Ch 2

Revealing the Brain's Secrets

Is space truly the final frontier? Not according to scientists who are probing what they call the most complex and challenging structure ever studied: the human brain. "It is the great unexplored frontier of the medical sciences," said neurobiologist John E. Dowling, professor of natural science at Harvard University. Just as space exploration dominated science in the 1960s and 1970s, the human brain is taking center stage in the 1990s.

It may seem odd to compare an organ that weighs only about three pounds to the immensity of the universe. Yet the human brain is as awe-inspiring as the night sky. Its complex array of interconnecting nerve cells chatter incessantly among themselves in languages both chemical and electrical. None of the organ's magical mysteries has been easy to unravel. Until recently, the brain was regarded as a black box whose secrets were frustratingly secure from reach.

Now, an explosion of discoveries in genetics and molecular biology, combined with dramatic new imaging technologies, have pried open the lid and allowed scientists to peek inside. The result is a growing understanding of what can go wrong in the brain, which raises new possibilities for identifying, treating, and perhaps ultimately preventing devastating conditions such as Alzheimer's disease or stroke.

"The laboratory bench is closer to the hospital bed than it has ever been," said neurobiologist Gerald Fischbach, chairman of neurobiology at Harvard Medical School, where the brain and its molecular makeup are a primary focus of research.

One important challenge is to understand the healthy brain. By studying brain cells and the genetic material inside them, scientists are discovering how groups of specialized cells interact to produce memory, language, sensory perception, emotion, and other complex phenomena. Figuring out how the healthy brain goes about its business is an essential platform that researchers need in order to comprehend what goes wrong when a neurological disease strikes.

There have also been great strides toward elucidating some of the common brain disorders that rob people of memory, mobility, and the ability to enjoy life. The most promising of these fall into several broad categories.

- The discovery of disease-producing genetic mutations has made it possible not only to diagnose inherited disorders, but in cases such as Huntington's disease, to predict who will develop them. These findings have also pointed the way toward new therapies.
- Insights into the programmed death of nerve cells may lead to drugs that can halt the progression of degenerative diseases or contain stroke damage.
- Naturally occurring chemicals that protect nerve cells from environmental assaults may hold clues about preventing disease or reversing neurologic injury.
- Information about brain chemistry's role in mood and mental health has already helped people burdened by depression, for example, and is expected to benefit others as well.

Genetics opens a new door

Discovering a gene associated with a disease is like unlocking a storehouse of knowledge. Once researchers have such a gene, they may be able to insert it into experimental systems such as cell cultures or laboratory animals. This makes it easier to discern the basic mechanisms of the disorder, which in turn helps scientists figure out what diagnostic tests or therapies might be best. When a new treatment is proposed, genetically engineered models of human diseases make testing quicker and more efficient.

In recent years, scientists have found abnormal genes associated with Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), one form of epilepsy, Tay-Sachs disease, two types of muscular dystrophy, and several lesser-known neurological conditions.

A decade-long search for the HD gene ended in 1993, when Harvard researchers Marcy MacDonald and James Gusella, working with scientists at other institutions, identified a sequence of DNA that produces symptoms of the disease if it is repeated enough times. Huntington's is a progressive and ultimately fatal hereditary disorder that affects about 25,000 people in the United States. It typically strikes at midlife, and the researchers discovered that the more copies of the sequence a person inherited, the earlier symptoms show up.

Scientists quickly developed a highly reliable assay that enables people with a family history of HD to find out if they or their unborn fetus harbors the dangerous mutation. But because no cure for the disease exists, few people have rushed to have themselves tested.

