ington, D.C.

"This is obviously a very serious matter," the university said in a brief statement. "We know that Dr. Wilson understands its importance, is reviewing the letter carefully and intends to respond in a timely way." Wilson has 30 days to reply to the FDA's letter. After reviewing Wilson's response, FDA administrators will make a final decision.

This is a "drastic" step, says Inder Verma of the Salk Institute for Biological Studies in La Jolla, California, who headed a special working group at the National Institutes of Health that investigated the Gelsinger trial. But Savio Woo, a gene therapy researcher at Mount Sinai School of Medicine in New York City and past president of the American Society of Gene Therapy, says that vigorous FDA oversight will strengthen gene therapy research. **–GRETCHEN VOGEL**

NEUROSCIENCE

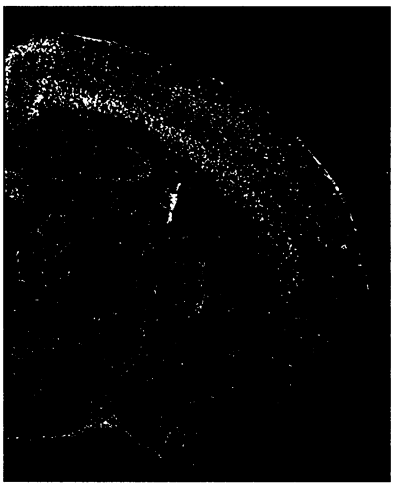
Immune Molecules Prune Neural Links

The developing brain starts off as a tangle of neuronal connections, then activity reinforces some of these connections and causes others to atrophy. Over the past few years, neurobiologists have been on the prowl for molecules that help the nervous system make and break these connections, and they've come up with a few contenders. But now Carla Shatz's team at Harvard Medical School in Boston is proposing an unlikely new candidate: a type of protein previously known for its role in helping the immune system fend off viruses and other foreign invaders.

In work described on page 2155, Shatz and her colleagues suggest that the class I major histocompatibility complex (MHC) proteins are necessary for the formation of normal neuronal connections in a visual area of the brain during development. Later in life, they're called into play in the hippocampus, a brain area involved in memory and learning. The work shows "a completely unexpected function for the molecules," says neurobiologist Marc Tessier-Lavigne of the University of California, San Francisco.

The current results are an outgrowth of observations that Shatz's team, then at the University of California, Berkeley, reported 2 years ago. While examining how gene expression patterns in the brain react to changes in retinal activity, the researchers found, to their surprise, that the genes encoding class I MHC proteins are active in the developing brain. To explore what these seemingly alien molecules were doing there, Gene Huh, a postdoc in the Shatz lab, turned to three strains of mice that had been genetically altered. Two of these strains lacked the ability to display class I MHC proteins in their normal location on the cell surface; the third lacked part of a receptor that T cells use to respond to class I MHC proteins. In the first phase of their work, Huh and his colleagues tested how these gene knockouts affected the development of the animals' visual systems.

Like many animals, mice aren't born with the ability to see. The visual system matures only when neural signals, originating either from spontaneous neural firing in the retina before the eyes open or from looking around afterward, help organize the parts of the brain that receive and process visual information. Huh found that this process, which involves both strengthening frequently used connections and pruning useless ones, is disrupted in all three knockout mice.



CREDIT: G. HUH ET AL.

Sort it out. As indicated by the colored staining patterns, different class I MHC genes are expressed in different brain areas.

The visual signal's first stop after the eye is the lateral geniculate nucleus (LGN). There, neuronal projections from the retina normally form what Huh describes as a "big misshapen doughnut." The doughnut itself, occupying most of the LGN, receives input from the eye on the opposite side of the body, while a small "doughnut hole" in the middle of the LGN gets projections from the same-side eye. But in the knockout mice the doughnut hole is much larger, implying that the inputs from the two eyes overlap. The finding suggests that in the absence of functioning class I MHC proteins, the normal pruning of connections that should have occurred in the LGN is defective.

Similar strengthening and weakening of neuronal connections is thought to occur during memory formation in the adult hippocampus. So Shatz and her colleagues next looked at synapses in that brain region, where their earlier work had shown that the class I MHC genes are also active.

