tribal elders or priests were allowed.

Such a transformation could not have been undertaken lightly. Patton cites estimates that at La Hougue Bie, 200 people would have been needed to move just the largest stone involved in construction of the tomb. This amount of labor devoted to an activity not involved with subsistence tells us a great deal about the life of the community, he notes. "We tend to imagine that Neolithic people were scraping a bare living from the earth," Patton says. "But I suspect life here was actually pretty good. I think they might have been living on lobsters and oysters and all kinds of things that we pay a lot of money for."

But if Neolithic life was relatively comfortable and organized, then an even greater puzzle remains: Why, after the mammoth effort of construction, were the monuments deliberately sealed up and abandoned? In the past, many prehistorians assumed that the Neolithic farmers sealed up the tombs to protect their dead from Bronze Age peoples who moved into the area and eventually displaced the original communities. Patton argues, however, that accurate radiocarbon dating indicates that many of the tombs were abandoned well before the Bronze Age began. He proposes that the decline of megalithic tombs corresponded with a breakdown in the stratified social structure they represented—possibly because the tribal elders were replaced by a new elite whose status depended more upon accumulated wealth than ancestral lineage. Kinnes takes a somewhat different view. He cites ambiguous but intriguing evidence that abrupt climatic changes and warfare between competing groups also occurred around the time the megaliths were abandoned.

The monument at La Hougue Bie, with its excellent state of preservation, could help provide answers to many of these questions. Next summer, Patton is planning to extend his excavation at the site, exploring the area in front of the tomb entrance for evidence of religious activities that might have taken place outside the tomb, such as ritual fires and perhaps even additional burials. Although access to the inner chamber is thought to have been restricted to a small group of elders or priests, he and other archeologists have become increasingly curious about what role the less-exalted members of Neolithic societies might have played. Patton is enthusiastic about the prospects: The new wave of excavations is "for the first time providing the material evidence on which we can base these [new] interpretations. And I suspect that over the next 5 or 6 years, this will form the basis of what is debated within the field."

–Michael Balter

Michael Balter is a science journalist based in Paris.

NEUROBIOLOGY

London Meeting Explores The Ins and Outs of Prions

A decade ago, neurologist Stanley Prusiner made a proposal that was nothing short of heresy in the world of infectious disease research. Prusiner was studying a neurodegenerative disease of sheep, known as scrapie, that had puzzled scientists for more than two centuries. While there was good evidence that scrapie could be transmitted from animal to animal, presumably by a virus, nobody had ever been able to get their hands on the putative infectious agent. Prusiner's heretical suggestion: scrapie was caused instead by something he called a "prion"—an infectious particle made up of proteins, needing no nucleic acid for its activity.

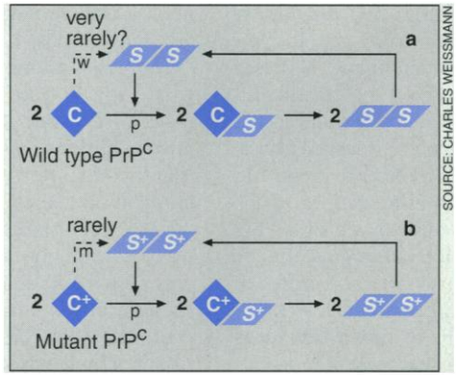
At the time, such a thing was unknown and, in fact, it was assumed that no infectious particle could do without nucleic acids to provide a blueprint for its replication. As a result, Prusiner's suggestion met with skepticism, if not out-and-out derision. Since then, however, Prusiner's group, as well as several others, have produced a growing body of evidence to support his challenge to orthodoxy.

What's more, prions may cause at least three rare human neurodegenerative conditions, as well as bovine spongiform encephalopathy, or BSE, also known as "mad cow disease," which caused a stir when it turned up in England in 1986, because of worries that it might be transmitted to people who ate the meat from infected cows. Indeed, prion research has gained sufficient credibility that last month the Royal Society in London was able to devote a 2-day meeting to it, with most participants presenting evidence in favor of the idea that the protein particles can cause neurodegenerative diseases of both animals and humans. "The weight of the evidence is quite heavily in favor of the prion hypothesis," says Charles Weissmann of the University of Zurich, who co-organized the meeting with John Collinge of St. Mary's Hospital Medical School in London.

