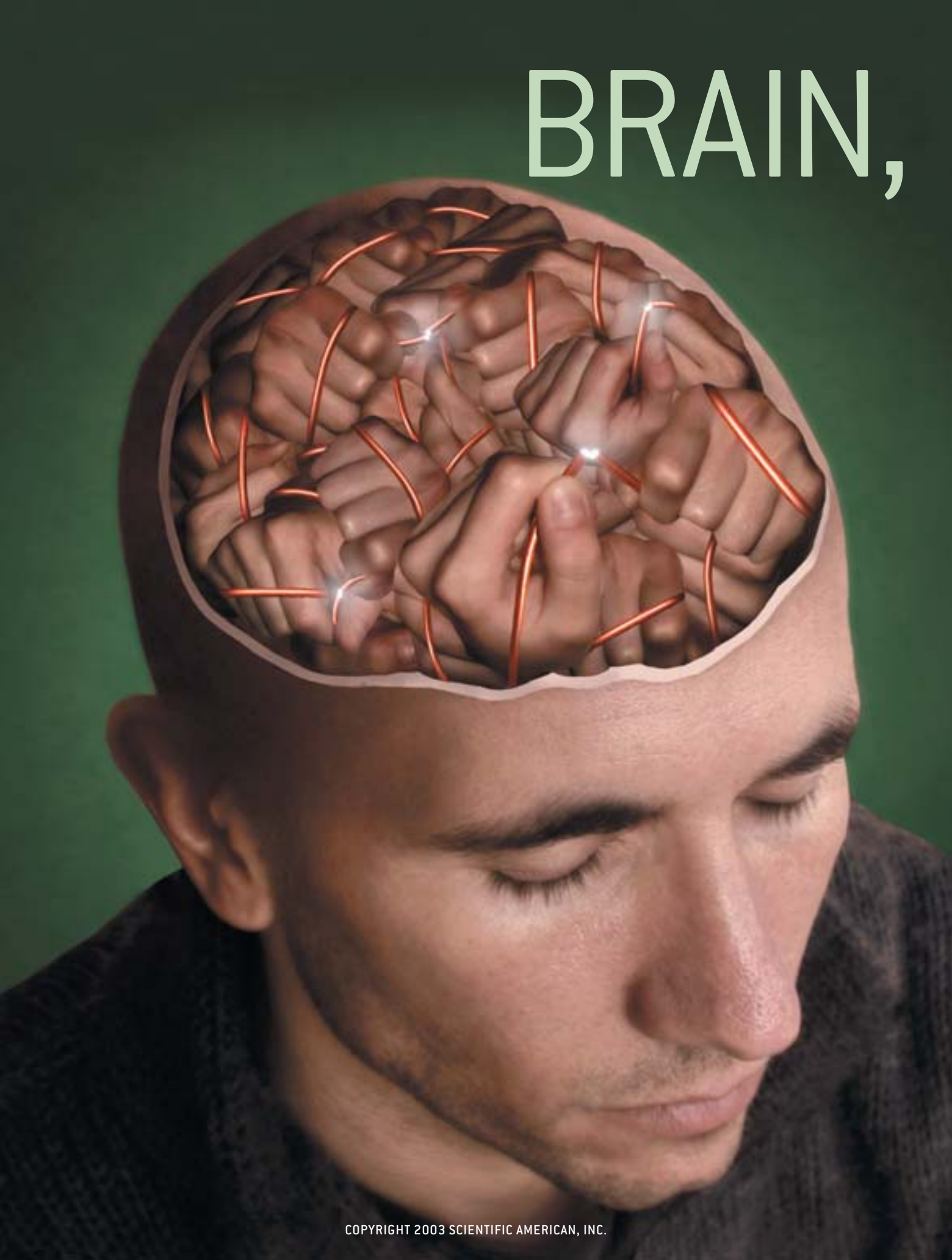
# BRAIN,



# REPAIR YOURSELF

HOW DO YOU FIX A BROKEN BRAIN? THE ANSWERS MAY LITERALLY LIE WITHIN OUR HEADS. THE SAME APPROACHES MIGHT ALSO BOOST THE POWER OF AN ALREADY HEALTHY BRAIN **BY FRED H. GAGE**



MELISSA SZALKOWSKI

The human brain has the capability to rewire itself to some extent.

