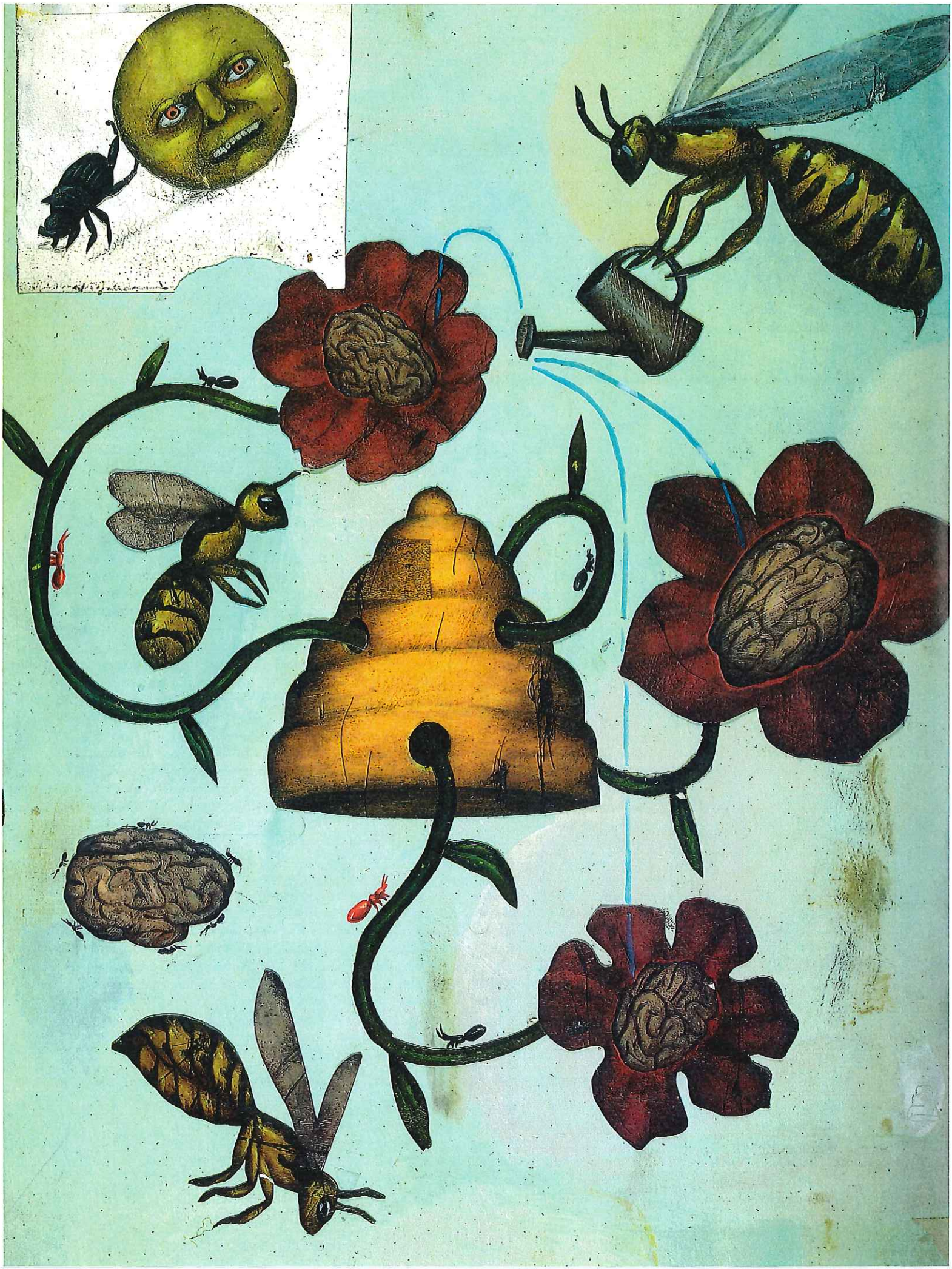


This story begins with more excitement than most. It's not just the subject: the cells called glia that fill about half the volume of our brain. And it's not just the recent discoveries of what glia can do: form nerve cell connections in the brain, organize nerve cells for the fast transmission of messages, and even transmit their own messages.

