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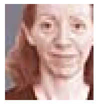

Harnessing Stem Cells To Battle Alzheimer's Is at Least Worth a Try

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Now that news cycles seem to be measured in mere minutes, I'd swear that backlashes are coming before lashes.

In Round 1, proponents of embryonic stem-cell research seized on Nancy Reagan's May 8 speech supporting such experiments and piggy-backed on her husband's death from Alzheimer's disease to urge President Bush to lift the crippling restrictions he placed on stem-cell studies.

Opponents immediately fired back. Citing a Washington Post article that called Alzheimer's "among the least likely to benefit" from stem-cell therapy, pro-life Web sites and periodicals accused scientists and "abortion scammers" of trying to pull a fast one.

CHECKUP

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See drugs in the pipeline[2] for treating Alzheimer's disease.

8/26/03

To paraphrase Mark Twain, reports that stem-cell therapy for Alzheimer's will never work are somewhat exaggerated.

In the early 1990s, "the idea that you could achieve cellular repair of the highest-level, most complex neural circuitry," like that ravaged by Alzheimer's, "was widely considered absurd," says neuroscientist Jeffrey Macklis of Harvard Medical School, Boston. But after a decade of discoveries, especially the finding that the adult brain contains "precursor cells' able to morph into neurons, "we're seeing that what people thought was impossible -- to get new neurons wired into existing circuitry -- isn't."

Not that it will be easy. Even in brain diseases way less complex than Alzheimer's, results have been underwhelming.

In Parkinson's Disease, for instance, only one kind of neuron (making the neurotransmitter dopamine) in only one part of the brain dies. You'd think that would be straightforward to fix. Indeed, when scientists took mouse embryonic stem cells, coaxed them to bloom into dopamine-making neurons, and transplanted them into the brains of rats suffering from a Parkinson's-like disease, the rats' motor function improved. But in other such studies the cells either disappeared or reverted to an essentially useless type, notes Eugene Redmond, who directs neural transplantation at Yale University.

Human studies have also been disappointing. In Parkinson's, some patients have improved after receiving fetal (not embryonic) cells; others got worse. The story is much the same in Huntington's disease and spinal-cord injury.

In Alzheimer's, the challenge is greater. Entire circuits underlying memory and thought, in many regions of the brain, are wiped out. Expecting transplanted neurons to weave themselves into the fraying circuits seems about as likely as a skein of yarn inserting itself into a damaged tapestry and recreating the original. As Dr. Redmond says, "getting new cells to make the proper connections is daunting."

But maybe not impossible. In one tantalizing study, neuroscientist Kiminobu Sugaya of the University of Central Florida, Orlando, transplanted about 10,000 human neural stem cells from fetuses into the brains of memory-impaired rats, whose age of 24 months corresponds to a human age of about 80. After the transplant, most of the once-forgetful rats could navigate a water maze, a test of memory, as adeptly as rats one-fourth their age.

Even more strikingly, microscopic examination showed that the stem cells had not only differentiated into neurons. They had also "become incorporated into brain areas related to spatial memory," says Prof. Sugaya.

The key, he believes, was injecting the stem cells into the region of the mouse brain from which its own neural stem cells surge out and migrate to their targets. Maybe damaged neurons send out an SOS, attracting replacement cells. If so, then transplanted cells may also receive the SOS and find the target.

That seems to explain Prof. Macklis's success, too. When he induced the death of neurons in complex circuits in mouse brains, mimicking Alzheimer's, he found that the "synaptic partners" of the dying neurons acted like abandoned lovers: They started calling for new partners.

Specifically, the now-partnerless neurons emitted signals that coaxed precursor cells in the mice's brains to become newly minted neurons. About half of the new neurons migrated to the site of cell death, Dr. Macklis and colleagues found. Most made the same receptors and neurotransmitters as the lost neurons; many hooked up with the neurons that had called to them.

"It is now feasible to think about incorporating new neurons into the adult brain," says Dr. Macklis. "Though it will be difficult, I think we as a field will be able to rebuild neural circuits." For simple circuits, such as those severed in spinal-cord injury, that may happen within 10 years. Repairing the complex circuits of Alzheimer's may take 30.

Which cells will make the best "neuroreplacements"? Those from embryonic stem cells, which are so ethically fraught? Or the brain's own precursor cells, which sit in a sort of reservoir, waiting to morph into neurons and enter the fray?

"We are years away from using the brain's precursor cells therapeutically," says neurologist Mark Mehler of New York's Albert Einstein College of Medicine. "In the meantime, we should use anything we have, including embryonic stem cells."

The obstacles are formidable. All the more reason to throw everything we can at these diseases.

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