**FOR MOST OF ITS 100-YEAR HISTORY, NEUROSCIENCE** has embraced a central dogma: a mature adult's brain remains a stable, unchanging, computerlike machine with fixed memory and processing power. You can lose brain cells, the story has gone, but you certainly cannot gain new ones. How could it be otherwise? If the brain were capable of structural change, how could we remember anything? For that matter, how could we maintain a constant self-identity?

Although the skin, liver, heart, kidneys, lungs and blood can all generate new cells to replace damaged ones, at least to a limited extent, until recently scientists thought that such regenerative capacity did not extend to the central nervous system, which consists of the brain and spinal cord. Accordingly, neurologists had only one counsel for patients: "Try not to damage your brain, because there is no way to fix it."

Within the past five years, however, neuroscientists have discovered that the brain does indeed change throughout life—and that such revision is a good thing. The new cells and connections that we and others have documented may provide the extra capacity the brain requires for the variety of challenges that individuals face throughout life. Such plasticity offers a possible mechanism through which the brain might be induced to repair itself after injury or disease. It might even open the prospect of enhancing an already healthy brain's power to think and ability to feel.

Neuroscientists, of course, have tried to come up with fixes for brain injury or brain disorders for decades. Such treatment strategies have primarily involved replacing diminished neurotransmitters, the chemicals that convey messages between nerve cells (neurons). In Parkinson's disease, for instance, a patient's brain loses the ability

to make the neurotransmitter dopamine because the cells that manufacture it die. A chemical relative of dopamine, L-dopa, can temporarily ameliorate the symptoms of the disease, but it is not a cure. Neuroscientists have also attempted to implant brain tissue from aborted fetuses to replace the neurons that perish in Parkinson's disease—and in other neurological disorders such as Huntington's and spinal cord injury—with modest success. Lately, some have turned to neurons derived from embryonic stem cells, which under the right conditions can be coaxed in laboratory dishes to give rise to all the cell types of the brain [*see box on page 50*].

**The ULTIMATE VISION is that physicians would be able to DELIVER DRUGS that would stimulate the brain to REPLACE ITS OWN cells.**

Although stem cell transplants have many advantages, switching on the innate capacity of the adult nervous system to repair itself would be much more straightforward. The ultimate vision is that physicians would be able to deliver drugs that would stimulate the brain to replace its own cells—and thereby rebuild its damaged circuits.

## Newborn Nerve Cells

MANY INVESTIGATORS are now pursuing exactly that vision. The hope that repair might be feasible stems from a series of exciting discoveries made starting about 40 years ago. Researchers first demonstrated that the central nervous systems of mammals contain some innate regenerative properties in the 1960s and 1970s, when several groups showed that the axons, or main branches, of neurons in the adult brain and spinal cord can regrow to some extent after injury. Others (including my colleagues and me) subsequently revealed the birth of new neurons, a phenomenon called neurogenesis, in the brains of adult birds, nonhuman primates and humans [see "New Nerve Cells for the Adult Brain," by Gerd Kempermann and Fred H. Gage; SCIENTIFIC AMERICAN, May 1999].

Shortly thereafter scientists began to wonder why, if it can produce new neurons, the central nervous system fails to repair itself more reliably and completely in the wake of disease or injury. The answer lies in understanding how—and perhaps to what end—adult neurogenesis normally occurs and how the brain's natural inclination to fix itself might be amplified.