The excitement comes directly from Stanford's Barbara Barres, PhD, an associate professor in neurobiology. "Nobody ever thinks that glia are interesting," says Barres. But she is not complaining — far from it. Her words come with the conviction that others will soon see the light. And she is prepared to talk for over an hour, at breakneck speed and with few gasps for breath, if that will win over a few more converts. ■ Glia have been neglected because nerve cells, or neurons, are the more likely suspects for directing our every emotion, thought

filled with glia

Once scorned as mere filler, glial cells may shape the way the brain thinks.

by William Wells
ILLUSTRATIONS BY JASON HOLLY

and action. The outside lining of neurons is packed with channels that let specific charged molecules (or ions) into the cell or out of the cell. When one neuron passes a neurotransmitter (a chemical message) to another neuron, the second cell responds by opening lots of channels. Ions rush in, the cell becomes charged, and the charge of the cell opens still more channels. A wave of channel opening and ion rushing races down the length of the neuron, ending with the release of more neurotransmitters at the far end of the cell.

This is called an action potential. It happens every time you lift a finger or think a thought. It happens fast, it can travel a long distance, and it can be added to or subtracted from other action potentials. Clearly then, neurons run the body.

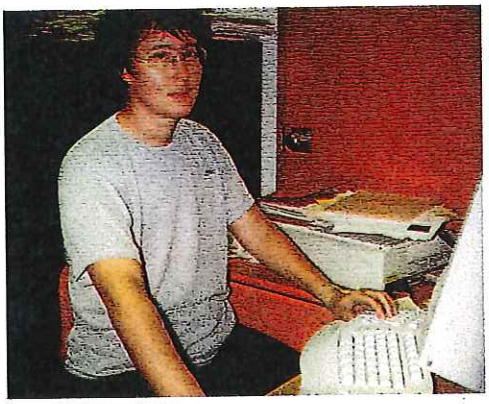
Glia seem rather dull in comparison. The two main types of glia, the astrocytes and the oligodendrocytes, provide support for the neurons: They nourish them, keep them alive, and prevent crossed wires, but they can't generate action potentials. The star-shaped astrocytes swarm around neurons, wrapping the connections between them and filling in any other gaps. The oligodendrocytes' most obvious function is to generate the myelin sheath, a greasy covering that insulates the long spidery extensions of neurons. When the im-

Neurons are affected by the glial factor only after two days of constant exposure, she says, which just happens to be how long the brain takes to cement a new lesson into long-term memory.

mune system inappropriately destroys the myelin in multiple sclerosis (MS), a progressive loss of control over everything from walking to breathing ensues.

Some of the first clues that glia might be more than the brain's packing material came from Barres. She found that glia make most of the proteins that neurons use to communicate among themselves. The glia make the neurotransmitter messengers, they make the receptors that translate the messages, and also the channels that carry out the instructions. So, a lively chatter between the neurons and the glia is a clear possibility.

Stanford's Stephen Smith, PhD, a professor of molecular and cellular physiology, has found another intriguing thing about glial cells: They have a novel way of sending messages to each other. Smith made his discovery while investigating not glia but neurons. Using fluo3, a molecule that fluoresces in the presence of a lot of calcium, he set out to observe changes in the calcium levels of neurons growing in culture dishes. The waxing and waning of calcium in the neurons was unexceptional. But the fluo3 also got into the astrocytes that were supporting the growth of the neurons. The result was a series of flashes reminiscent of a pinball machine announcing a free game.



BARBARA BARRES

Barres found an early clue that glia might talk to other nerve cells: Glia make most of the same proteins neurons use to send messages.

EITHER SPONTANEOUSLY, or in response to a puff of neurotransmitter, the astrocytes release large amounts of calcium from an internal store, Smith found. A wave of calcium sweeps through the sea of the cell's interior, with the original burst of calcium triggering the release of still more calcium. The wave can even travel between the astrocytes by way of narrow connections called gap junctions.

Smith repeated his experiment in thin slices of brain. Turning on neurons in one part of the brain slice set off a calcium wave in a distant part of the brain slice, confirming that the neurons could instruct the glia to make a wave. The experiment also dispelled concern that the wave was simply an artifact of life in a culture dish.

