The Race to Preserve Your Memory

BY ROBERT LANGRETH | FROM FORBES

BIOTECH FIRMS are tantalizingly close to unraveling the mysteries of memory. On the way are drugs to help fading minds remember and let haunted ones forget.

In a lab in northern New Jersey, for instance, researchers probe the molecular intricacies of memory in hopes of creating a kind of Viagra for the brain. You know, the kind of chemical that reinvigorates an organ that is past its prime.

Tiny metal electrodes zap minute jolts of electricity into slices of rat brain suspended in nutrient broth. This simulates electrochemical changes that occur in brain cells when a new memory is created. Meanwhile

ILLUSTRATED BY JASON HOLLEY

a robotic pump drips experimental drugs onto the brain cells, while electrodes measure how each drug alters the cells' activity. Most drugs have little effect, but a few fit a cherished profile: They help the neurons form stronger, longer-lasting connections.

Memory Pharmaceuticals, the biotech firm doing this work, is at the forefront of an intense scientific race to devise truly effective memory-enhancing drugs, an idea that has long been the stuff of science fiction. This new generation of drugs could mend memory loss in the seriously ill or the merely absent-minded.

"My friends keep asking when the little red pill is coming," says Eric Kandel, 73, a Columbia University researcher and an elder statesman of the field. He cofounded Memory Pharmaceuticals in 1998 and shared the Nobel Prize in Medicine in 2000. "If we continue making the kind of progress we are now, we will have drugs for age-related memory loss in five or ten years," he says.

Kandel's serious rival in this race is Timothy Tully, 48, a New York researcher at Cold Spring Harbor Laboratory and a founder of Helicon Therapeutics, a biotech firm in Farmingdale. Other companies also are in pursuit of what will be one of the next huge global pharmaceutical markets.

Total Recall

The first users of such a pill could be the four million Americans with Alzheimer's disease. Ultimately, however, memory drugs might help millions of others who have mild cognitive impairment, head trauma, Down syndrome or mental retardation, or are recovering from severe strokes. Some new medications may even block unwanted memories.

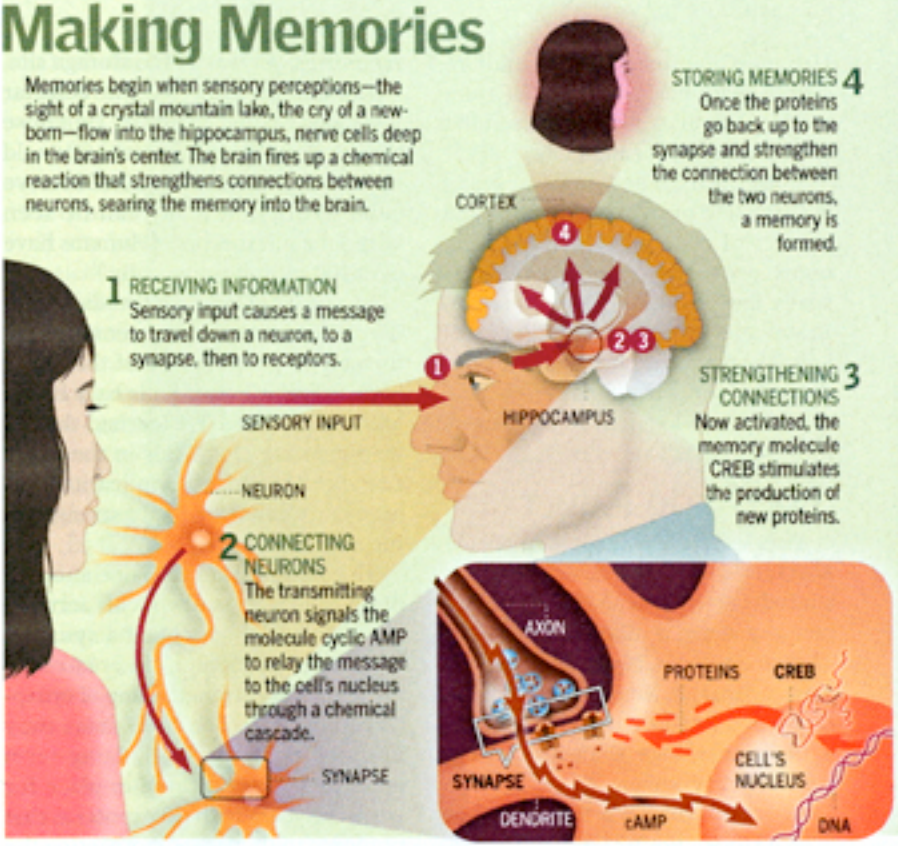
The big score: treating 50 million middle-aged Americans who don't have dementia, but who may welcome a way to reverse the frustrating forgetfulness that comes with age. Says James McGaugh, a neuroscientist at the University of California, Irvine: "Drug companies won't tell you this, but they are really gunning for the market of nonimpaired people—the 44-year-old salesman trying to remember the names of his customers."

But a pill popped by millions of healthy people looking for a mental edge could pose serious risks. A too-potent drug might wreak havoc on emotions or fill the brain with useless clutter. The pill would have to be free of serious side effects before it could be used for such mild deficits. Regulators aren't likely to clear a lifestyle drug that has any dangerous risk associated with it.