We now know that the birth of new brain cells is not a single-step process. So-called multipotent neural stem cells divide periodically in the brain, giving rise to other stem cells and to progeny that can grow up to be either neurons or support cells named glia. But to mature, these newborn cells must migrate away from the influence of the multipotent stem cells. On average, only half of them make the trip; the rest die. This seemingly wasteful process mirrors that which takes place before birth and during early childhood, when more brain cells arise than are needed to form the developing brain. During that period, only those cells that form active connections with other neurons survive.

Whether the young cells that persist become neurons or glia depends on where in the brain they end up and what type of activity is occurring in that brain region at the time. It takes more than one month from when a new neuron is formed from a stem cell until it becomes fully functional and able to send and receive information. Thus, neurogenesis is a process, not an event, and one that is tightly controlled.

Neurogenesis is regulated by a variety of naturally occurring molecules called growth factors that are currently under intense investigation. A factor dubbed sonic hedgehog that was first discovered in insects, for example, has been shown to regulate the ability of immature neurons to proliferate. In contrast, another factor named notch and a class of molecules called the bone morphogenetic proteins appear to influence whether newborn cells in the brain become glial cells or neurons. Once young cells are committed to becoming either neurons or glial cells, other growth factors—such as brain-derived neurotrophic factor, the neurotrophins and insulinlike growth factor—play important roles in keeping the cells alive and encouraging them to mature and become functional [*see table on page 53*].