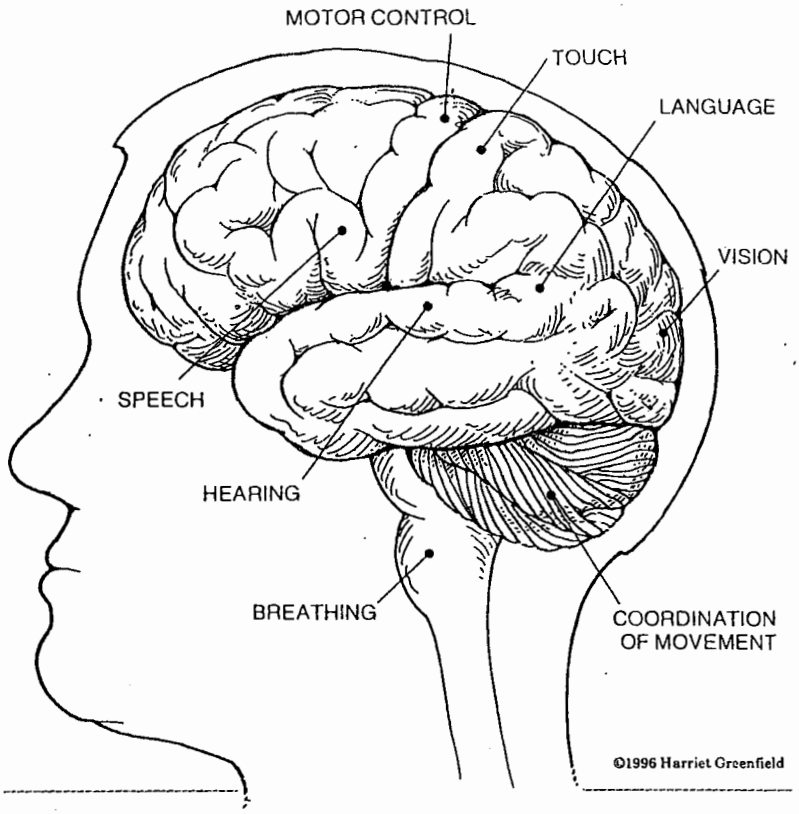
Demand might increase, however, if scientists can use the HD gene to design effective treatments. Genes contain the assembly instructions for proteins, the molecules that carry out the day-to-day operations of the body. Scientists strive to identify the protein made by a disease-producing gene and to figure out what it does, which in turn helps them understand the event that initiates the disease process.

The HD gene codes for a protein that appears to contribute to the premature death of certain neurons. It is the loss of these cells that results in the involuntary movements and mental deterioration typical of Huntington's. When researchers know more about this protein, they may be able to develop drugs or other therapies that could slow the onset of symptoms or even block them entirely.

A downward spiral

The gradual extinction of certain brain cells is also the underlying cause of Alzheimer's disease. In this case, the impact is progressive loss of memory, changes in personality, loss of impulse control, and deterioration in reasoning power. Under the microscope, the brains of people who died with AD are studded with abnormalities called amyloid plaques and neurofibrillary tangles. About 20% of all AD cases are inherited, and these people develop symptoms earlier in life than those with the more common form, which typically appears well after age 65.

In recent years, scientists have discovered several different genetic mutations that can cause the unusual, inherited form of AD. One of these abnormal genes has successfully been introduced into mice by researchers at several pharmaceutical companies, and experts believe that this animal model will help them understand how all forms of the disease progress at the cellular and molecular level.



So far, it looks as though some of the animals' brains develop amyloid plaques like the ones that build up in humans. Long-standing doubt about whether plaques cause symptoms may be resolved by future observations of whether these genetically engineered mice show signs of memory loss. If there is a strong correlation between amyloid accumulation and symptom severity, these mice will be used to test drugs that might keep plaques from forming.

The cell death story

Unlike other types of cells, nerve cells (neurons) are meant to last a lifetime because they can't reproduce themselves. Struck by the realization that abnormal cell death is the key factor in neurologic problems ranging from Alzheimer's to stroke, scientists have embarked on a crusade aimed at understanding why nerve cells die and how this might be prevented.

It's normal to lose some brain cells gradually. Trouble arises when a large population of cells dies all of a sudden, as in a stroke, or when too many of a certain type die over time, such as in Alzheimer's or Parkinson's (PD) disease. While

some scientists remain skeptical that inquiries into cell death will ever lead to effective means for preventing or treating neurodegenerative diseases, many others are enthusiastically pursuing this line of research.

