

Copper Could Be the Culprit in Brain Disease

by Jamie DeSoto

Prion diseases are a terrible death sentence. When people become infected by one of these neurodegenerative diseases, they often die within a year. Along the way, dementia destroys their brain. Patients lose their memory, their personality, and their ability to speak or walk. To make matters worse, their own body is to blame.

Prion diseases do not arise from a virus or bacteria, like many other infections. Instead, they are caused by special proteins in the brain called prion proteins. While everyone has these proteins, those in a person with a prion disease are misshapen and can't perform normally. The real danger is that all it takes is one misshapen protein to switch normal prion proteins to the infectious shape. As the abnormal proteins multiply, they begin to destroy the brain.

Neuroscientists know little about how these proteins create holes in the brain, making treatment almost impossible. Biochemist Glenn Millhauser and his team at UC Santa Cruz are working to discover what makes these proteins go haywire. They are looking at what might trigger the shape change, and how such a small difference in the prion protein can have such a disastrous effect. They recently discovered an apparent role for copper in certain neurodegenerative diseases.

A diagnosis of prion disease or any other neurodegenerative disease, such as Alzheimer's or Parkinson's, leaves little hope for patients. "With cancer, you hear about people getting chemotherapy, radiation therapy, or cancer going into remission," Millhauser says. "With neurodegenerative diseases, there is no remission. Nobody ever gets better. The disease may slow for a period of time, but it is a one-directional disease: It only gets worse."

There are several types of prion diseases. Most cases are sporadic, where a prion protein randomly mutates and then changes the shape of normal prion proteins. Smaller numbers of people inherit the misshapen proteins from their parents. Prion diseases are different from other neurodegenerative infections in that they can also be "caught" by another individual. However, it takes more than a sneeze. One of the misshapen proteins must travel almost directly from one organ into another, which can occur through contaminated surgical instruments or by eating infected meat.

Although they are rare, widespread prion infections are devastating. The first human neurodegenerative epidemic was a prion disease called Kuru. In the 1920s,

one out of every ten members of the Fore tribe in Papua New Guinea was killed by this disease. Each body was then eaten by the other members in tribal rituals. The prion disease spread through this cannibalism. Only when the missionaries and medical researchers living among the Fore people forbade them from eating their members did the scourge stop spreading.

Mad Cow is another type of prion disease, affecting domestic cattle. As was evident from the recall of European beef from supermarkets in 1989, transmission of prion diseases can cross among species. With so little known about these infections, health officials take no chances. Individuals who lived in areas with Mad Cow outbreaks, whether they ate beef or not, are still not allowed to donate blood two decades later. All it would take is for one misshapen protein to sneak by, and the disease could find another human host.

Scientists such as Millhauser believe that a deeper knowledge of prion proteins will ease these fears. While studying a rare, inherited form of the common Creutzfeldt-Jakob prion disease, the Millhauser research team discovered a connection between copper in the brain and prion diseases.

Copper is a vital part of proteins in the brain. It latches onto oxygen molecules like Velcro, bringing them to the proteins that need oxygen. Too much copper, on the other hand, can poison the cells. Regulation is needed to keep copper levels in the brain at a steady, healthy level.

Normal prion proteins are in charge of this copper control. The healthy prion proteins grab more copper when the concentration of copper in cells is higher, to keep it below toxic levels. However, when the protein is misshapen as in prion diseases, it doesn't pick up the extra copper.

"Part of the problem is that we just don't have a good understanding of metal ions in the brain," says Millhauser. "They are essential for brain function, but regulation is essential for brain's integrity." With the knowledge that prion proteins help take in copper, the team began to wonder why the misshapen disease proteins can't perform that task.

Prion proteins have an arm-like extension that appears to grab copper and give it to nerve cells in the brain. This arm is made of repeating protein sections, and the length of the arm changes depending on the number of repeats. Each individual repeat is made up of eight segments, giving the pieces the name of octarepeats. The number of repeats varies among individuals. In this rare disease, a prion protein containing more than four octarepeats is misshapen, and the longer arm

cannot snatch up copper as well. Without copper, the needed oxygen cannot be picked up; the free oxygen can then produce compounds toxic to nerve cells.

Prion proteins with more than four octarepeats are rare, but their presence in the form of Creutzfeldt-Jakob disease studied by Millhauser revealed a linkage between copper and prion disease. As the number of repeats increases, people begin to show disease symptoms at younger ages. The average age for first symptoms in someone with five to seven repeats is 64, while the age drops to 34 for people with more than eight repeats. Millhauser's research team reviewed data about the disease in a small sample of about 108 individuals and 30 families to discover this surprising and disheartening correlation.

"Individuals that have four repeats, they're fine," Millhauser says. "Individuals that have five, six, seven repeats all have a high probability of having the prion disease. At eight repeats, something happens. You get a prion disease, but instead of getting it in your 60s, 70s or 80s, as is typical, you get it in your 20s, 30s, or 40s. There's a shift of about three decades of life, which is very substantial."

Although this research is still in early stages, the findings suggest that one day a diseased person could gain decades of life by removing several octarepeats, restoring the ability to pick up copper. However, treatment would have to remove the repeats in every prion protein floating around the body. If one misshapen protein was left behind, it could create hundreds more. It seems impossible that a treatment could guarantee 100% removal of the extra octarepeats.

The research team also understands that the extra octarepeats on the prion protein arm may not be the only cause of the disease. Future research could uncover other players in prion diseases that could complicate treatments—or lead to new ones. While these therapies are decades away, any new understanding of prion diseases, such as the role of copper, provides promise for the future.

Millhauser has worked on prion diseases for more than a decade. He was first introduced to neurodegenerative diseases while researching a misshapen protein involved in Alzheimer's. He switched projects when a colleague informed him of the advances being made in prion diseases. While it seems that prion disease research has created more questions than it has answered, he remains motivated. "Once you start working on prions, it's hard to give it up," he says. "It is so interesting, and there are so many unknowns dealing with neurodegenerative disease. It is very engaging work."

His lab group is now working on several prion disease projects. One is to obtain a more global understanding of the role of the normal prion protein in the brain. Another is to discover the specific role of metal ions in neurodegenerative diseases. His current hypothesis is that the inability of the misshapen prion protein to pick up copper allows these toxic nutrients to poison the brain. While his recent research supports this hypothesis, Millhauser's colleagues admit they still know little about how the brain works.

The brain is the most difficult organ to study. Like other neurodegenerative disorders, prion diseases remain mostly a mystery. As researchers painstakingly uncover more details, thinking of the people suffering from prion diseases drives them forward. Says Millhauser: "I don't even think we are at the dawn of understanding these diseases, and they are only going to become more prevalent as our society gets older."

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Jamie DeSoto, who recently earned a B.S. in biochemistry and molecular biology, wrote this article in spring 2009 for SCIC 160: Introduction to Science Writing.