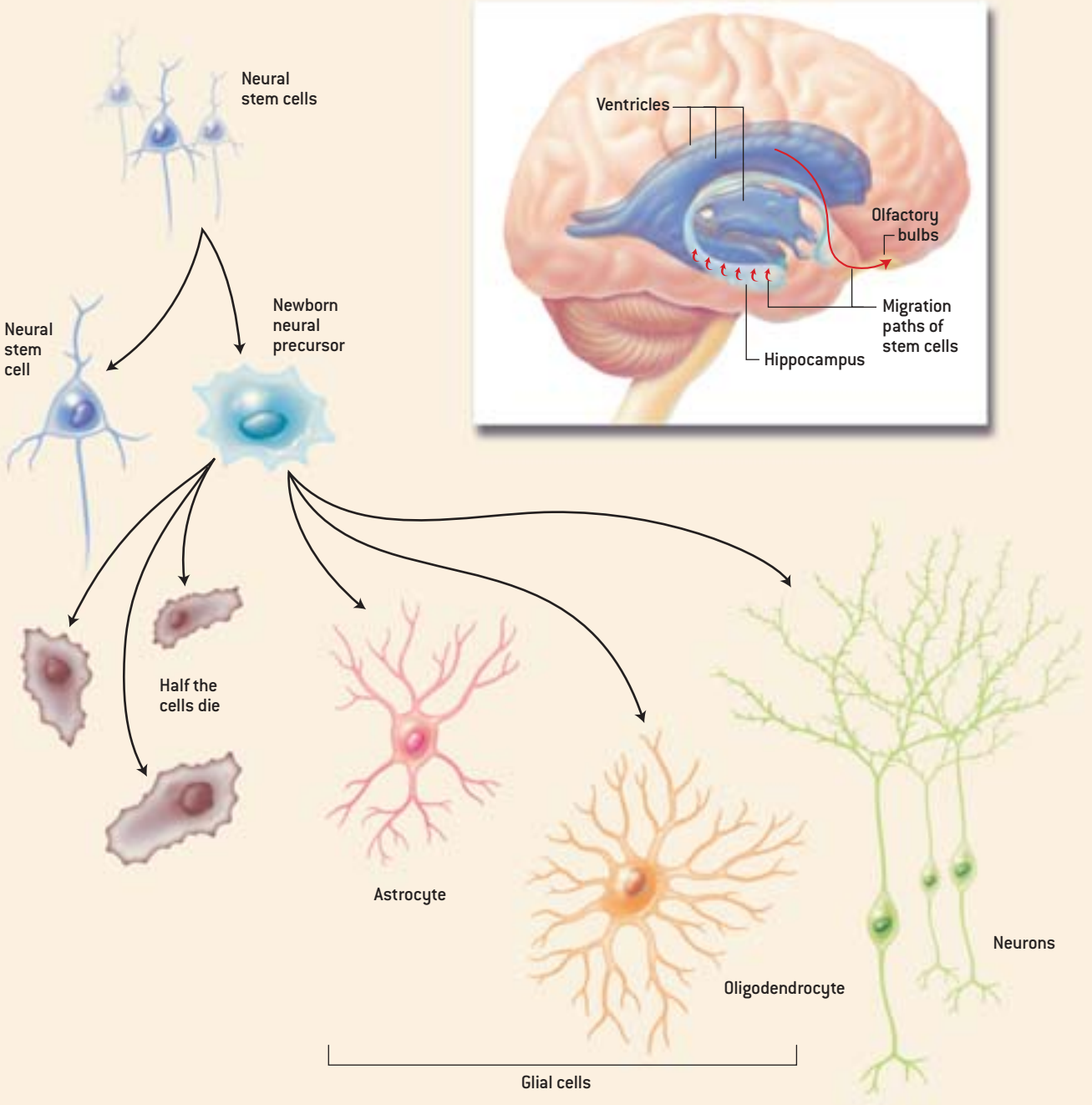
## OVERVIEW/*New Adult Nerve Cells*

- Naturally occurring growth factors in the adult human brain can spur the production of new nerve cells in some instances.
- The growth factors—or more easily administered drugs that prompt their production—might be useful as therapies for various brain disorders and for brain or spinal cord injuries.
- The factors could potentially be tested to enhance normal brain function, but questions remain about whether the strategy would work.

# HOW THE BRAIN MAKES NEW NEURONS

NEURAL STEM CELLS are the fount of new cells in the brain. They divide periodically in two main areas: the ventricles (*purple, inset*), which contain cerebrospinal fluid to nourish the central nervous system, and the hippocampus (*light blue, inset*), a structure crucial for learning and memory. As the neural stem cells proliferate (*cell pathways below*), they give rise to other neural stem cells and to neural precursors that can grow up to be either neurons or support cells, which are collectively termed glial cells (astrocytes or oligodendrocytes).

But these newborn neural stem cells need to move (*red arrows, inset*) away from their progenitors before they can differentiate. Only 50 percent, on average, migrate successfully (the others perish). In the adult brain, newborn neurons have been found in the hippocampus and in the olfactory bulbs, which process smells. Researchers hope to be able to induce the adult brain to repair itself by coaxing neural stem cells or neural precursors to divide and develop when and where they are needed. *—F.H.G.*




ALICE Y. CHEN

## STEM CELLS AS THERAPIES

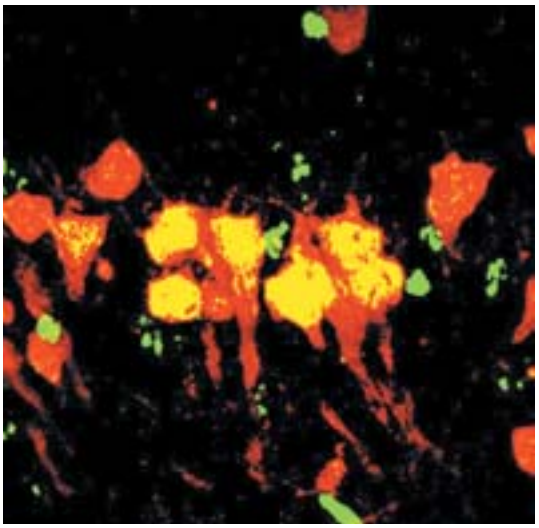
SCIENTISTS ARE INVESTIGATING two types of stem cells for possible use in brain-repair strategies. The first are adult neural stem cells: rare, primordial cells left over from early embryonic development that are known to occur in at least two areas of the brain and that can divide throughout life to yield new neurons as well as support cells called glia. The second are human embryonic stem cells that have been isolated from very early human embryos, at the stage in which the embryos consist of only 100 or so cells. Such embryonic stem cells have the potential to make any cell type in the body.

