thing, these students were culturally close to nature. For another, passing mainstream science was one of the toughest obstacles on their road to graduation. There was only one problem—Godoy-Gonzalez himself knew very little about science.

So he sought help wherever it was available. During his first year, he enrolled in the Summer Institute in Life Science, an HHMI-sponsored program at the University of Washington in Seattle, which introduced him to hands-on science instruction. Since then, he has participated in other enhancement programs, including the HHMI-supported Science Education Partnership at Seattle's Fred Hutchinson Cancer Research Center, where secondary school teachers partner with faculty scientists for hands-on science workshops and research experiences. He even spent two summers assisting scientists who use DNA microarrays to study the genetics of plant-seed dormancy.

Like apple growers diverting water to their orchards, Godoy-Gonzalez has channeled this knowledge straight to his classroom with activities that bring lessons to life. When he taught about the stars and planets, members of the Yakima Astronomy Club accompanied his students and their families on a late-night stargazing session, bringing telescopes that were powerful enough to pick up vivid detail in the Moon's craters. After learning about volcanoes, Godoy-Gonzalez gave his students shovels, and they began digging in a nearby roadside. Several inches down, they were amazed to find a layer of ash from the 1980 eruption of Mt. St. Helens.

In the past two years, 16 of Godoy-Gonzalez's students have gone on to community college. One is studying agriculture at Washington State University. Another is en route to becoming a doctor. "Had we not had Mario and the program he has developed, these kids would have been lost," says the school's principal, Jack Hill. "They would have dropped out."

In 2000, Godoy-Gonzalez was named the state's migrant teacher of the year. His model is both simple and practical, says Sylvia Reyna, program supervisor at Washington's Migrant Education Program. "He really is making some pathways for others to follow."

—GARRY HAMILTON

Lost on the Tip of the Tongue

Memory loss is a common complaint among the elderly. In the early stages of Alzheimer's disease, conjuring up a memory becomes an impossible chore. In both cases, according to HHMI investigator Susumu Tonegawa, the memories are sitting dormant in the brain; the challenge is retrieving them.

"As all of us age, we experience some memory impairment in which we have more trouble remembering, say, the name of a person we definitely know," says Tonegawa, who directs the Picower Center for Learning and Memory at the Massachusetts Institute of Technology (MIT). "We feel like the name is just on the tip of the tongue, but it won't quite come."

Tonegawa led a team of researchers, including then HHMI postdoctoral fellow Kazu Nakazawa, in identifying a gene involved in the type of memory-retrieval process called pattern completion—the ability to recall complete memories from partial cues. Their hope is that this work, published May 30, 2002, in *Science Express*, the online version of *Science*, and in the July 12, 2002, issue of *Science*, may ultimately lead to new or better targets for drugs that help counter some of the deficits of Alzheimer's disease and relieve those frustrating "senior moments" that begin to emerge in middle age. Tonegawa's coauthors included colleagues at MIT and scientists at Baylor College of Medicine in Houston and Hokkaido University School of Medicine in Japan.

"Memories are sitting dormant in the brain; the challenge is retrieving them." —**Susumu Tonegawa**

For these studies, the researchers generated and analyzed mice with a genetically altered hippocampus, a brain structure involved in learning and memory. They showed that the CA3 region of the hippocampus is responsible for the retrieval of complete memories from partial cues—and that age or disease might impair the functioning of this region.

Mathematical models of memory from the 1970s suggested that, based on its anatomy and wiring, the CA3 region of the hippocampus was a likely center for associative memory, says Tonegawa. Pattern completion was hypothesized to be a key function of such associative memory centers, he says. But, until now, researchers have not had a tool to test this hypothesis in live animals. Tonegawa and his colleagues developed a method called "spatial targeting" that enables them to knock out a gene in a specific area of the brain. For this study, they knocked out the gene for the NMDA receptors in the CA3 region. The neurons in the CA3 region are wired together in a characteristic way—each sends axons that synapse onto themselves or other cells of the same kind, forming a "recurrent network." When the NMDA receptors are knocked out, the efficiency of the nerve-signal transmission throughout this network is drastically compromised, according to Tonegawa.

The researchers engineered the mutant mice so that the gene for the NMDA recep-

COURTESY OF TONEGAWA LAB

Swimming in water filled with pellets that obscure the exit platform, the mice must rely on outside cues and memory to find a way out of the pool.

tor ceased functioning after the animals had matured—eliminating the possibility that knocking out the gene would affect development of the CA3 region. They were able to show that the CA3 region functioned normally except for the NMDA receptor.

