Challenging the "No New Neurons" Dogma

Canadian researchers have found cells from the brains of adult mice that are capable of making new nerve cells

THE BODY IS CONSTANTLY REPLACING ITSELF. The bone marrow, for example, cranks out new blood cells. Skin cells are replenished from layers of dividing cells below them. But there is a critical exception to this rule: the nerve cells of the brain and spinal cord. Damage those neurons, and nothing replaces them—as victims of brain injuries know all too well. That's why the report (on page 1707 of this issue) by University of Calgary neuroscientist Samuel Weiss and his graduate student Brent Reynolds is so surprising.

The two found that cells from the brains of adult mice could produce new nerve cells in culture. At first they could hardly believe their own findings: "It challenged everything I had read; everything I had learned when I was a student," says Weiss. "I couldn't imagine how I would try to convince people this was real." But after more tests it began to seem clear that—in culture, at least—these cells can be triggered by growth factors to produce neurons. So far, there is no evidence that these cells ever make neurons in the adult brain. But the fact that they have that latent ability promises both new insights into brain development and new possibilities for treating nervous system damage.

Added to that potential is the pure intellectual excitement of an unexpected discovery. "It is a very surprising finding," says developmental neurobiologist Mary Beth Hatten of Columbia University. "There are progenitor cells hanging around [in adult brain], and we don't know what they are doing....The dogma would say they [should be] dead."

That "dogma" originated at the end of the last century, when biologists focused their microscopes on slices of brain from adult animals, looking for dividing cells—and didn't find any. Half a century later, armed with radioactive markers that are taken up by dividing cells, investigators still found little action. What cell division they did see produced not neurons but glia—non-neuronal brain cells that provide support, nourishment, and waste-removal services for neurons. They concluded that, while glia may be produced in adults, the brain gets all its neurons during embryonic development, and none are added later in life—presumably because there are no cells left that are able to make them.

Startling sight. *Samuel Weiss and Brent Reynolds (looking through microscope) found that adult mouse brain tissue has the capacity to produce new neurons.*

As is true for most dogmas, a few exceptions to the "no new neurons" rule have sprung up over the years, in the brains of songbirds, goldfish, even in a few special cases in rodents. But the dogma remained intact for the brain region called the striatum where Weiss and Reynolds found their cells.

When the two researchers started their experiments in 1989, they had no intention of challenging any view of the adult brain; they were simply studying the effects of epidermal growth factor (EGF) on undifferentiated cells from the brains of embryonic mice. EGF enabled the cells to survive and multiply in tissue culture, and when the researchers put the growing cells onto a surface they could cling to, the cells differentiated into neurons and glia.

That initial finding was not surprising, because Reynolds and Weiss were working with the embryonic brain, which is full of cells that divide to produce both neurons and glia. Although that activity ends before adulthood, the researchers decided to follow a hunch and look in the brains of adult mice for cells that would respond to the growth factor. "We had read that EGF receptors are present in the adult brain," says Weiss, "so we decided to push it."

The decision paid off. In the adults, they found cells similar to those from embryonic mice—cells that, in culture, would produce both neurons and glia. But just because they can make neurons in the lab doesn't mean that's what they do in the adult mouse. "We believe this is the same cell that is present in the embryonic brain," Weiss says, "but it may be under some form of stringent control." It may simply be that EGF isn't present to stimulate the cells in the adult brain.

Why the cells don't produce new neurons in mature brain tissue is only one of the questions raised by the discovery. Others have to do with the cells' identity, and whether they are already known in a different context. The researchers are now testing to see whether the cells belong to a peculiar group of cells, recently discovered by Cindi Morshead and Derek van der Kooy of the University of Toronto, that divide continually but don't seem to differentiate.

Another possibility is that Weiss' cells do differentiate in the brain—but not into neurons. MIT neurobiologist Ron McKay suggests that they may be the cells that normally produce new glia. That would be news to researchers who have assumed that those cells lack the potential to become neurons.

Then there is the less likely possibility that these cells do make neurons in the brain, but that somehow that activity has been missed. Pasko Rakic of Yale, who has repeatedly sought dividing neurons in the monkey brain—and found none—acknowledges that a negative finding isn't conclusive but adds that if neurons are produced in the striatum, it must be at very low levels.

Beyond the question of what these cells normally do is the question of what they might be able to do for people with brain damage. The striatum is the brain region affected by Huntington's disease, and is also damaged by oxygen deprivation and excitatory amino acids. "If we understand how these cells can be manipulated, we may be able to manipulate them in vivo to replace cells lost to injury or disease," Weiss says. "Alternatively we may be able to remove them from the adult brain, induce them to proliferate in culture, and then use them for autologous [brain-cell] transplants."

Weiss admits that such thinking amounts to little more than dreaming until more experiments are done. But, he adds with a note of optimism: "What we're finding out [from these cells] is that just because things don't occur, it doesn't mean we can't make them occur." ■ MARCIA BARINAGA