Some scientists are racing to develop *neuroprotective* drugs that could guard brain cells against damage and death or even help them regenerate. There are many different ideas about how to do this.

For example, although Harvard scientists have identified the gene for HD and the protein it makes, they don't understand the mechanisms that lead to symptoms. One theory is that a phenomenon called *excitotoxicity* is responsible, and that Huntington's is only one of many diseases in which this process plays a role.

The idea behind excitotoxicity is that too much of a good thing is bad for cells. Glutamate, for example, is an ordinarily benign chemical messenger that stimulates certain routine cellular activities. Under extraordinary circumstances, however, "cells can be so excited by glutamate that they wear themselves out and die," said John Penney Jr., a neurologist at Massachusetts General Hospital and a Harvard professor of neurology.

Sending a signal

One of the many types of doorways built into the walls of nerve cells is a structure called an NMDA receptor. One of its functions is to allow small amounts of calcium (a substance usually shut out of the cell) to enter it. This happens when the NMDA receptor is stimulated by glutamate. If excess glutamate is present, too much calcium rushes in — an influx that is lethal to the cell.

Someday it may be possible to halt the advance of Huntington's by injecting drugs which block the NMDA receptor so that calcium can't get in. In animal experiments, scientists have demonstrated that such receptor-blocking agents can keep brain cells from dying. Harvard researchers are seeking approval for a clinical trial that will test such neuroprotective drugs in patients with symptomatic disease. If participants obtain any relief from this treatment, the next step will be to determine whether this approach can prevent symptoms in patients who have the gene but do not have symptoms.

Scientists also hope that neuroprotection can be used to limit brain damage due to stroke. When a stroke shuts down the supply of blood to part of the brain, neurons in the immediate area die within minutes. Over the next several hours, more distant cells in the region are killed as excitotoxic signals spread. In an effort to limit the extent of brain damage, researchers are currently treating small numbers of patients with intravenous doses of experimental agents such as NMDA receptor blockers and free radical scavengers. Other neuroprotective agents under development, include protease inhibitors, nitric oxide inhibitors, and nerve growth factors.

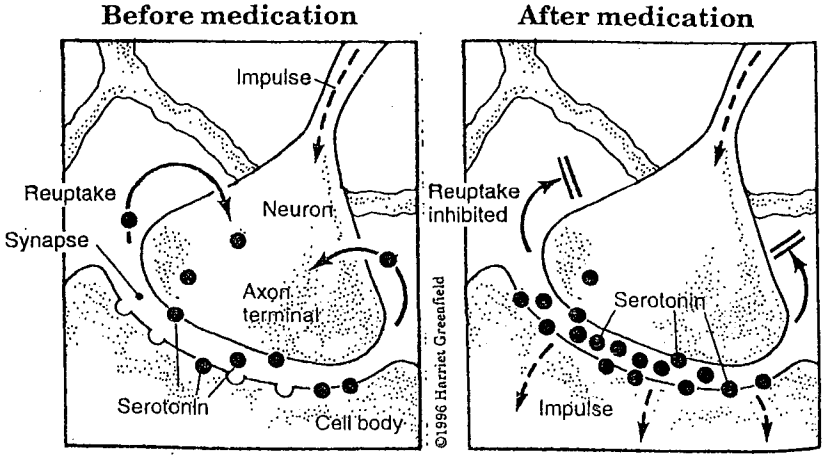
"Our dream is a safe and effective neuroprotectant that can be given to the stroke patient in the ambulance or shortly after arrival in the emergency room," said neurologist Seth Finklestein, an associate professor at Harvard Medical School who conducts basic research at Massachusetts General Hospital. "That's the holy grail of neuroprotective treatment."

