Polluted blood fails to deliver infection

Prions, the cause of mad cow disease and related illnesses, cannot dock easily on the shores of the brain. Like passengers stuck on a large ocean liner in a rocky lagoon, they need a landing vehicle, new research suggests.

Although the chemical nature of prions and the method by which they produce disease remain controversial (SN: 9/24/94, p. 202), a molecule called prion protein (PrP) plays a central role. It exists in several versions, only some of which provoke trouble.

Healthy people carry normal PrP molecules on nerve cells but can acquire deviant ones by ingesting tainted meat. The infectious agent travels to the brain, where it inflicts its hallmark damage—transforming this organ into a hole-ridden sponge.

Although scientists have known that the agents of destruction must spread from the gut to the central nervous system, the details of this journey remained vague. Now researchers have discovered that the infectious material must make several connections. They report that prions cruise around the body in blood cells, but these vehicles cannot deliver them directly to the brain. Adriano Aguzzi of the University of Zurich and his colleagues describe their work in the Sept. 4 NATURE.

One current hypothesis holds that when a person or animal acquires an altered form of PrP, the misbehaving protein causes even normal PrP molecules to glom on to each other, thereby wreaking havoc in nerve cells. In fact, to succumb to disease, animals must have normal PrP in their cells: Mice engineered to lack these proteins resist infection.

"It's like dominoes," says Aguzzi. "You throw the first one over and they go thk, thk, thk along the surface of nerve cells." Cells that don't contain normal PrP break the link in the infectious chain of events, he says.

To examine that chain, Aguzzi's group in previous work implanted a piece of brain containing normal PrP into the head of a mouse that lacks PrP. Infectious material caused damage to the implanted tissue only when the researchers delivered the agent directly to the brain. When injected into the bloodstream, the altered PrP caused no harm to the grafted tissue.

Scientists explained this result by saying that blood cells in these mice don't contain any normal PrP and therefore can't carry the infection to the brain, says Pierluigi Gambetti at Case Western Reserve University in Cleveland, who studies an inherited prion disease called fatal familial insomnia, which makes people unable to sleep and eventually causes death.

In the new study, the researchers replaced the bone marrow of mice that lack PrP with bone marrow containing normal PrP. They then injected infectious material into the mice, expecting that the blood cells, now equipped with PrP, would convey the infection to the brain. Instead, the graft remained healthy—even though the corrupt protein converted normal PrP to the altered form inside blood cells.

"The big happening is what did not happen," says Gambetti. "The animals did not get infected, even with abnormal prions running around in the blood."

The investigators concluded that, to complete the link with the brain, some other tissue needs to produce PrP.

"This is good news because it means that prions stay where they are unless there are PrP-expressing cells that pick them up and move them around," says Aguzzi. "I'd like to identify the bottleneck and do something to block it [in people exposed to prions]."

Other groups have also attempted to trace infectious prions through the body. Their results point to the peripheral nerve cells, those outside the brain and spinal cord, says Aguzzi. Prions may require normal PrP in these cells in order to migrate to the brain.

In his efforts to devise therapeutic interventions, Aguzzi is focusing on the blood cells that harbor infectious PrP. In principle, people who have eaten contaminated meat could take drugs that attack these cells. Researchers have not yet identified which of the many types of blood cells carry the agent.

"There's a tremendously long incubation period between ingestion and brain infection—possibly even 20 or 30 years," says Aguzzi. "We have a window of opportunity during that time."

—E. Strauss

New tools for muscular dystrophy research

Years of telethons have painted an indelible image of the debilitating effects of muscular dystrophy. The most common form, Duchenne muscular dystrophy, strikes about 1 in 3,500 boys, first wasting their muscles and then killing them in early adulthood. These youngsters lack dystrophin, a muscle protein that acts as scaffolding for muscle fibers.

The identification of dystrophin in 1987 led quickly to the idea of treating the disease by injecting dystrophin-producing cells into diseased muscles. But that strategy hasn't worked. Muscle cells grown from tissue samples taken from healthy parents of muscular dystrophy patients haven't helped the patients' musculature.

The dystrophin-rich muscle cells seem to vanish, although they are not usually attacked by the recipient's immune system. "You inject a million cells, and 95 percent are gone in the first day," says Louis M. Kunkel of the Howard Hughes Medical Institute at Children's Hospital in Boston. Now, however, he and his collaborators have learned that the remaining injected cells were still in place up to 6 months later. What's more, their genes hadn't been silenced. Some of the cells were producing dystrophin, reviving hope for the cell-transplant approach.

The researchers used a technique that combined traditional tissue analysis with a complex series of chemical treatments to reanalyze muscle tissue taken from six muscular dystrophy patients 1 month and 6 months after they had been injected with muscle cells from a healthy parent.

The new technique, developed by Emanuela Gussoni of Children's Hospital, located up to 14 times as many transplanted cells as had been previously detected in this same tissue. Of the cells injected, 5 percent had survived and half of those were producing dystrophin. The patients, however, hadn't regained use of the muscles.

Before Gussoni devised the method, "we didn't have a way of following donor nuclei at the cell level," says study coauthor Helen M. Blau, a molecular pharmacologist at Stanford University School of Medicine. The findings appear in the September NATURE MEDICINE.

The greatest number of donor cells persisted in the healthiest tissue, suggesting that younger patients might benefit most from such cell transplantation, Blau says.

Kunkel believes that better purification of the donor cells may enable more to survive in the patient. Studies in mice lacking the dystrophin gene have shown that to keep the muscle from degenerating, cell injections must result in 10 percent of the donor cells producing dystrophin. "The assumption is, that's true for humans, too," Kunkel says.

Meanwhile, two teams of researchers—at Washington University School of Medicine in St. Louis and at the University of Oxford in England—report in the Aug. 22 CELL that for the first time they have bred mice with the symptoms of Duchenne muscular dystrophy. Previous attempts to use mice as models for the disease had left researchers baffled because a lack of dystrophin didn't seem to hinder the rodents. Unlike humans, they appear to compensate with a related protein, utrophin.

Both groups have now produced mice that lack genes encoding dystrophin and utrophin, explains R. Mark Grady of Washington University, creating a model for scientists to study. "You can use them to try therapies that you wouldn't want to try out on children," such as gene therapy and strong drugs. *—N. Seppa*