Thirty years after Stanley Prusiner identified a prion disease as the cause of death in a patient for the first time, scientists are still no closer to knowing the true biological nature of a prion or how it achieves its disease pathology at the molecular level. Yet, over this period, the stakes have been raised dramatically: prions are now known to pose a hitherto uncontemplated threat to public health. *Nature Medicine* spoke to prion expert Adriano Aguzzi about this area of biomedical investigation.

Adriano Aguzzi

According to Aguzzi, one of the most exciting aspects of science is that it is global, "Science was global before economy became global." Aguzzi, head of the Institute of Neuropathology at the University Hospital Zurich, is living proof of this statement. So far during his career, the Italian-born Aguzzi has worked in Germany, Austria, the United States, and Switzerland. Furthermore, the laboratories he runs are "international by design," hosting scientists from all over the world.

By contrast, Aguzzi's field of research has been restricted in geographical terms—at least until now. In the 1980s prion diseases, or transmissible spongiform encephalopathies (TSE), were widely believed to be the sole concern of the United Kingdom, which was battling bovine spongiform encephalopathy (BSE) in cattle. In recent years, however, continental Europe has been forced to acknowledge the existence of BSE within its borders, as has Japan; and the United States is also facing up to the presence of another prion disease, chronic wasting disease (CWD), within its shores (see page 1338).

Much of Aguzzi's recent work has focused on the means by which prions enter the central nervous system from the periphery, which he has shown to involve a period of lymphoreticular colonization resulting from lymphotoxin-β-dependent presentation of prions to follicular dendritic cells. "There has been an incredible shift in knowledge. Ten years ago, we thought there was no involvement of the immune system in prion diseases, and now we would argue that they are one of the best-understood paradigms for neuroimmunological contamination."

In addition to conducting basic research, Aguzzi's institute is also responsible for national surveillance of the human TSE, Creutzfeld-Jakob disease (CJD). Fortunately, he explains, Switzerland imposed a restriction on the human consumption of central nervous system tissue from cattle early on—something that other European countries did not do for many years despite BSE in the UK. "It's a horrible scandal that France, Italy, Germany, Spain and others waited until the first quarter of 2001 to ban the use of cow brain for human consumption because they claimed they didn't have BSE."

Although Switzerland has had no cases of new variant (nv) CJD—the strain caused by eating BSE-infected cattle—there has been a dramatic rise in cases of sporadic CJD in the country in recent years. "This went up last year by two-fold and this year by even more," Aguzzi says. "The reasons for this remain a mystery. We're researching the problem to see whether it is iatrogenic or related to prion diseases of farm animals." The rise is happening only in Switzerland, and Aguzzi's group has even carried out socioeconomic calculations to determine whether the explosion is due to increased spending on surveillance systems, which appears not to be the case.

International man of science

As for the rest of Europe, Aguzzi remains cautiously optimistic that the anticipated epidemic of nvCJD will not materialize. "Every day that passes without more cases being identified makes me feel that this will not be a problem on the scale that we had feared." But he is less confident about the reservoir of subclinically infected people. "I think the consequences will reverberate for the next 50 years because even if we get rid of BSE in cows completely within the next decade, those people who are infected run the risk of transmitting this to others. It's a long-term problem. Public health policy should be aimed at preventing human-to-human transmission, and so far we think that the vectors could be blood and blood products and implements for surgery."

As one of only a handful of expert scientists in this field, Aguzzi finds himself in increasing demand worldwide. He is presently a consultant to the US Institute of Medicine Committee on TSE, and is also hosting American researcher Christina Sigurdson from Fort Collins, Colorado, in his lab, where she will spend the next few years researching CWD (*Nature Med.*, **8**, 431; 2002).

Given the nature of his work, public relations is an integral part of Aguzzi's job. He received impromptu but in-depth training in this area four years ago when the Swiss populace held a referendum on the ethics and value of genetic research. "I ceased my scientific work for three months in order to campaign and educate the public, via the media, as to what medical research is and why it should not be prohibited." The public voted in favor of science, and Aguzzi is now proud to work in "the only country in the world in which biomedical research has been legitimized by a popular vote with an overwhelming majority."

Despite this, Aguzzi admits the Swiss may be falling behind in the field of molecular medicine (*Nature Med.*, **8**, 539; 2002), a position that was articulated acutely by this year's chemistry Nobel laureate, Kurt Wuthrich, who announced his retirement and move to the Scripps Institute in California. "The US has a wonderful culture of believing that science and knowledge is fundamental to the common good," says Aguzzi, "and a wonderful culture of philanthropy, where those who have earned big bucks feel they should give back to universities." He would love to see such a culture develop in Switzerland.

In the meantime, Aguzzi is enjoying his "well-functioning lab," and says he's having the time of his life. New projects focus on how and why prion protein damages the brain whereas accumulation of other proteins does not. "Most of the grants that I'm writing now center on this, because we can also learn things that apply to other neurodegenerative diseases such as the destruction by β-amyloid in Alzheimer disease and the accumulation of synuclein in Parkinson disease."

His team is also working on the related issue of elucidating the function of normal prion protein. "By knowing the role of the normal protein, we will understand what goes wrong in disease. Normal prions aren't there just to bestow the prion disease on us," he quips.

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