Most studies have involved observing neural stem cells while they are growing in laboratory culture dishes. Such cultured cells can multiply and be genetically marked in culture and then be transplanted back into the nervous system of an adult. In these experiments, which have so far only been performed using animals, the cells survive well and can differentiate into mature neurons in the two areas of the brain where the formation of new neurons normally occurs, the hippocampus and the olfactory bulbs. Adult neural stem cells do not readily differentiate into neurons when transplanted into any other brain areas, although they can become glia.

The problem with adult neural stem cells is that they are still immature. Unless the adult brain into which they are transplanted is making the necessary signals to direct the stem cells to become a particular neural cell type, such as a hippocampal neuron, they will either die, become glial cells or merely persist as undifferentiated stem cells. The solution would be for scientists to determine which biochemical signals normally prompt adult neural stem cells to become a particular neuronal type and then induce the cells toward that lineage in a culture dish. Once transplanted into a particular part of the brain, the cells would be expected to continue becoming that cell type, form connections with other brain cells and begin to function. —*F.H.G.*

### Where the Action Is

NEW NEURONS DO NOT arise spontaneously in every part of the adult mammalian brain but appear so far to form only in fluid-filled cavities called ventricles in the forebrain and in a seahorse-shaped structure called the hippocampus that is buried deep in the brain. Researchers have shown that cells destined to become neurons travel from the ventricles to the olfactory bulbs, a pair of structures that receives input from odor-sensing cells in the nose. Although no one is sure why the olfactory bulb requires so many new neurons, we can more easily speculate why the hippocampus needs them: this structure is crucial for learning new information, so adding neurons there would presumably spur the formation of connections between new and existing neurons, increasing the brain's capacity to process and store novel information.



One month after treatment with neural growth factors, the brain of a rat that had experienced a stroke generated new neurons (*yellow*).

A handful of reports have purported to find new neurons in areas outside the hippocampus and olfactory bulb, but those results have not yet been substantiated. One reason is that the methods used to prove the existence of neurogenesis are complex and difficult to carry out. Newer, more sensitive techniques may detect neurogenesis elsewhere in the adult brain and spinal cord as well. As we learn additional details about the molecular mechanisms that control neurogenesis and the environmental stimuli that regulate it, we anticipate that we will be able to direct neurogenesis anywhere in the brain. By understanding how growth factors and different cellular environments control neurogenesis in the normal brain, for instance, we hope to be able to develop therapies that can prompt a diseased or damaged brain to fix itself.

Several neurological diseases might be ameliorated by stimulating neurogenesis. A stroke, for instance, occurs when a clot restricts blood flow to part of the brain, cutting off the oxygen supply and killing neurons. After a stroke, neurogenesis commences in the hippocampus in an apparent attempt to produce new neurons to heal such damaged brain tissue. Most of the newborn cells die, but some successfully migrate to the damaged area and have been reported to become adult neurons. Although such microrepair is not sufficient to reverse the damage of a major stroke, it is probably adequate to help the brain recover from small, often unrecognized strokes. Epidermal growth factor (EGF) and fibroblast growth factor (FGF) are now being used to try to enhance this intrinsic repair process, with encouraging results.