When postdoc Lisa Boulanger stimulated the hippocampal neurons, she found that neurons in the knockout mice reacted strangely. Long-term potentiation (LTP), the strengthening of signals with stimulation, was enhanced: Hippocampal neurons in the knockout mice responded more dramatically than did those in normal mice to a high-frequency stimulus that can evoke LTP. And when she applied low-frequency stimulation, which causes the synapse weakening known as long-term depression, neurons in the knockout mice failed to rein in their signals as they should have. "To us," says Shatz, "the results imply that there may be a commonality of cellular and molecular mechanisms" in how neurons in the hippocampus and the developing nervous system respond to activity.

Huh and Shatz suspect that the class I MHC proteins also help neurons tune their connections in other areas of the brain. The mouse carries about 30 different varieties of the protein. When Huh tested where four of the genes are expressed, he found that different ones are active in different places in the brain (see figure), possibly tailoring nearby neurons to fit into the correct neural pathways.

Despite the evidence indicating that the class I MHC proteins are somehow involved in refining neuronal connections in the brain, researchers don't yet know how the molecules are acting. Immunologist Hidde Ploegh of Harvard says he's "intrigued by the possible role of [these molecules] in something that appears to have no immunological correlate." But he awaits the details of how they might be helping the nervous system figure out which connections should atrophy.

–LAURA HELMUTH

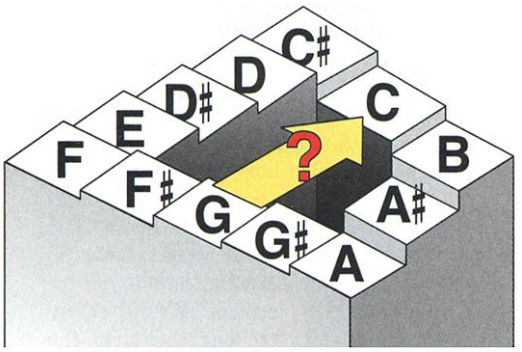
NEUROPSYCHOLOGY

Language Affects Sound Perception

NEWPORT BEACH, CALIFORNIA—Neuropsychologists may owe a debt to the devil. At the 140th meeting of the Acoustical Society of America here last week, University of California, San Diego, psychologist Diana Deutsch demonstrated that an auditory illusion based on the tritone—also known as the "devil in music"—is perceived differently by listeners with different linguistic histories. And those perceptions might help psychologists understand how the brain rewires itself during childhood.

Played together, two notes a half-octave apart (such as C and F sharp) sound jarring; medieval musicians considered this combination, a tritone, so discordant that they dubbed it the "diabolus in musica." But a tritone is music to Deutsch's ears. For more than a decade, she has been studying an auditory illusion—the acoustical equivalent of an optical illusion—based upon the tritone.

With a computer, Deutsch created am-



Step lively. In this visual equivalent of the tritone paradox, no step is highest.

biguous notes by superimposing tones from many octaves and carefully shaping the relative loudness of the higher and lower frequency components, masking how high or low the note is. Although listeners can perceive one of these notes as, say, a C, they can't tell its octave, whether high C, middle C, or low C. Indeed, the tone doesn't really belong to any octave at all.

Things get interesting when people compare tritone pairs of ambiguous notes, such as an ambiguous C with an ambiguous F sharp. Even though neither note is higher or lower than the other—because higher and lower don't have any meaning with ambiguous notes—people consistently perceive one tone as high and the other as low. But strangely, they don't agree which is which. "The musical illusion is perceived very differently by different people," says Deutsch. This is the tritone paradox.

Things got even weirder when Deutsch played ambiguous tritones to different groups of people. In 1992, she noticed that people from California and people from Southern England hear tritones in the opposite way; if a Californian thinks that a C is above an F sharp, the Britisher will swear that the F sharp is higher than the C. This led some psychologists to believe that a person's perception of ambiguous tritones depends strongly upon the intonations of the language he learns as a child. Since then, psychologists have been trying to prove it.

