

brain

BRIEFINGS

MARCH 2002

THE CAUSE OF A GROUP OF BRAIN-ATTACKING DISEASES, KNOWN AS SPONGIFORM ENCEPHALOPATHIES, WAS ONCE A MYSTERY. RESEARCHERS SPENT YEARS TO NO AVAIL SEARCHING FOR A BACTERIUM, VIRUS OR OTHER TYPICAL DISEASE-CAUSING AGENT. NOW INCREASING RESEARCH POINTS TO AN UNUSUAL SUSPECT. MANY SCIENTISTS BELIEVE THAT A MERE PROTEIN, TERMED A PRION PROTEIN, IS BEHIND THESE DISEASES. THIS DISCOVERY IS HELPING RESEARCHERS GET CLOSER TO DEVELOPING TREATMENTS FOR THOSE WITH THE FATAL AILMENTS.

PRION PROTEINS

You open the tainted mail and inhale bacterial spores. Soon flu-like symptoms and breathing problems erupt. It's anthrax.

The bacteria behind the anthrax disease, as well as the smallpox virus and plague bacteria, for example, use nucleic acid to take hold of your body. This genetic material carries special codes that allow the microbes to replicate and create overpowering troops that swarm, attack and launch illness.

For years, scientists firmly believed that all infectious agents had to contain the nucleic acid replicating machines to trigger disease. But now mounting evidence debunks this dogma. An abnormal form of a simple protein that is free of nucleic acid—termed a prion protein—appears to cause a group of related diseases that affect humans and some other mammals. Known as spongiform encephalopathies (SE), these untreatable ailments, including Creutzfeldt-Jakob disease, mad cow disease and scrapie, leave the victim's brain pocked with holes, typically causing dementia and eventually death.

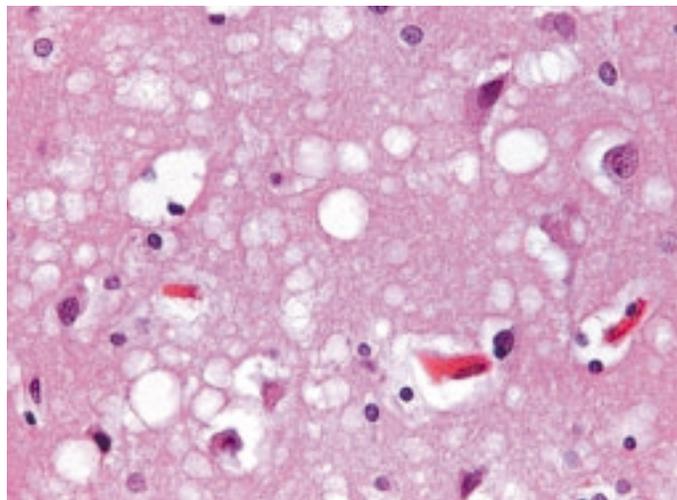
This new focus on the proteins is leading to:

- Fresh views on how disease emerges.
- Innovative treatment ideas.

People can acquire the well-known, yet rare SE, Creutzfeldt-Jakob disease, through both infectious and noninfectious routes. Exposure to infected human nervous system tissue during certain medical procedures can produce the disease. Most frequently, Creutzfeldt-Jakob

disease erupts spontaneously, with no detectable cause. Less frequently, it results from inheriting a faulty prion protein gene. Another form, variant Creutzfeldt-Jakob disease, recently emerged in Great Britain. It's creating great concern because some suspect that you can catch it by eating meat contaminated with infected nervous system tissue from cows with the cattle SE, mad cow disease. So far, it has killed approximately 100

▼ THE SWISS-CHEESE HOLES DEPICTED IN THIS SAMPLE OF BRAIN TISSUE FROM A PATIENT WITH CREUTZFELDT-JAKOB DISEASE ARE A TELL-TALE SIGN OF SPONGIFORM ENCEPHALOPATHY. IT APPEARS THAT ABNORMALLY SHAPED PRION PROTEINS ENTER THE BRAIN EITHER FROM EXPOSURE TO INFECTED TISSUE, OR FROM NON-INFECTIOUS ROUTES, SUCH AS BY INHERITING A FAULTY PRION PROTEIN GENE FROM A FAMILY MEMBER. THEN THEY CONVERT NORMAL VERSIONS OF THE PROTEIN, WHICH NATURALLY EXIST IN THE BRAIN, INTO THE PATHOLOGICAL FORM. THE PATHOLOGICAL PROTEINS SEEM TO CREATE AN AVALANCHE OF DESTRUCTION. HOLES OCCUR IN REGIONS WHERE BRAIN CELLS COMMUNICATE WITH EACH OTHER. THIS DISRUPTS INFORMATION TRANSFER BETWEEN THE CELLS, WHICH ULTIMATELY CAUSES BRAIN CELL DEATH AND THE END OF LIFE.



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people. Fortunately, findings on prion proteins provide a better understanding of these ailments and may provide some relief.

In 1982 researchers discovered prion proteins in brains infected with scrapie, an SE that occurs in goats and sheep. Since that time, studies that extend to a variety of SEs led many to blame abnormally shaped prion proteins as the triggering agent. It's thought that these proteins can appear in the central nervous system and convert naturally existing, normal forms of prion protein into a pathological form (see image).

Among other work, experiments designed to be free of contaminants, such as a virus or other typical infectious agent, back the protein trigger theory. In one, researchers found that under specific chemical conditions they could

get a normal form of the protein to convert itself into the abnormal form tied to disease. Other scientists believe they created a SE disease in certain mice by injecting them with a synthetic abnormal prion protein developed in a contaminant-free environment. Diseased tissue from these rodents also infected other mice, according to preliminary work.

While some still suspect that a stealth virus or other agent with nucleic acid is the real transporter of infection, it's clear that prion proteins at least play a major role in SEs. Therefore, many scientists are testing ways to target the protein and treat disease.

Quinacrine, one investigative treatment for Creutzfeldt-Jakob disease, will soon be tested in a human clinical trial. Some earlier work showed that quinacrine, which has been used for years to

treat malaria, and chlorpromazine, an antipsychotic drug, seemed to clear the abnormal form of the prion protein from infected cell samples through an unknown mechanism.

Other researchers are testing molecules that specifically target the prion conversion process. One method attacks the chemical structure of abnormal prion proteins and has some success in transforming them back into healthy forms, according to cell studies. The technique also delayed the appearance of symptoms in mice infected with scrapie.

In addition, scientists have developed attacking proteins, known as antibodies, which zone in on prions and prevent the conversion process in cell studies. They also rid infected samples of abnormal prion proteins. Next, the researchers plan to test the antibodies in animals.

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