Fruit-Fly Gene: Clue to Human Memory

By Neil Ulman
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For most people, sitting all day in a dark closet with hundreds of flies would be cruel and unusual punishment.

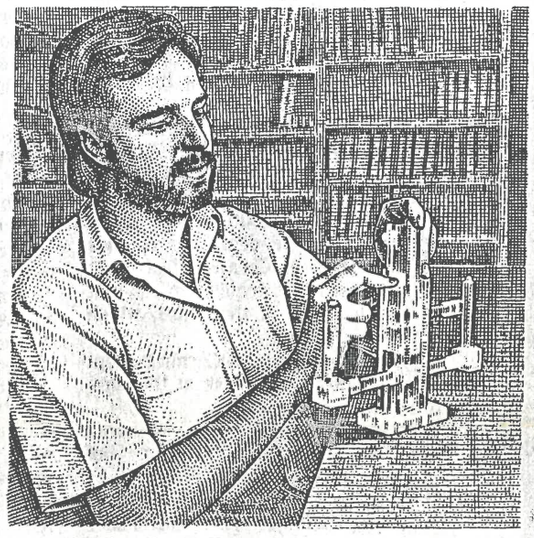
At Cold Spring Harbor Laboratory, it is called neuroscience: testing a genetic theory of memory, the foundation of mental life and individuality.

The theory holds that the essential mechanism of memory lies in a cellular process common to all nerve cells in all species, says Timothy Tully, the 41-year-old biologist who is Lord of the Flies at this privately funded institution overlooking an old whaling village on New York's Long Island.

Dr. Tully is chiefly concerned with formation of long-term memory, which fades with natural aging and collapses in those suffering from Alzheimer's disease. Though much further research remains, work being done at his laboratory could lead one day to memory-enhancing drugs.

"It's an early-stage project as far as drug discovery is concerned, but it's very exciting," says J. Gordon Foulkes, vice president and chief strategic officer of Oncogene Science Inc. The Long Island biotechnology company has been in discussions with the laboratory about a possible memory-research partnership, which might eventually include a major pharmaceutical partner.

Last year, Dr. Tully and his colleagues showed for the first time that it is possible to enhance the long-term memory of fruit flies through genetic manipulation. "It marked the end of psychology and the beginning of biology" in the study of long-term memory formation, he says.



Timothy Tully and fly-testing vials

Because large populations of the tiny fruit flies are easily housed, and mature and reproduce in a few weeks, *drosophila melanogaster* is considered ideal for genetic studies.

But extracting drosophila's secrets is exacting work. Seated in a darkened, windowless closet in Dr. Tully's lab, technician Clara Velinzon spends eight hours a day watching over an array of fly-filled test tubes that are attached to computer-controlled coils and pumps.

The apparatus allows the scientists to measure the learning capacity of the flies. It gives a batch of flies an electrical shock in the presence of an odor, then observes whether they later choose to move into a test tube containing that odor or another.

Avoidance of the odor associated with shocks, displayed by 95% of genetically "normal" flies, is taken as evidence of memory formation. After 10 training sessions, a normal fruit fly consolidates the lesson into long-term memory, Dr. Tully says.

Only weak infrared rays, invisible to the flies, illuminate the work. To preserve their sanity, lab technicians wear "Flies R Us" T-shirts and listen to music—a variety of selections known not to affect the flies. (Dr. Tully says he listened mostly to the Pretenders during his apprenticeship in a closet.)

With the biochemical impact on memory established by others, Dr. Tully and his colleague, Jerry Yin, have zeroed in on the role of a gene known as CREB that, in fruit flies, expresses both an "activator" and a "repressor" protein. Fluctuating levels of

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these two proteins within nerve cells govern the conversion of short-term memory into long-term storage, the researchers believe. When levels of CREB repressor cancel out activator, this conversion doesn't occur. If, on the other hand, activator levels overpower the repressor, long-term memory is formed.

For their experiment, Drs. Tully and Yin used biotechnology tools to rig a CREB repressor so it could be "turned on" by warming a test tube of flies in a tub of warm water. During electroshock training, the warmed fruit flies failed their long-term memory test — indicating that the excess CREB represssor did, in fact, prevent development of long-term memory.

In a second experiment, when the CREB activator was turned on by warming, the flies formed long-term memory after only one training session, instead of the usual 10.

Scientists here and elsewhere are producing similar results by manipulating the CREB gene in mice and sea slugs. That suggests to Dr. Tully that the mechanism by which CREB regulates memory is conserved by evolution from lower forms of life to higher, presumably including humans. And he speculates how and why:

When environmental stimuli start nerve cells communicating with one another, both forms of CREB increase. Repressor CREB inhibits long-term memory formation to save the brain from intolerable memory overload.

During periods of rest, however, CREB repressor decays faster than activator, Drs. Tully and Yin believe. During training interspersed with rest, CREB activator overpowers repressor, and some of the short-term memory is converted to long-term memory. As the stimuli continue, repressor levels catch up to activator levels and conversion into long-term memory is again inhibited.

This back-and-forth helps explain why students retain material best by studying steadily rather than at the last minute. "Cram all night and you may ace the exam with short-term memory," says Dr. Tully. "But you'll soon forget it all. Study a little everyday, and you'll retain the material for life."

It also suggests how the brain processes different stimuli. In the area of the brain where fear is stored, for example, Dr. Tully theorizes that the CREB "switch" is permanently "on." With CREB activator in the ascendency, long-term memory vital for survival can be stored after a single event — as with the genetically altered super-smart fly.

If these theories are proven, Dr. Tully envisions the possibility of a drug that could stimulate CREB activator — thus bolstering formation of long-term memory— in the remaining healthy brain cells of Alzheimer's patients. Or a CREB repressor could be administered to trauma victims, for example, to prevent formation of mentally disabling traumatic memories.

Columbia University neuroscientist Eric R. Kandel, whose experiments with sea slugs formed the basis for the current molecular memory work, is more cautious. He agrees that memory-drug research should focus on CREB. There may be only "a limited set" of switches for long-term memory, he says, though he adds that he would be "astonished" if the CREB regulators turned out to be the only ones.

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