had inferred for the Yucca Mountain region, based on how much nearby faults have slipped over hundreds of thousands of years. Wernicke and his colleagues suggest that the Yucca Mountain area may be undergoing a geologically brief episode of rapid crustal stretching, perhaps driven by magma rising beneath it.

That could change hazard estimates based on the low long-term deformation rate recorded on faults. Previous analyses had put the risk that, say, a new volcano would pierce the repository, due to open in 2010 at the earliest, at 1 chance in 10,000 during the next 10,000 years (*Science*, 8 November 1996, p. 913). But if the rate of crustal deformation is upped by a factor of 10, so are the geologic risks, says Wernicke.

So far, researchers such as Crowe who have helped to evaluate geologic hazards at the repository are cautious about changing their risk estimates. And others such as geophysicist Wayne Thatcher of the U.S. Geological Survey in Menlo Park, California, wonder whether the minute stretching the group observed is real. "The changes they're looking at are really small; that's a little worrisome. In this business, we don't usually look at such small changes," he says. He and others also find the error bars surprisingly small; if they were larger, the observed motions would shrink. But co-author Richard Bennett of CfA finds no sign of additional errors in the data.

Even if the crust is moving as fast as Wernicke's team finds, "I would expect the hazard to go up, but not by an order of magnitude, " says Crowe. A magmatic intrusion might first trigger new volcanoes near the youngest nearby volcano, Lathrop Wells, and so would pose less of a threat to Yucca Mountain, he says.

Some scientists also wonder whether the apparent crustal extension is being driven by anything as threatening as magma intrusion. Thatcher suggests that at least part of the apparent stretching may have been caused by a magnitude 5.4 earthquake that struck Little Skull Mountain in 1992, just 8 kilometers from the eastern end of the GPS line. What Wernicke's team may have measured, he says, is the crust's readjustment to the strain released by the earthquake, which had built up over centuries or millennia. But Bennett says he calculates that such quake-driven effects are quite small, much smaller than the motions observed via GPS.

Thatcher remains cautious, saying that the new work may be showing subtle movement that other studies missed—or errors or fleeting effects may be misleading everyone. Another 5 years of GPS surveying, he says, should suffice to decide whether recent history or the deep geologic past is the best guide to Yucca Mountain's future.

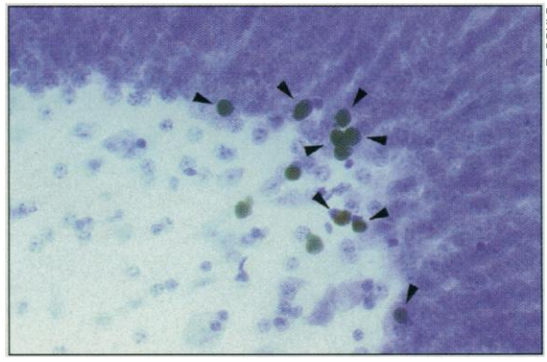
–Richard A. Kerr

NEUROBIOLOGY

No-New-Neurons Dogma Loses Ground

For many decades, both popular and scientific wisdom have held that adult brains can't make new neurons, so the ones we form when we're young have to last a lifetime. But last week, a research team from Princeton University, Rockefeller University in New York City, and the German Primate Center in Göttingen provided a challenge to this conventional dogma. In the 17 March issue of the *Proceedings of the National Academy of Sciences* (*PNAS*), they report that adult marmoset monkeys make new neurons in the hippocampus, a part of the brain associated with learning and memory.

Previous work had shown that lower species, including birds and rodents, produce brain neurons throughout their lives. But some neuroscientists have hailed the new result as a potential breakthrough, because it is the first evidence that the same may be true for primates—perhaps even humans, says neuroscientist Ron McKay, of the National Institute of Neurological Disorders and Stroke. If further work confirms that the adult human brain can make new neurons, and if these cells join existing functional networks in the brain—both of which are in the realm of speculation at this point—it may open doors for enhancing neurogenesis, as new neuron formation is called, to repair brain damage from disease or trauma.



E. GOULD

Newborn neurons. BrdU marks the nuclei of 3-week-old neurons (arrows) in the dentate gyrus of an adult marmoset.