"At the time it was completely unexpected," says Smith. "Making waves was not the kind of thing that astrocytes were thought to do."

But with the surprise discovery came a problem. Smith had not set out to find the waves, and now he didn't know what they were for. "To this very day people still only speculate about what these signals might mean and whether they are part of normal brain functioning," he says. "It seems like an answer without a question."

Like action potentials, the calcium waves can keep going for a long time without a change in the size or speed of the wave. But the calcium waves are tortoises. Their deliberate pace of around four millimeters per hour would not do for instructing a limb to move or for solving an algebra problem, but it might be just right for exerting more diffuse effects on the brain. In fact, some of the messenger systems of neurons work just as slowly and diffusely as the calcium waves. Neuron messenger molecules like dopamine and serotonin, for example, control many of the more poorly defined activities of the brain like wakefulness, emotion and mood. Like these molecules, the calcium waves may be neuromodulators, increasing or decreasing the impact of action potentials in an entire region of the brain. Smith suggests that such slow-moving and dispersed events may well have been treated as experimental noise in the past, and subtracted from measurements of action potentials in the brain because of the lack of an explanation.

There are some tantalizing clues about the effects of calcium waves but little hard evidence. The waves may be involved in the visual auras and spreading pain felt by migraine sufferers. When mapped back to the level of the brain, these sensations move at the same rate as calcium waves. And some general anesthetics block the gap junctions necessary for the spread of calcium waves. Although these greasy anesthetic molecules tend to stick to many parts of the cell, the amount of anesthetic needed to block the gap junctions is almost exactly the same amount needed to make a person unconscious.

Both Smith, who now works on neurons not glia, and Barres are hoping that the field will move beyond these types of correlations. With their calcium waves, neurotransmitters and channels, glia could be doing many things. "But rather than endlessly characterizing glia," says Barres, "we need to make hypotheses about the activities of glia and then test the hypotheses."

BARRES' APPROACH HAS BEEN, IN HER WORDS, to "tear the brain down into defined building blocks." By adding chemicals and growth-in-

ROBERT OLDING

ducing proteins, she has been able to cure glia and neurons of their co-dependency and get them to grow by themselves. This allows her to see what each can do without the other.

"Whenever we put a cell in a dish, our first problem is that the cell wants to kill itself," says Barres. Martin Raff at University College, London, discovered that cell suicide, or apoptosis, is common to most if not all cell types. While working with Raff, Barres showed that glial cells are among those that kill themselves. To overcome cell suicide she plied glia with various proteins normally made by the glia's neighbors. When she combined three proteins, she finally had a working cocktail.