Weissmann nonetheless notes that the case for the prion hypothesis is not air-tight. The strongest evidence against it at the moment, he says, is the existence of different "strains" of these agents, each of which causes a different range of disease characteristics when injected into mouse brains. Researchers are hopeful, however, that whether Prusiner proves right or wrong, the work may lead to drug therapies for the human dementias that have been linked to prions.

Although Prusiner, whose lab is at the University of California, San Francisco, has been the driving force behind much of the work that's earned prions their current respectability, the idea that the scrapie agent might be something as unconventional as a nucleic acid-free protein particle actually dates back to a suggestion made in the late 1960s by J. Griffith of Bedford College in London to help explain a problem with which scrapie researchers were then grappling.

Those researchers knew scrapie was transmissible, because when extracts from the brains of sick animals were injected into healthy animals, they caused the disease. But efforts to isolate a virus—or any other standard pathogen—were futile. And, in any case, if the scrapie agent were a virus it was going to have to be a very unusual virus, since treatments, such as exposure to ultraviolet light, that normally destroy nucleic acids and inactivate viruses had no effect on scrapie transmissibility. Therefore, it was necessary to look for something unconventional.



Bent out of shape. Scrapie prions (*above*) or mutants (*below*) may multiply by binding to and distorting the normal cellular protein.

In the early 1980s, Griffith's novel idea began to seem a little less fanciful when Prusiner and his colleagues purified from the brains of infected animals a protein that was apparently capable of transmitting scrapie on its own. What is more, the protein retained this ability despite all nucleic acid-destroying treatments. Proving that this prion, as Prusiner called it, was totally free of nucleic acid was very difficult—like proving any other scientific negative—and acceptance of the radical idea came slowly.

Then, in the mid-1980s, the idea moved closer to its current respectability, when Weissmann's group, working with that of Lee Hood, then at the California Institute of

Technology, cloned the gene for the protein Prusiner had purified. "They found that the gene coded for a normal cellular protein, even though at that time everyone thought it must be a viral encoded protein," says Collinge. (Prusiner himself does not give interviews to the press.) There are as yet few clues about what that the proteins's function might be, although it is known that the gene is particularly active in the brain.

Cloning of the prion gene paved the way for further discoveries. The human dementia Creutzfeldt-Jakob disease (CJD) resembles scrapie in many ways, an indication that they may have a common cause. The brain changes in both are similar, for example. But in addition to possibly being caused by environmental factors, CJD also exists in a hereditary form. And about 3 years ago, several groups, including Prusiner's, linked specific mutations in the prion gene to hereditary CJD and also to another inherited human dementia called Gerstmann-Sträussler-Scheinken syndrome (GSS).

Although the linkage studies suggested that the prion gene mutations cause the dementias, they didn't prove it. But Prusiner and his colleagues provided more direct evidence by transplanting a prion gene with the GSS mutation into mice. The animals developed pathological symptoms similar to those of the human patients (*Science*, 14 December 1990, p. 1509). In addition, when Prusiner's team inoculated normal mice with brain homogenates from the transgenic mice, they, too, fell sick. "This shows that you can produce an infectious disease by altering the mouse prion protein. It is very strong evidence that the prion hypothesis is correct," Collinge says. "For many people, this was a key turning point in the prion versus virus argument."

But while that is strong evidence, it's not conclusive. And obstacles remain. The work on scrapie strains, for instance, puts a damper on the protein-only prion hypothesis. These strains have been identified by virtue of their different effects on genetically identical mice. Mice injected with one strain, for example, may take a long time to develop disease, while mice injected with another fall sick quickly. And the areas of the brain affected can also vary with the strain type. Moreover, each strain retains its own particular set of characteristics even when it is sequentially transmitted from one mouse to another.

To most biologists the stability of the strain characteristics would suggest that the information is encoded and maintained in a nucleic acid genome. "A strain has a set of characteristics, so it must carry some information with it that specifies those characteristics," says Moira Bruce, from the Institute for Animal Health in Edinburgh, who works on BSE. Indeed, Bruce's own presentation at the meeting shows that the characteristics of the agent causing BSE are remarkably stable.