To test the effect of disabling the NMDA receptor, the scientists studied how both normal and mutant mice behaved in the Morris water maze, which consists of a pool filled with murky water that has a small platform hidden just beneath the surface. A black curtain surrounds the dimly lit pool, and on the curtain in each of four directions the scientists placed visual cues consisting of distinctive spotlighted patterns.

In their experiments, they found that normal and mutant mice placed in the pool were equally capable of learning and remembering where the hidden platform was located. The researchers saw stark differences, however, when they removed three of the four visual cues and tested the animals' ability to recall the platform's location. "Normal animals had no problem remembering where the platform should be, based on only one cue," says Tonegawa. "But the mutant animals showed a severe impairment in recalling the memory based on partial cues. It was a very specific deficit."

In addition to the behavioral testing of the knockout mice, researchers in collaboration with coauthor Matthew A. Wilson of MIT studied the neurophysiological basis of the CA3 deficit. They used microelectrodes to measure the electrical activity of specific cells in the CA1, another region of the hippocampus (which affects its output and overall performance), as the animals explored an open arena surrounded by four visual cues. They found that when three of the four visual cues were removed, the knockout mice showed impaired ability to reactivate the hippocampal cells that had become active when the animals were first acquiring memory of that location.

"The combination of behavioral and neurophysiological studies of these knockout mice constitutes a very rigorous demonstration of the importance of the CA3 NMDA receptors in associative memory recall," says Tonegawa.

—DENNIS MEREDITH

GRAHAM TROTT

Carlos D. Bustamante uses statistics to sort out questions about evolution.

Biology by Numbers

The mapping and sequencing of tens of thousands of genes from humans, fruit flies, yeast and several other organisms has created a data windfall for research into the long-standing question of how the living world came to be so diverse. The interpretation of this trove of information requires a new breed of scientist.

Enter Carlos D. Bustamante, 27, who has assembled a formidable collection of skills for attacking questions about evolution. A recent Ph.D. from Harvard University, where he had an HHMI predoctoral fellowship, Bustamante has firm grounding in classical biology, population genetics and molecular biology and is well versed in computational and statistical methods of analysis.

Darwin of course focused on natural selection—the preservation of traits that enable organisms to adapt to specific environments—as the chief force propelling evolution. Even he, however, noted that natural selection wasn't the only evolutionary force. In more recent times, scientists have argued that small, random changes in the frequency of genes in populations—known as genetic drift—can increase certain genes' prevalence even when they don't confer a selective advantage. The question of how much of the genetic differences between species is due to natural selection and how much to random processes is still hotly debated.

Sorting out the enormous number of molecular variations that occur within and between organisms in order to examine the effects of evolutionary forces poses a huge mathematical challenge. As lead author of an April 4 paper in *Nature*, Bustamante used advanced statistical tools to study this question in the fruit fly (*Drosophila*) and the mustard weed (*Arabidopsis*). He and his colleagues deployed their statistical firepower, including a tool developed originally in statistical physics known as the Markov-chain Monte Carlo method.

"The novelty about the statistical approach used by Bustamante is that it allows the information from multiple different genes to be combined in a statistically rigorous way," says Rasmus Nielsen, a population geneticist at Cornell University who was second author on the *Nature* paper. "This allows us to learn much more from large data sets," such as those involved in the *Drosophila* and *Arabidopsis* research, says Nielsen.

The study revealed that both genetic drift and natural selection have been involved in the evolution of genes in the two species but that the process is not the same in both because *Drosophila* and *Arabidopsis* have different mating systems. In *Arabidopsis*, negative selection (selection against new variants) is dominant, presumably because of high levels of self-fertilization. In contrast, in *Drosophila*, which does not self-fertilize, positive selection (selection for new favorable variants) dominates.

Daniel L. Hartl of Harvard, a population geneticist who oversaw Bustamante's Ph.D. work, hailed the *Nature* paper as "gorgeous. It opens the door to a genome-wide analysis of protein evolution in virtually any organism."

While he was still in high school, after immigrating to the United States from his native Caracas, Venezuela, Bustamante was drawn to the work of evolutionary biologist Stephen Jay Gould and geneticist Richard C. Lewontin, who were both at Harvard. After