Recent studies even suggest that stress reduction or an enriching experience can boost neurogenesis in some cases. In the current work, Elizabeth Gould from Princeton and her colleagues Bruce McEwen at Rockefeller University and Eberhard Fuchs at the German Primate Center found that stress decreases the rate of birth of new neurons in marmosets, while recent research on rodents by Fred Gage of the Salk Institute in La Jolla, California, and his colleagues has shown that an enriched environment can increase the neurogenesis rate. Together, the results "suggest that behavioral stimuli can regulate neuronal replacement rates," says McKay. "That is what I find so exciting."

Other researchers in the field caution that it's a big leap from marmosets to humans, especially when one considers work that both the *PNAS* paper and a *New York Times* report on it failed to mention: a set of experiments published in the mid-1980s by neuroscientist Pasko Rakic and his colleagues at Yale that found no evidence of new neurons being born in the hippocampus of adult rhesus monkeys. Rhesus monkeys are more closely related to humans than marmosets are, and neuroscientists have interpreted those experiments as indicating that higher primates, and probably humans as well, lack the ability to generate new brain neurons.

Gould and her colleagues chose to do their experiments on marmosets—a New World primate native to South America—because these animals are more readily available and less expensive than Old World primates like rhesus monkeys or chimpanzees, which are more closely related to humans. For their studies, the team injected adult male marmosets with bromodeoxyuridine (BrdU), which labels dividing cells. Two hours later, they sacrificed half of the animals and examined their brains for new cells that had picked up the BrdU. They found lots, in a part of the hippocampus called the dentate gyrus. Indeed, Gould calculated that "thousands of cells per day" were being born there. Three weeks later, when the team examined the brains of the remaining marmosets, they found that 80% of the BrdU-labeled cells looked like neurons and were making a neuron-specific protein. "A significant number of [the cells] survived," says Gould, "and the majority of those ... became neurons."

In a separate experiment, the researchers put adult male marmosets into the home cages of other adult males—a situation that is very stressful for the so-called "intruder" animals—and then injected the intruders with BrdU. The stress apparently decreased the number of new cells by 30%, suggesting it has a chilling effect on neuron replacement.

Gould's group had shown last year that tree shrews, close relatives of primates, grow new neurons in their hippocampuses, and marmosets represent another step up the evolutionary ladder. To Gould, the combined discoveries of neurogenesis in the adult brains of rodents, tree shrews, and marmosets suggests that this is a common phenomenon, which

she expects to occur in humans as well. But some in the field caution against making that leap from these data until there is an explanation for Rakic's negative result in rhesus monkeys. "The idea that they can extrapolate on to humans is blocked in part" by Rakic's results, says Salk's Gage.

Gould counters that Rakic used a different—and less sensitive—method for detecting new neurons and thus might have missed their formation. Rakic acknowledges that his group could have overlooked a low level of neuron production but says "certainly we would not miss several thousand a day."

The issue will remain open, says Harvard neuroscientist Connie Cepko, until more tests on primates, including a reexamination of rhesus monkeys with the newer methods, are performed. "If one monkey species does it and one doesn't, we can't extrapolate to [humans]," she says, "but if all monkeys do it," such an extrapolation would seem a safer bet. Some researchers aren't waiting to make their wagers: "I'll make a bet," says McKay. "This is going to happen in humans. The question is under what circumstances, and what difference does it make?"

Indeed, "one of the challenges for this field is to try to come up with some biological significance for this late-stage neurogenesis," says Gage. That significance, says Stanford neuroscientist Susan McConnell, hinges on the question, "What is the actual result of putting new neurons into a circuit? Does it, for example, help you learn or remember better?" If it does, psychologists and neuroscientists will have a field day putting these results to practical use.

–Marcia Barinaga

DEVELOPMENTAL BIOLOGY

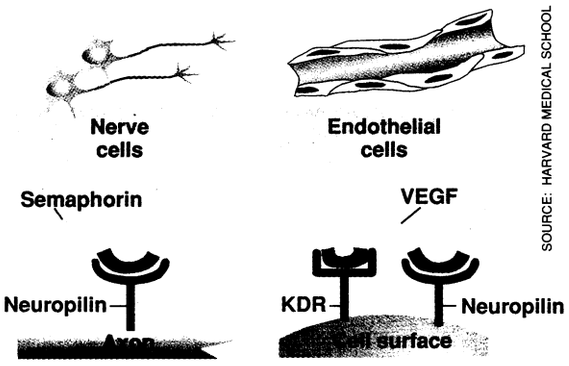
Receptor Links Blood Vessels, Axons

Veins gather blood and return it to the heart, Leonardo da Vinci mused in one of his notebooks, in the same way that rivers channel water back to the oceans. But a recent discovery suggests that da Vinci's analogy was more impressionistic than accurate. Rather than following random paths like water trickling downhill, it appears that blood vessels may instead use detailed chemical cues to navigate to prearranged addresses—much as nerves do.