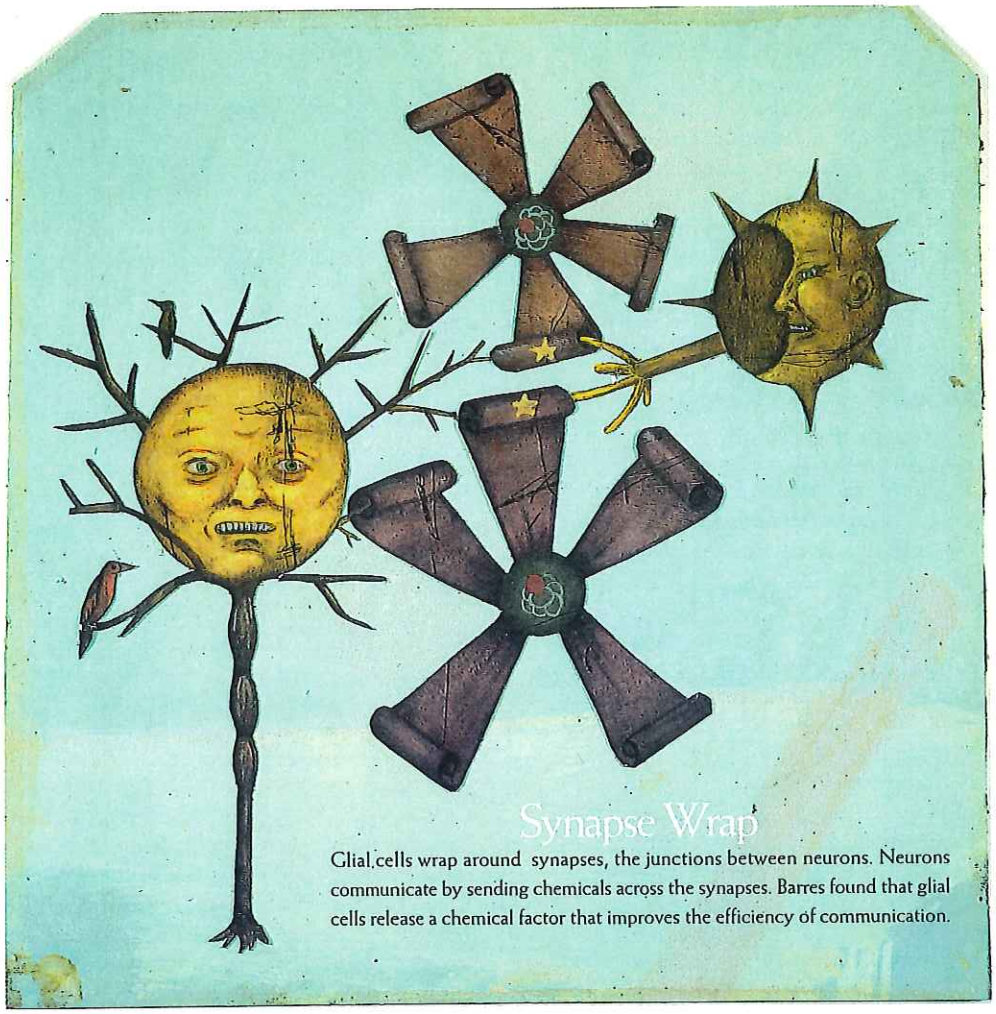
BUT TO OVERCOME cell suicide in brain neurons, she needed to use another strategy. Although researchers had managed to grow peripheral neurons (those from outside the brain and spinal cord) using a growth-promoting cocktail similar to Barres', brain neurons apparently needed something extra (see sidebar). Barres identified that extra something when she found that the brain neurons survive in the culture dish only when induced to fire off action potentials.

This is the brain's version of "use it or lose it." Neurons that never get wired into active circuits, or that fall into disuse, are simply allowed to die off. This may explain why we can learn to play the piano and then forget all but a few chords after a year of not practicing.

After the hard work of tracking down the correct growth conditions, Barres' strategy of breaking down the brain into its components is beginning to pay off. Once Barres had the neurons growing by themselves, she noticed that, on the surface, they appeared to be doing quite a good job without the glia. They formed their special connections, called synapses, and even used the synapses to pass on messages. But the transfer of messages was inefficient and often failed. When Barres and postdoctoral fellow Frank Pfrieger added back glia, the connections rarely failed and the neurons passed on more and stronger signals.

So, glia have something to do with strengthening the lines of communication between nerve cells. But what exactly do they do? Barres and Pfrieger demonstrated that the glia make a protein or chemical and that it is this factor — not necessarily the glial cells — that is needed.

In the presence of the glia or the glial factor, the transmitting neurons released their chemical messengers more readily in response to an incoming electrical



Synapse Wrap

Glial cells wrap around synapses, the junctions between neurons. Neurons communicate by sending chemicals across the synapses. Barres found that glial cells release a chemical factor that improves the efficiency of communication.

bad glia

Devastating problems result when good glia go bad.

Here's what two Stanford researchers are doing to help understand the role of glia in disease:

Marion Smith, PhD, professor of neurology at the Veterans Affairs Palo Alto Health Care System, is trying to work out why and how a type of glia called microglia eat up the insulating myelin, thus causing multiple sclerosis. An infection-fighting material called complement may mistakenly attach itself to myelin, she suspects. Complement is normally a marker for infected cells, so the microglia are only doing their duty in destroying the complement-labeled myelin.