Unfortunately, EGF and FGF are large molecules

HIROFUMI NAKATOMI ET AL. IN *CELL*, VOL. 110; AUGUST 23, 2002

that have difficulty crossing the blood-brain barrier, the meshlike network of tightly woven cells that lines the blood vessels of the brain. Wyeth-Ayerst Laboratories and Scios, a biotechnology company based in Sunnyvale, Calif., halted clinical trials of FGF to treat stroke in 1999, in part because the molecule was not reaching the brain. Several research groups have tried to overcome this obstacle for FGF by linking it to another molecule that tricks the cells into taking it up and transferring it into brain tissue or by genetically engineering cells to make FGF and then transplanting those cells into the brain. So far such approaches have been tested only in studies involving animals, however.

Stimulating neurogenesis could also lead to a new type of treatment for depression. Chronic stress is believed to be the most important causal factor in depression aside from a genetic predisposition to the disorder, and stress is known to restrict the number of newly generated neurons in the hippocampus [see "Taming Stress," by Robert Sapolsky, on page 86]. Many currently available drugs for treating depression, such as Prozac, augment neurogenesis in experimental animals. Interestingly, most of these drugs take up to one month to elevate mood—the same time required for neurogenesis. This finding has led to the hypothesis that depression is in part caused by a decrease in neurogenesis in the hippocampus. Recent clinical imaging studies have confirmed that the hippocampus is shrunken in chronically depressed patients. But long-term administration of antidepressants appears to spur neurogenesis: rodents that were administered such drugs for months had new neurons sprouting in their hippocampus.

## Do-It-Yourself Brain

ANOTHER DISORDER in which prompting neurogenesis might be beneficial is Alzheimer's disease. Several recent studies have demonstrated that mice genetically engineered to contain human genes that predispose to Alzheimer's display various abnormalities in neurogenesis. Those engineered to overproduce a mutant form of the human amyloid precursor protein, for instance, have fewer than normal neurons in the hippocampus. And the hippocampus of other mice carrying the mutant human gene for a protein named presenilin has a decreased number of dividing cells, resulting in a reduced number of surviving neurons. If growth factors such as FGF can reduce the trend, they might be useful therapies for this devastating disease.

The challenge now is to learn more about the specific growth factors that govern the various steps of neurogenesis—the birth of new cells, the migration of newborn cells to the correct spots, and the maturation of those cells into neurons—as well as the factors that inhibit each step. In diseases such as depression, where cell division is reduced and cell loss results, the goal is to find drugs or specific therapies that increase cell proliferation. In epilepsy, where it appears that new cells are born but then migrate to the wrong locations, finding ways to redirect errant neurons could be the key. In the brain cancer glioma, glial cells proliferate and form deadly, rapidly growing tumors. Although the origin of gliomas is still unclear, some speculate that they arise from neural stem cells. Natural substances that regulate the division of such stem cells might hold promise as a treatment.

**Several neurological DISEASES might be AMELIORATED by stimulating NEUROGENESIS.**

In stroke, where cells die or fail to mature, it will be important to identify growth factors that support neuronal survival and teach immature cells to become healthy, well-connected neurons. Disorders such as Huntington's, amyotrophic lateral sclerosis (ALS) and Parkinson's—in which very specific cell types die and cause particular cognitive or motor symptoms—might be the easiest initial targets because the cells that are responsible for the disease are in discrete areas of the brain that can be pinpointed.

An important concern will be how to control the amount of neurogenesis a particular treatment prompts, because the overproduction of new neurons can also be dangerous. In some forms of epilepsy, for example, neural stem cells continue to divide past the point at which new neurons can form useful connections. Neuroscientists speculate that these aberrant cells not only end up in the wrong place but

THE AUTHOR

*FRED H. GAGE* is Adler Professor in the Laboratory of Genetics at the Salk Institute for Biological Studies in San Diego and an adjunct professor at the University of California, San Diego. He received his Ph.D. in 1976 from Johns Hopkins University. Before joining the Salk Institute in 1994, Gage was a professor of neuroscience at U.C.S.D. He is a fellow of the American Association for the Advancement of Science and a member of both the National Academy of Sciences and the Institute of Medicine. He served as president of the Society for Neuroscience in 2002, and his honors include the 1993 Charles A. Dana Award for Pioneering Achievements in Health and Education, the 1997 Christopher Reeve Research Medal, the 1999 Max Planck Research Prize and the 2002 MetLife Award.