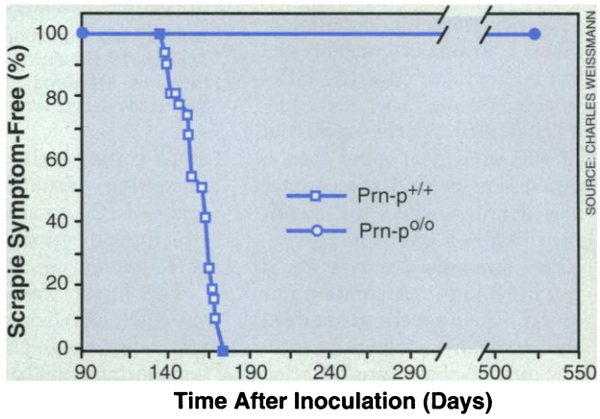
Bruce and her colleagues took brain homogenates from several cattle suffering from BSE (from widely spaced geographical locations), and from cats and two exotic ungulates (the kudu and nyala) that developed the equivalent disease after eating food containing the BSE agent. When the researchers then inoculated mice with the homogenates, the animals eventually developed disease, with incubation times and patterns of pathology that were, Bruce said, "strikingly similar" in each case.

Chris Bostock, head of the division of molecular biology of the Institute of Animal Health, which includes the AFRC/MRC Neuropathogenesis Unit where Bruce works, says: "Here you have PrP^{sc} from several different species going into mice and you get the same biological properties. I think the people who support the protein-only hypothesis will find it very difficult to explain that." Even Weissmann, who thinks the evidence favors the prion hypothesis agrees: "Her results demand a very satisfactory explanation. A very special effort will be needed in order to integrate them into the protein-only hypothesis." How that might be done is currently unclear.

But those who think the prion protein must be associated with nucleic acids have problems of their own. Despite searches that Weissmann describes as "extraordinarily thorough," only very small nucleic acids, which couldn't carry enough information to specify strain characteristics and are presumably contaminants, have been found associated with prions. Prusiner summed up his talk with an emphatic denial that scrapie and the other diseases are caused by a virus. "All the data taken together argue persuasively that prions lack a nucleic acid," he said.

But even if he's right, a big question remains to be answered: namely, how might prions, which can't reproduce like ordinary pathogens because they lack genetic material, produce disease? A possible solution comes from earlier observations in which the Prusiner group found that the scrapie-causing prions (designated PrP^{sc}), have an insoluble core that resists breakdown by protein-splitting enzymes. In contrast, the normal protein, designated PrP^{c} (for cellular prion protein) is completely broken down by the enzymes. What causes this physical difference is unclear, but it suggests a way that prions may "multiply" in the brain—by interacting with the normal prion protein and converting it into more PrP^{sc} by changing its three-dimensional shape, or conformation. Proteins are well known to induce such conformational changes in one another.

One of the predictions of this hypothesis is that an animal that lacks PrP^{c} wouldn't be susceptible to scrapie—a prediction borne out by a recent experiment by Weissmann and his colleagues. About 18 months ago, the Weissmann group, in collaboration with Prusiner's, used genetic engineering techniques to knock out the normal prion gene in mice, which contrary to everyone's expectations turned out to be completely healthy. In the more recent work, Weissmann group's injected the animals with PrP^{sc}. The animals remained healthy for over a year after inoculation with PrP^{sc}, he says, whereas normal mice would have fallen ill within about 120 days. What is more, homogenates of the brains of the knockout mice that had been given PrP^{sc} failed to make normal mice sick. This result indicates that the scrapie prion cannot propagate in the absence of the normal protein.



Winning by a knockout. Normal mice fall victim to scrapie, whereas the prion gene knockouts (*upper line*) resisted.

It may be possible to harness these findings to produce a drug therapy for the human diseases, researchers believe. Collinge says one approach may be to develop drugs that selectively bind to the abnormal form of the prion protein and thus halt the catalytic chain reaction. Whether this can be done remains to be seen, and meanwhile, the researchers would like to pin down the prion hypothesis once and for all. Collinge suggests a possible way to do this. The latest research suggests that PrP^{sc} is folded into a three-dimensional structure different from that of PrP^{c}. Collinge's idea is to synthesize PrP^{c} in the lab, then induce it to undergo the structural change and see if it acquires the ability to cause scrapie. That, everyone says, is the experiment waiting to be done.

–Sharon Kingman

Sharon Kingman is a free-lance writer based in London.