In the 20 March issue of *Cell*, a group led by biochemist Michael Klagsbrun at Children's Hospital in Boston reports that it has identified a new receptor molecule on the endothelial cells that line blood vessels. The receptor, called neuropilin, picks up a signal from VEGF, a protein made by tissues—including cancerous tumors—that need new blood vessels. VEGF was already known to stimulate blood vessel growth, or angiogenesis, but most researchers thought the actual paths of the vessels are as random as da Vinci's watercourses. The new receptor, however, turns out to be the same one that nerve axons use to detect Semaphorin III, a protein that helps steer axons to their proper destinations in the developing nervous system.

"It's a very exciting discovery," says Marc Tessier-Lavigne, a developmental biologist at the University of California, San Francisco, whose laboratory, along with one in Baltimore, identified the semaphorin receptor last year. The receptor's dual role, he says, raises the intriguing possibility that angiogenesis, far from being random, is in fact as highly scripted as axonal pathfinding, which is regulated by a whole menagerie of extracellular messengers in addition to Semaphorin III. He and Klagsbrun also note that if neuropilin allows VEGF to act on neurons and semaphorins to act on endothelial cells, this might indicate an unexpected level of coordination between the developing nervous and circulatory systems. The discovery, finally, could even provide researchers with a new target for drugs that might fight cancer by blocking tumor growth.

Shay Soker, an instructor in Klagsbrun's lab and the *Cell* paper's lead author, cleared the way for the recent advance in experiments he performed 2 years ago. Using a biochemical technique called crosslinking, Soker found that VEGF forms two different kinds of complexes with molecules from the surfaces of endothelial cells. Because two VEGF receptors, designated KDR and Flt, had already been discovered, he assumed that one of these complexes contained VEGF and KDR and the other consisted of VEGF and Flt. But one of the complexes had a molecular weight too low to be either—implying that it contained an entirely new VEGF receptor.



SOURCE: HARVARD MEDICAL SCHOOL

Double duty. Neuropilin is present both on neurons, where it's involved in axonal guidance, and on endothelial cells, where it aids angiogenesis.

Soker, Klagsbrun, and co-workers Seiji Takeshima, Hua Quan Miao, and Gera Neufeld set out to clone this receptor. They first made a "library" of DNA clones representing the genes active in a line of human cells that lack both KDR and Flt yet are still able to bind VEGF. They then introduced small subsets of these DNAs into cells that can't bind VEGF and looked for cells that acquired that ability. These cells had to be carrying sections of the gene encoding the VEGF-binding segment of the new receptor. Those gene segments, the group discovered, were identical to sequences from the human gene encoding neuropilin. "It was a big surprise," Klagsbrun says, "that we were dealing with a molecule that's well known in the developmental neuroscience field."

Neuropilin's role in angiogenesis seems to be different from its role in axonal guidance, however. When Semaphorin III binds to the receptor on the growing tips of neurons, it repels the cells, keeping them from getting off track. But on developing blood vessels, neuropilin seems to work in concert with KDR to stimulate vessel growth toward a VEGF source; cells to which the researchers added the genes encoding both receptors were four times more effective at binding VEGF than were cells carrying KDR alone.

Although the researchers still have a lot to do to uncover neuropilin's exact role in angiogenesis, their work so far clearly shows, says Klagsbrun, that endothelial cells have more ways of sensing and responding to navigational signals than was previously supposed. Tessier-Lavigne adds, "I certainly think it's conceivable" that blood vessel growth follows patterns similar to those governing neuronal development. He says researchers will also want to know "how much cross talk there is" between developing nerves and blood vessels, a question Klagsbrun's group is already investigating.

On the medical front, Klagsbrun has found that neuropilin is abundant on some kinds of cancer cells, suggesting that VEGF doesn't merely attract blood vessels but also feeds back on tumor cells themselves, perhaps helping them to stay alive. Developing a drug that blocks neuropilin-VEGF binding, therefore, might be a double whammy against tumors, depriving them of their survival factor while also deafening blood vessels to VEGF's siren song. And that's a benefit that Leonardo, a practical engineer as much as a perceptive artist, would have appreciated.

–Wade Roush