

THE OUTLOOK FOR THOSE WITH THE DEVASTATING DISORDER HUNTINGTON'S DISEASE IS IMPROVING. ALREADY THE DISCOVERY THAT A FAULTY VERSION OF A GENE CAUSES THE BRAIN AILMENT HAS LED TO THE DEVELOPMENT OF A DIRECT GENETIC TEST THAT CAN HELP CONFIRM A DIAGNOSIS. WHAT'S MORE, IT HAS HELPED REVEAL NEW INSIGHTS THAT ARE GENERATING EXCITEMENT FOR POSSIBLE FUTURE TREATMENTS. IN ONE LINE OF WORK, RESEARCHERS ARE DETERMINING HOW THE ABNORMAL GENE LEADS TO THE PROGRESSIVE DEGENERATION AND DEATH OF BRAIN CELLS THAT UNDERLIE THE DISORDER AND ARE FINDING WAYS TO SLOW THE PROCESS.

HUNTINGTON'S DISEASE

The man twists and thrashes about, perpetually in a fidgety, sometimes violent-looking, swirl of motion.

Drugs? Too many cocktails? Following one misunderstanding after another, a troubling reality comes to light. Huntington's disease.

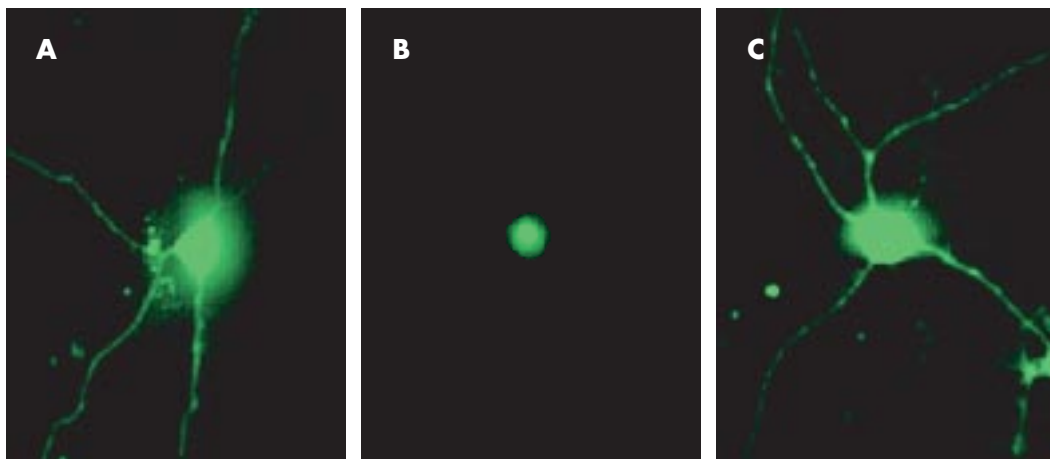
Once, this brain disorder was difficult to diagnose, never mind treat. Folk singer Woody Guthrie, for example, was considered an alcoholic for years before being properly diagnosed with Huntington's disease or HD, which can spur odd movements while it slowly robs a person's ability to walk, talk, think, and reason. But

now thanks to the 1993 discovery that a single abnormal gene produces HD, the outlook for the estimated 30,000 Americans living with the disorder is improving. Already the discovery has resulted in the development of a direct test that can help confirm a diagnosis. It's also propelled the study of new treatments. The advances stemming from the finding are leading to:

- A better understanding of how the disorder develops.
- The creation of new therapies that may be able to slow or possibly prevent the development of HD.
- Insight on how to treat related disorders that affect the

function of the brain and nervous system.

Our genes produce proteins that control brain development and function. In HD, however, a faulty version of a gene produces a flawed protein that somehow makes the system go awry. As a result, people that have the faulty gene experience cell damage and destruction in the brain's basal ganglia and cortex. This can affect coordination, thought, perception, and memory. Many experience involuntary movements of the arms, legs, body, and face. Often these symptoms are accompanied by mood swings, depression, irritability, slurred speech, and



▲ SOME WORK SUGGESTS THAT IN PEOPLE WITH HUNTINGTON'S DISEASE THE FAULTY HD GENE AND THE DEFECTIVE HD PROTEIN IT PRODUCES INTERFERE WITH PROCESSES THAT NORMALLY HELP CELLS SURVIVE IN THE BRAIN. ONE STUDY DEPICTED ABOVE FOUND THAT THE HD PROTEIN HIJACKS THE MOLECULE CREB BINDING PROTEIN (CBP), WHICH NORMALLY AIDS CELL SURVIVAL. IMAGE "A" SHOWS A NORMAL NERVE CELL. IMAGE "B" SHOWS A NERVE CELL INJECTED WITH GENETIC MATERIAL THAT PRODUCES THE DEFECTIVE HD PROTEIN. THE LACK OF THIN EXTENSIONS INDICATES THAT THE CELL IS DYING. IMAGE "C" SHOWS WHAT HAPPENS WHEN A VERSION OF CBP ALTERED TO RESIST THE NEGATIVE EFFECTS OF THE HD PROTEIN IS ADDED TO A CELL WITH THE HD GENETIC MATERIAL. THE ALTERED CBP CAN RESUME ITS PROTECTIVE ROLE AND ALLOWS THE NERVE CELL TO REMAIN HEALTHY.

IMAGES ABSTRACTED WITH PERMISSION FROM SCIENCE. 2001; VOLUME 291. FIGURE 4. NUCIFORA TC ET AL. COPYRIGHT 2006 AAAS.

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clumsiness. While the disease progresses, the afflicted can have problems swallowing, or experience loss of balance, impaired reasoning, and memory problems. Death is commonly caused by a complication of the disease such as choking, or an injury related to a fall.

Recently researchers have started to specifically determine how the abnormal HD gene leads to the degeneration and death of brain cells that characterize HD, which has opened doors for treatment development. For example, some work (see images) suggests that the defective protein produced by the HD gene interferes with additional types of gene activity that normally help cells survive, among other functions.

Scientists also found that drugs termed HDAC inhibitors appear to counteract these gene activity problems

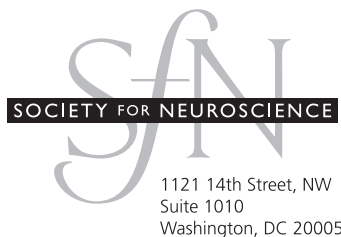
and have potential for aiding HD. First they tested the drugs in fruit flies that model HD. HD flies raised on food containing HDAC inhibitors had reduced levels of brain cell damage and lived longer than HD flies that didn't receive the drugs. Next, scientists found that HDAC inhibitors also produce positive results in mice that model HD. The drugs, for example, reduced brain cell damage and improved movement abilities. Currently researchers are testing an HDAC inhibitor in about 60 patients with HD.

These drugs also may aid other disorders characterized by cell damage, such as the movement-impairing ailment, amyotrophic lateral sclerosis (ALS). Following positive results in ALS mice, researchers have started a study of an HDAC inhibitor in ALS patients.

Other researchers are testing a treatment technique, known as RNA interference, which could potentially target the abnormal HD gene directly. RNA interference straightjackets or "silences" select genes and reduces their problematic protein production. Recently researchers tested an RNA interference technique that targeted the abnormal human HD gene in a mouse line that models the disorder. They found that the technique prevents some of the physical symptoms and brain abnormalities caused by HD. Earlier work also shows that the RNA interference technique benefits mice with spinocerebellar ataxia, a disease caused by a similar type of abnormality.

These and other advances could improve care in the future and help patients live a longer, healthier life.

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