Simple Creatures

The big question, of course, is if these drugs will do what is expected of them. If Kandel and Tully succeed, they will forever alter medicine and how we view the world.

Ever since 17th-century French philosopher René Descartes divided the world into two parts—"extended things" (the physical world) and "thinking things" (the mind)—philosophers



and scientists have debated whether the human mind is so elusive as to be unknowable. Says Tully: "Descartes was wrong. Memory is a biological process that can be manipulated like anything else. Not only can you disrupt it, you can improve it."

Should a bottle of memory pills appear on your nightstand one day, a heap of credit will go to Tully and Kandel, with an assist from two of God's lowliest creatures: the fruit fly and the sea slug.

Kandel's role in this race grew out of an early childhood experience. Born in Vienna in 1929, he fled to the United States just before World War II began. The vivid memory of Nazi horrors, in part, drove him to study the mind. A promising young psychiatrist, he gambled his career on a hunch that studying sea slugs could yield insights into human memory. In the decades since, his lab has dominated the field.

Tully's route was more straightforward. A down-to-earth Irish Catholic raised in Peoria, Ill., he studied genetics at the University of Illinois at

Urbana-Champaign. His small research team has produced, in a dramatic series of experiments, fruit flies with photographic memory.

At the heart of both men's research is a startling principle: The basic mechanics of memory formation in humans probably resemble those of snails, flies and other simple creatures. Brain cells seem to be similar in *all* animals; the difference is in the complexity of the wiring that links them. "Humans are like laptop computers; flies are like Philco radios," says Tully.

The Fade Effect

This wasn't obvious when Kandel got started in the 1950s. Scientists assumed the mechanisms of human memory were far different from those of simple animals. Planning to become a psychoanalyst, Kandel detoured into research after becoming fascinated with neurobiology as a way of studying human behavior.

About this time, scientists got their first serious clue to how and where memories are formed. A 27-year-old patient, known only as H.M., had severe epilepsy. In an attempt to cure his disease, surgeons removed his hippocampus, a small ridge in the center of the brain. The patient's seizures mostly went away and his reasoning capacity remained intact—but he could no longer recall new facts for longer than a few seconds. Oddly, though, H.M. had no trouble remembering his childhood. That hinted the hippocampus was crucial for converting immediate perceptions into memories, yet wasn't the storage site.

Kandel focused on the cellular workings behind memory. He chose the sea slug, *Aplysia*, because it would be easy to study: It has 20,000 nerve cells so big that many can be seen without a microscope. (Humans have over 100 billion nerve cells.)

In a series of landmark studies, Kandel showed how simple memories are formed by gauging one of the slug's basic reflexes: how it pulls back its gill when threatened. He learned that by manipulating chemicals in the slug's nerve cells (and, by implication, human brain cells), he could strengthen the slug's memory.

To communicate with one another, brain cells release chemicals across a gap between them called a synapse. A short-term memory is created by the temporary strengthening of synaptic connections. The effect fades away minutes or hours later. Long-term memories are cemented in place for weeks or years with new proteins that reinforce the synapses connecting the cells. Imagine a phone number you'll need to use just once; you look it up and punch it in, and within a few minutes, you forget it. But a number you'll want to use over and over, you'll repeat to yourself frequently so it stays in your memory. Even long-term memories, however, erode with time.

Smart Flies

The advances in molecular biology in the 1970s allowed Kandel and other researchers to explore memory on a molecular level. This was crucial.

Once these molecular workings are understood, then drug targets become easier to find.

Kandel showed that a messenger—a molecule called cyclic AMP—played a central role in memory formation. It sits inside the cell and, when signaled by a neuron, springs into action, activating proteins that temporarily boost the connection between two nerve cells. (Think of a runner in a relay race being handed the baton.) But cyclic AMP is just a messenger; it doesn't churn out the new proteins that are needed to build long-term memories.

In 1990 Kandel found that an intriguing molecule, called CREB, was critical for learning and memory. His team was able to show that blocking CREB in sea slug nerve cells also blocked the process that creates new long-term memory without affecting short-term memory.

The most dramatic proof in understanding how CREB influences memory came from Tim Tully and his colleague Jerry Yin. Tully's fruit flies had advantages over sea slugs: a wider range of behavior, easy genetic engineering and an ability to be bred by the millions in test tubes. In 1994 Tully and Yin created fruit flies with photographic memories by engineering them with the CREB protein switched into the "on" position.

Normal flies took ten training sessions to learn not to enter a scented chamber where they would get an electric shock. But Tully's superflies learned after just one session. Since then, other researchers have proved CREB plays a similar role in mice.

A Done Deal?

These snail and fly experiments showed that CREB helps produce new proteins that etch permanent connections between nerve cells. It is in these links that long-term memories are stored. The Tully and Kandel teams also found a second factor: CREB repressor. Yin and Tully engineered flies with excess CREB repressor, and they failed to form memories even after many tries.

Cyclic AMP and CREB are targets for drug development. In the meantime, Tully and Kandel are also looking for other genes and proteins that affect memory.

Success, says Tully, is only a matter of time. "It's not an *if*," he says. "It's a *when*."

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