At the Acoustical Society of America's meeting last week, Deutsch described her latest experiment, in which she played ambiguous tritones to two groups of subjects who had emigrated to California from Vietnam. The first group came to the United States as children, and although Vietnamese was their first language, most no longer spoke it fluently. The second group, on the other hand, arrived in the United States as adults and spoke little English. The two groups perceived the tritones in the same way—but differently from their California neighbors. "This study presents strong evidence, we believe, that individual differences [in perceiving the tritones] are caused by individual speech patterns to which [the subjects] are exposed early in infancy," says Deutsch.

"It reinforces the idea that early linguistic background affects perception," says Magdalene Chalikia, a psychologist at Minnesota State University in Moorhead, who has shown that Greek speakers and English speakers perceive tritones differently. The tritone paradox gives neuropsychologists intriguing hints about the effects of training on the brain. The results suggest that as an infant learns its first language, the brain may adjust its neural connections in a way that affects the perception of sounds. But for the moment, scientists have little idea which languages cause which interpretation of the tritone paradox, much less how each language rewires the brain differently. "You can't make predictions," sighs Chalikia. "It's frustrating." The devil, it turns out, is in the details.

–CHARLES SEIFE

ACADEMIC RESEARCH

California Sets Up Three New Institutes

Three University of California (UC) campuses were chosen yesterday as sites for a new $900 million program designed to keep the state a world leader in research and to bolster its economy. Each of the three schools will receive $25 million a year for 4 years from the state, with companies and other sources putting up at least twice that amount.

The money will create California Institutes for Science and Innovation at the Los Angeles (UCLA), San Francisco (UCSF), and San Diego (UCSD) campuses. UCLA will team up with UC Santa Barbara on a nanosystems institute that will be led by Martha Krebs, former director of the U.S. Department of Energy's Office of Science. UC Berkeley and UC Santa Cruz will join with UCSF in an institute on bioengineering, biotechnology, and quantitative biomedical research headed by David Agard, a UCSF professor of biochemistry and biophysics. The third institute, on telecommunications and information technology, will be a collaboration between UCSD and UC Irvine led by UCSD computer science and engineering professor Larry Smarr.

"We'd like this to be a magnet for the best and brightest of the scientific community," says California Governor Gray Davis, who pushed the idea through the state legislature (*Science*, 26 May, p. 1311). "We can't make them come, but we'd like them to know they're welcome." Davis also promised to lobby next year for a fourth center, based at Berkeley, that would apply information technology to critical societal problems such as transportation, education, emergency preparedness, and health care. The Berkeley proposal fell just short in a competition among six finalists.

The contestants were encouraged to dream up novel collaborations and projects, and the winners were eager to describe how their research plans will push the boundaries of their field. "The growth of the wireless Internet will lead to radical change," says Smarr, describing sensors embedded in bridges, cars, and even people that may someday transmit information to a computer miles away that can assess problems such as stresses during an earthquake or wear-and-tear on a vehicle's brakes. "Wouldn't it be nice if you got a call on your cell phone that said, 'Hello, we thought you'd like to know that your right front brake will fail in about 100 miles.' "

Officials also emphasized that the institutes should tackle topics not historically addressed on their own campus. Developing innovations in engineering and technology, says Agard of UCSF, a campus devoted to the health sciences, is "a new game in biology and [requires] resources that go beyond what normal medical schools can come up with."

Although winning entrants were restricted to the 10 UC campuses, the new institutes are also hoping to work with some of the state's most prestigious private schools, including Stanford and the California Institute of Technology. "I envisioned a research process open to the best minds, wherever they were," says Davis. The same goes for collaboration with industry, which is expected to contribute heavily to the new institutes. "Places like Hewlett-Packard and Sun want our students," says Krebs, "and they also want access to the results of our research."

–EVELYN STRAUSS

NEW CALIFORNIA INSTITUTES

Institute	Director/Host	Partners
Bioengineering, Biotech, and Quantitative Biomedical Research	David Agard/UCSF	UC Berkeley, UC Santa Cruz
Nanosystems	Martha Krebs/UCLA	UC Santa Barbara
Telecommunications and Information Technology	Larry Smarr/UCSD	UC Irving