## MAKING CRUCIAL CONNECTIONS

BECAUSE IT TAKES roughly one month from the time neural stem cells divide until their offspring become integrated into the functional circuits of the brain, the role that the new neurons play in behavior probably has less to do with the birth of the cells and more to do with how new or existing cells connect to one another (form synapses) and to existing neurons to form circuits. In the process of synaptogenesis, so-called spines on the arms, or dendrites, of one neuron make connections with points on the main branch, or axon, of another neuron. According to recent studies, dendritic spines (*below*) can change their shapes in a matter of minutes, suggesting that synaptogenesis might underpin learning and memory. The solid-color micrographs (*red, yellow, green* and *blue*) were taken one day apart in the brain of a living mouse. The multicolor image (*far right*) shows the color photographs superimposed on one another. Areas where no change occurred appear white. —*F.H.G.*

also remain immature, contributing to the miswiring of the brain that causes seizures. Growth factor treatments for stroke, Parkinson's and other disorders might prompt neural stem cells to divide inappropriately and cause similar symptoms, so researchers must first better understand how to use the growth factors to trigger growth, the migration of new cells to specific places, or their maturation into adult cells.

In treating spinal cord injury, ALS or multiple sclerosis, the strategy may be to induce stem cells to yield a subset of glial cells called oligodendrocytes. These cells are essential for neurons to communicate with one another because they insulate the long axons between neurons, preventing the electrical signal carried by the axons from dissipating. Stem cells in the spinal cord have already been shown to have the capacity to make oligodendrocytes at low frequency. My colleagues and I—as well as other groups—have also used growth factors to induce the proliferation of oligodendrocytes in animals with spinal cord injury, with beneficial results.

### A Brain Workout

ONE OF THE MOST STRIKING aspects of neurogenesis in the hippocampus is that experience can regulate the rate of cell division, the survival of newborn neurons and their ability to integrate into the existing neural circuitry. Adult mice that are moved from a rather sterile, simple cage to a larger one that has running wheels and toys, for instance, will experience a significant increase in neurogenesis. Henriette van Praag in my laboratory has found that exercising mice in a running wheel is sufficient to nearly double the number of dividing cells in the hippocampus, resulting in a robust increase in new neurons. Intriguingly, regular physical activity such as running can also lift depression in humans, perhaps by activating neurogenesis.

Once neurogenesis can be induced on demand in a controlled fashion, it could change our very conception of brain disease and injury. I imagine a time when selective drugs will be available to stimulate the appropriate steps of neurogenesis to ameliorate specific disorders. Such pharmacological therapies will be teamed with physical therapies that enhance neurogenesis and prompt particular brain regions to integrate the newly developed cells. These potential treatments offer great promise for millions of people suffering from neural diseases and spinal cord injury. The links between neurogenesis and increased mental activity and exercise also suggest that people might be able to reduce their risk of neural disease and enhance the natural repair processes in their brains by choosing a mentally challenging and physically active life.

Just as exciting is the possibility that healthy individuals might become "better than well" by stimulating their brains to grow new neurons. It is unlikely, however, that people seeking to boost their brainpower would want to have regular shots of growth factors, which cannot be taken orally and have difficulty crossing the blood-brain barrier once injected into the bloodstream. Scientists are now seeking small molecules that can be made into pills that would switch on growth factor genes in a person's brain so that the individual's brain cells make more of the factors than usual. For instance, a company named Curis, based in Cambridge, Mass., has devised small molecules that regulate the production of sonic hedgehog, a factor that plays a role in neural development. Other companies have generated similar molecules that might be made into drugs.