Lawrence Eng, PhD, professor of pathology at the VA, is looking at the response of glia to any number of injuries or infections in the brain. In all cases the glia grow inappropriately, make a protein called glial fibrillary acidic protein (GFAP) that can block regrowth of other cells, and produce messengers that bring in blood cells that do more harm than good. He is trying to turn off production of GFAP and the messengers in a rat model of brain injury. WILLIAM WELLS

signal. The glia are almost certainly needed for the formation of strong synapses as the brain develops. Although it remains to be proved, Barres believes that glia may also control the strength of synapses in the fully developed brain, beefing up some circuits and turning down others, perhaps even in response to calcium waves. Neurons are affected by the glial factor only after two days of constant exposure, she says, which just happens to be how long the brain takes to cement a new lesson into long-term memory. But whether a connection exists between glia and memory will have to wait for further experiments.

STEPHEN SMITH

Star-shaped glial cells, called astrocytes, have a special way of communicating, Smith found. The mechanism's purpose remains unknown.

ANOTHER GLIAL FACTOR helps neurons send messages at the greatest possible speed. Neurons send their express messages by a process called saltatory conduction, in which the electrical signal jumps from one relay station to another, skipping the intervening, myelin-coated stretch of the neuron. The relay stations, called nodes of Ranvier, are specialized structures with no myelin coat but a huge quantity of ion channels that respond to the electrical signal.

"Every place there is a gap in the myelin there is an astrocyte touching," says Barres. So the astrocytes might be herding the channels together to form the nodes, she says, "but there is no proof."

"The amazing thing," says Barres, "is that in culture we can make the nodes form by using glial-conditioned media, without any cell contact. The surprise was that the signal comes from the oligodendrocytes and not the astrocytes," Barres says.

The oligodendrocytes also provide the factor in the body. The delicate touch of the astrocytes at each node is, it seems, a red herring. This experiment also tells Barres that the neuron knows where it wants the nodes, and it is merely waiting for a delocalized signal from the oligodendrocytes to make it happen.

With each new experiment, Barres discovers another sentence in the dialogue between neurons and glia. The experimental system has been established, the evidence is pouring in, and the proselytizing can begin. More research will mean more discoveries, she says, and "since most of the cells in the brain are glia, we need more people studying glia." SM

mending christopher reeve Barres offers hope for those with injured spinal cords.

Barres started her career as a neurologist but switched to research when she found that much of what she wanted to do — such as curing spinal-cord damage and neurodegenerative diseases, like Alzheimer's — was beyond her reach. "It was so depressing. We just couldn't do much to help in these diseases," she says.

The discovery of various growth factors brought hope, but this was not enough to revive the spinal-cord and brain neurons of the central nervous system (CNS). "You can deliver these factors until you are blue in the face, but if the cells are not responsive the factors won't do any good," she says. "We need to pair these factors with activity."

Results with neurons in arms, legs and fingers — the peripheral nervous system (PNS) — were the original source of hope and then disappointment. "The CNS and PNS are fundamentally different in terms of what they need to survive," says Barres. "The PNS regenerates — it's amazing. But injure the same pathway in the brain and you're Christopher Reeve: You're paralyzed forever. Not only do the neurons not repair themselves, they die."

Now Barres has found out something that could turn around the lives of the hundreds of thousands of Americans who like Reeve have severe spinal-cord damage. Reeve, an actor and prominent supporter of spinal cord-injury research, became partially paralyzed when he fell from a horse during an equestrian competition in 1995.

Like the PNS neurons, the CNS neurons need growth factors in order to live. Barres realized that, unlike PNS neurons, the CNS neurons won't survive unless they send the nervous system's missives. They must fire off action potentials. It doesn't matter where the messages are going or what they are telling the body to do, but the neurons must be actively communicating to stay alive. Severed nerves in a spinal cord are dormant and, in the CNS, dormant nerves will soon be dead.

Barres has shown that the pairing of factors and activity is necessary for CNS neurons to survive in both the brain and the culture dish. Inactive CNS neurons don't respond to the growth factors because of an act of subterfuge: The CNS neurons keep the receptor proteins that detect the growth factors hidden inside the cell.

But if neurons are made to think they are functional, says Barres, it may become a self-fulfilling prophecy. With the addition of a simple chemical, neurons can be fooled into believing that they are actively sending messages. Adding this chemical to the growth factors might just tip the balance and get Christopher Reeve's spinal-cord neurons to grow again, linking his legs to his brain. WILLIAM WELLS

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