Applications for Alzheimer's

Neuroprotection is also making waves in Alzheimer's research, as scientists strive to inhibit the type of cell death that typifies this disease. One group of investigators has identified several *peptides* (small protein molecules) that block the formation of amyloid plaque in the test tube, said neurobiologist Huntington Potter, an associate professor at Harvard Medical School. The researchers hope to test these peptides in humans.

Brain cells manufacture several neuroprotective chemicals on their own, which scientists call *neurotrophic* or nerve growth factors. These small proteins may hold the key to keeping cells alive even in the face of stroke, degenerative diseases, or even spinal cord injury.

Relieving Depression



People who are depressed have less of the neurotransmitter serotonin than those who aren't. In the picture on the left, the axon terminal of one nerve cell releases serotonin, which travels across the synapse and activates the cell body (receiving cell). Serotonin is then reabsorbed by the *sending cell*. On the right, a selective serotonin reuptake inhibitor (SSRI), such as the antidepressant Prozac, slows the reabsorption of serotonin, keeping it in the synapse longer and boosting its effect on the receiving cell.

For example, several different neurotrophic factors are being tested in the laboratory to determine if they could protect the dopamine-producing cells that die prematurely in people with Parkinson's disease. Other uses are being studied as well, and some researchers anticipate that these chemicals will be tested in humans before the decade draws to a close.

Mood, mind, and brain chemistry

Scientists have discovered that a surprising number of mental disorders, from depression to schizophrenia, are the result of brain chemistry gone awry. And this understanding has led them to design new medications for treating specific mental disorders and behavior problems.

The best known of this new breed of drugs is fluoxetine (Prozac), one of several selective serotonin reuptake inhibitors (SSRIs). It was possible to design these agents, which are widely prescribed to alleviate depression and related disorders, only after scientists came to understand how nerve cells communicate at the molecular level.

Each nerve cell has an *axon,* a long branch that reaches out and touches other nerve cells. A tiny space called a *synapse* separates the axon terminal (which sends a message) and the cell body (that receives it), and this is where the action is. The sending cell releases *neurotransmitters* (chemical messengers) into the synapse which either excite or inhibit a receiving cell that is equipped with the proper receptors. Messages pass from cell to cell in this manner, eventually leading to a physiologic action. In each synapse, the cell that sent the message sops up leftover neurotransmitters and stores them for future use. People who are depressed have less serotonin than those who aren't, and the SSRIs block the reuptake of this chemical, thereby boosting the effect of a small amount on the receiving cell. *(See illustration* "Relieving Depression.")

But Prozac and its relatives are only the tip of the iceberg. As researchers work to understand the roles of different chemical messengers and the highly specific receptors that bind them, a whole new approach to the treatment of mental disorders is evolving. The identification of highly specialized receptors is already paving the way for ever more specific drugs to treat these conditions.

Schizophrenia therapy is a case in point. As devastating as this form of mental illness is, treatments have sometimes appeared worse than the disease. Until very recently, the only drugs that relieved symptoms could also lead to spasmodic, uncontrollable movements known as *tardive dyskinesia.* This is because these agents block all types of receptors for dopamine, a neurotransmitter that is a key player in normal movement as well as in this mental disorder. Now there is a new drug for schizophrenia, clozapine, that blocks only a small subclass of dopamine receptors. It relieves symptoms of the illness in some people without leading to abnormal movements. Still, it can have other serious side effects.

Tailored to fit

The bottom line for the treatment of behavior and emotional disorders may be that drugs will become ever more specialized. Just as computers now help salespeople fit blue jeans to the individual purchasers, it is not inconceivable that psychopharmacologists may someday tailor drugs to the needs of each patient.

What does the future of brain research hold? Dr. Dowling anticipates that medications that can slow the process of degenerative disease, correct the chemical imbalances that cause mental disorders, prevent stroke damage, and repair spinal cord injuries may all be on the horizon. "We have learned so much about the cellular and molecular aspects of the brain," Dr. Dowling said. "We stand at a time of great opportunity, when we can take tremendous advantage of these things and turn them into practical clinical therapies."

— KATHLEEN CAHILL ALLISON