Another strategy that could conceivably be used to improve brain performance involves gene therapy and cell transplantation. Under such a scenario, researchers would genetically engineer cells in the

KAREL SVOBODA *Cold Spring Harbor Laboratory*

## SELECTED NEURAL GROWTH FACTORS UNDER DEVELOPMENT

These factors might be used as drugs on their own, or scientists might design other drugs to stimulate or block the factors.

| NAME | FUNCTION | POTENTIAL DISEASE TARGETS | SOME COMPANIES INVOLVED IN RESEARCH |
|---|---|---|---|
| Brain-derived neurotrophic factor (BDNF) | Keeps newborn neurons alive | Depression (abandoned for amyotrophic lateral sclerosis) | Amgen, Thousand Oaks, Calif. |
| Ciliary neurotrophic factor (CNTF) | Protects neurons from death | Huntington's disease (now testing against obesity) | Regeneron Pharmaceuticals, Tarrytown, N.Y. |
| Epidermal growth factor (EGF) | Spurs stem cells in brain to divide | Brain tumors and stroke | ImClone Systems, New York City |
| Fibroblast growth factor (FGF) | In low doses, supports survival of various cell types; at high doses, induces cells to proliferate | Brain tumors and stroke | ViaCell, Boston |
| Glial cell line–derived neurotrophic factor (GDNF) | Prompts motor neurons to sprout new branches; prevents cells that perish in Parkinson's disease from dying | Parkinson's disease and ALS | Amgen |
| Glial growth factor-2 (GGF-2) | Favors production of glial (support) cells | Spinal cord injury, multiple sclerosis and schizophrenia | Acorda Therapeutics, Hawthorne, N.Y. |
| Insulinlike growth factor (IGF) | Fosters the birth of both neurons and glial cells | Multiple sclerosis, spinal cord injury, ALS and age-related dementia | Cephalon, West Chester, Pa. |
| Neurotrophin-3 (NT-3) | Promotes formation of oligodendrocytes (type of glial cell) | Multiple sclerosis, spinal cord injury and ALS | Amgen and Regeneron Pharmaceuticals |

laboratory to overproduce specific growth factors and then implant the cells into particular regions of a person's brain. Alternatively, scientists could insert the genes that encode the production of various growth factors into viruses that would ferry the genes into existing brain cells.

But it is not at all clear whether any of these approaches would necessarily enhance the capabilities of a normal, healthy brain. A handful of animal studies using nerve growth factor suggests that adding growth factors can actually disrupt normal brain function. It is possible that the brain requires a delicate balance and that too much of a good thing can lead to just as many problems as too little. Growth factors could induce tumors to form, and transplanted cells could potentially grow out of control, causing cancer. Such risks might be acceptable for people with diseases as dire as Huntington's, Alzheimer's or Parkinson's but might not be palatable for healthy individuals.

The best ways to augment brain function might not involve drugs or cell implants but lifestyle changes. Like many other organs, the brain responds positively to exercise, a good diet and adequate sleep, which are already known to enhance normal brain function with fewer side effects and potential problems than most of the other strategies described above. I predict that if more people knew that a proper diet, enough sleep and exercise can increase the number of neural connections in specific regions of the brain, thereby improving memory and reasoning ability, they would take better care of themselves.

A final consideration is the environment in which we live and work. More and more experimental evidence indicates that environment can affect the wiring of the brain. This opens up vistas of possibility for architecture and suggests that future homes and offices might be designed with an eye toward how they might provide an enriched environment for enhancing brain function.

More immediately, however, if science can better understand the self-healing abilities of the brain and spinal cord, that insight could constitute one of the major achievements of our time. Neurologists of the future might be able to expand their capabilities by strategically activating the brain's own toolkit for self-repair and enhancement. SA

### MORE TO EXPLORE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**Neurogenesis in the Adult Brain: New Strategies for CNS Diseases.** Dieter C. Lie et al. in *Annual Reviews of Pharmacology and Toxicology* (in press).