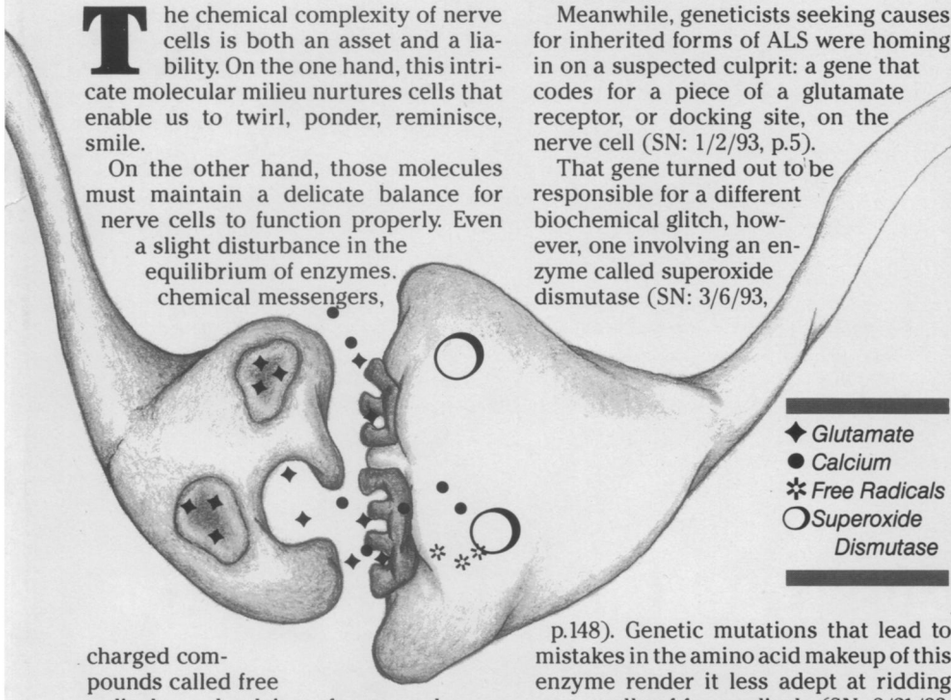
Neurodegeneration: A Chemical Conspiracy?

By ELIZABETH PENNISI

The chemical complexity of nerve cells is both an asset and a liability. On the one hand, this intricate molecular milieu nurtures cells that enable us to twirl, ponder, reminisce, smile.

On the other hand, those molecules must maintain a delicate balance for nerve cells to function properly. Even a slight disturbance in the equilibrium of enzymes, chemical messengers, charged compounds called free radicals, and calcium, for example, can lead to the death of a cell, the destruction of its neighbors, and, ultimately, the development of neurodegenerative disease.



The quest to determine what gets out of whack in the nerve-muscle disorder amyotrophic lateral sclerosis (ALS) has led researchers down different, sometimes confusing, paths. Only recently have they begun to realize that these paths may all wind up at the same place.

In 1992, researchers implicated one molecule, an amino acid called glutamate, in ALS. Typically, nerve cells use glutamate as a chemical messenger. They release this substance into a tiny space, called a synapse, which it crosses to excite a neighboring nerve cell (see diagram). Though essential to nerve-to-nerve communication, glutamate in excessive amounts can excite a cell to death, says Jeffrey D. Rothstein, a neurologist at Johns Hopkins University in Baltimore.

Rothstein and his colleagues analyzed tissue taken from the spinal cords and brains of ALS patients. In some sections, they found that cells had failed to remove glutamate adequately from the synapse. As a result, this messenger piled up until nerve cells self-destructed, they suggested in the May 28, 1992 NEW ENGLAND JOURNAL OF MEDICINE.

A year later, they confirmed that this glutamate buildup gradually — and selectively — destroys motor neurons. They reported their finding in the July 15, 1993 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Meanwhile, geneticists seeking causes for inherited forms of ALS were homing in on a suspected culprit: a gene that codes for a piece of a glutamate receptor, or docking site, on the nerve cell (SN: 1/2/93, p.5).

That gene turned out to be responsible for a different biochemical glitch, however, one involving an enzyme called superoxide dismutase (SN: 3/6/93, p.148). Genetic mutations that lead to mistakes in the amino acid makeup of this enzyme render it less adept at ridding nerve cells of free radicals (SN: 8/21/93, p.116). These renegade charged molecules eventually cause motor nerve cells — and the muscles they control — to die, says James O. McNamara, a neurologist at Duke University in Durham, N.C.

This finding prompted him and others to suggest that problems with the nerve cell's control of free radicals might also account for "sporadic" ALS, in which the disease arises without a clear genetic basis. But that idea may not hold up. Several unpublished studies indicate that superoxide dismutase and other free radical processors are normal in many people with sporadic ALS, Rothstein says.

Yet even as scientists shift their focus back to glutamate (see accompanying story), some sense that it may not be a lone assailant. Glutamate and inept superoxide dismutase may both figure into a chemical conspiracy. These substances help create a molecular cabal that leads to nerve destruction not only in Lou Gehrig's disease but also in several other neurodegenerative disorders, say Stuart A. Lipton and Paul A. Rosenberg of Harvard Medical School in Boston.

In the March 3 NEW ENGLAND JOURNAL OF MEDICINE, these neurologists suggest that a disruption of the normal balance between the creation (or activation) and destruction (or sequestering) of many essential substances causes nerve cells to die. Because these processes are linked, upsetting one molecule's equilibrium can destabilize another molecule. For example, the docking of glutamate at a cell membrane spurs production of free radicals. In healthy cells, superoxide dismutase and other enzymes dispose of free radicals before they can do any damage. But excess glutamate can overwhelm the cells' ability to cope, leading to excess free radicals that may exacerbate glutamate's destructive potential.

Unpublished data from Rothstein's group further support this conspiracy theory. When these researchers disabled superoxide dismutase in cultured spinal cord tissue, motor neurons committed a slow suicide, called apoptosis (SN: 11/21/92, p.344), dying differently than they do when simply overexcited by glutamate. Next, the scientists blocked the removal of glutamate from its docking sites; these cells died even faster.

In contrast, when the researchers kept glutamate away from nerve cells by preventing it from docking at one particular type of receptor, or when they treated nerve cells with antioxidants, the cells did not die. It appears that nerve cells slightly damaged by free radicals become very susceptible to glutamate's harmful effects, Rothstein adds.

Any number of events, including an autoimmune response or exposure to a toxin, may disturb the balance of glutamate and perhaps lead to the degeneration of nerves. "We don't know what the fundamental deficiency is, but we know it does feed into this common pathway," says Lipton. "There are only certain ways that neurons die."

This commonality suggests ways to halt nerve death, no matter what the cause. Riluzole, for example, inhibits glutamate release from nerve cells. The drug thus diminishes the amount of glutamate available to stimulate a destructive cascade.

Any potential nerve-saving drug needs, like Riluzole, to modulate, not block, glutamate activity: It must allow this messenger to do its job but not to do damage. "You just want to turn [its activity] down a little bit," Lipton says. In the December 1993 TRENDS IN NEUROSCIENCES, he describes the potential of two agents that can interfere with the docking of glutamate at a nerve cell. Although finding the right drug and dosage that will control glutamate or free radicals enough but not too much is no easy task, Lipton finds reason for optimism.

He thinks the time is coming when neurologists will not have to stand by as patients disintegrate and eventually die. "Neurology is where cardiology was 40 years ago," he notes. "Things are really starting to look up. We can now begin to think about treating them." □