturbing memories of a traumatic event. "We have preclinical evidence that suggests that they might selectively block traumatic memories that have formed before," Tully said.

Memory Pharmaceuticals is especially high on its MEM 1414 molecule--a fascination ratified in July 2002 when Roche agreed to be a partner in its development. "What is really interesting, you see the same kind of age-associated memory impairment in nonhuman primates and rodents as you see in humans," Unterbeck explained. About 50 percent of aged animals, he continued, are unable to form new memories, yet MEM 1414 restored age-related effects in the animals' recall to close to normal. The company launched Phase I tests (for safety) of the compound earlier this year.

Even an ideal progression through clinical testing and federal drug approval, however, adverts to a slow and perilous timeline. "MEM 1003 could--and it's a big could--be on the market in 2008," said Tony Scullion, Memory's CEO, "and 1414 wouldn't be too far behind." But as Unterbeck knows from his previous tenure at Bayer, the promise of a new drug often doesn't unravel until late in the game, when the large number of patients typically enrolled in Phase III trials can reveal not only less-than-optimal efficacy but more-than-expected side effects. "Drug companies put $500 million
down," he said, and you get failure in Phase III." Larry Squire, an elder statesman of memory research at the University of California at San Diego, added, "In fact, you could say the whole history of the field has been to deal with side effects."

Moreover, there is hardly unanimity that CREB is the best or only route to a blockbuster memory drug. "There's not very strong biology in the CREB pathway, especially in mammalian systems," one neuroscientist who requested anonymity pointed out. "The targets are not well validated, and CREB is expressed everywhere, very early on." Another prominent neuroscientist told me that even a scientific adviser to Memory Pharmaceuticals has privately expressed the view that the new drugs may prove no more effective than caffeine. Nor is CREB the only portal to memory manipulation. Tsien, creator of the smart mouse at Princeton [see Building a Brainier Mouse," by Joe Z. Tsien; SCIENTIFIC AMERICAN, April 2000], is pursuing a different memory pathway involving a receptor of the neurotransmitter NMDA that is limited to the forebrain; and Gortex's ampakine technology is focused on a different neurotransmitter system. "Frankly speaking, we still know little," Tsien said. "We know no principles, no operating code for memory. We know a lot of genes, but we don't have a coherent picture, and I think that is the problem with the whole area of therapeutic research and development."

Researchers are resigned to the continuing bioethical debate on the drugs, no matter how premature the science or how fuzzy the future. "We've got our hands full just showing that these drugs will work," admitted Tully, who has a long history of being keenly attentive to the social implications of scientific research. "Having said that, do I think there will be off-label use if it works clinically? Yes, I do. In principle, these compounds could improve the motor skills required to play the piano or second-language acquisition. The off-label use of drugs happened with Viagra, and it didn't stop Viagra, it didn't stop Ritalin, and it didn't stop amphetamines. But the fact is, off-label use of prescription drugs is dangerous because of unanticipated side effects. You may create unknown psychological problems. But it's not worth even talking about at all except as science fiction. We simply have to wait until we put these drugs into people and see what happens."

Given that we are most likely five or 10 years away from "seeing what happens," we're probably destined to read a lot more about smart drugs before we actually have any pills in hand. But there may be a cautionary warning in a little episode that happened when I visited Tsien at Princeton. He was walking me through the animal facility, which houses his genetically engineered "smart" mice, when one of the lab
technicians walked by holding a mouse trap with two unhappy occupants. Tsien looked down at the two cognitively enhanced rodents in the trap, shook his head and said simply, "Not so smart."

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Eric Kandel's Nobel address is available online at www.nobel.se/medicine/laureates/2OOO/Kandel-lecture.html

STATE OF THE ART FOR SMART COGNITIVE ENHANCEMENT drugs, some of which are still under development, focus so far on treating dementia and other disorders. Some compounds on the market are also being used or tested to improve normal functioning, such as to increase wakefulness in shift workers or to help pilots perform under stress.