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BSE – virtually disappeared thanks to intensive research

Adriano Aguzzi: Prion research inconceivable without animal models

It began 25 years ago in the county of Kent, South East England. The veterinary practitioner Colin Whitaker was called to look at a sick and unusually jumpy and aggressive dairy cow. Attempts at treatment failed, and the animal eventually had to be put down. What began with a few cows in the county popularly known as the «Garden of England» soon spread to the rest of the United Kingdom – and later to an unparalleled epidemic with some cases also spreading beyond the national boundaries: in 1992, which marked the peak in the wave of disease, the UK authorities registered 37,280 animals affected by «mad cow disease», of bovine spongiform encephalopathy (BSE). Quick answers were need to some important questions: What triggered this hitherto unknown bovine disease? Was there any risk of infection for other animals and humans?

BSE battled successfully

In the meantime, BSE has long since disappeared from the headlines, because the situation has been substantially defused. In the past year, for example, there have only been 11 cases of BSE in Great Britain, 5 in France, 13 in Spain and no cases in Switzerland. BSE is under control and virtually eradicated from the livestock, says Adriano Aguzzi, Director of Switzerland's National Reference Center for Prion Diseases and Director of the Institute of Neuropathology at the University of Zurich.

«The reason for this success lies in the rapid and intensive work of the international scientific community, who quickly established, for example, that the disease was transmitted via contaminated animal meal», says Aguzzi. Feeding with animal meal was banned as early as July 1988, a measure that led to a marked decrease in the number of BSE cases a few years later. It also quickly became apparent that this new bovine disease was a chronic degenerative disease of the central nervous system, in which nerve cells are destroyed and typical sponge-like holes occur in the brain tissue, causing the conspicuous behavioral and locomotor disorders that always ran a fatal course.

BSE has long been a research topic

Unlike the general public, whose attention was aroused by the BSE epidemic, scientists had already been occupied with «spongiform encephalopathy» for many years before this. Apart from scrapie in sheep, which had been known for over 250 years, this group of diseases also includes kuru and the rare Creutzfeldt-Jakob disease in humans. The French veterinarians Jean Cuillé and Paul-Louis Chelle had already established in 1936 that these diseases can be transmitted from one individual to another. When they administered brain material from animals with scrapie to healthy sheep, these sheep likewise fell sick in the course of the next one to two years.

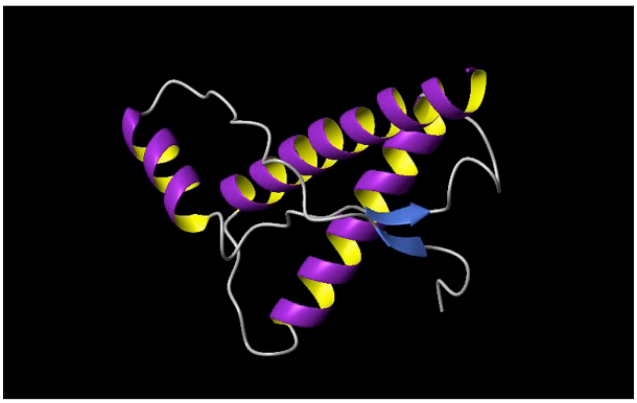

Fig. 1: The three dimensional structure of the intact bovine cellular prion protein

Researchers found themselves feeling around in the dark for many years in their search for the disease pathogen. It was mostly assumed to be due to a mysterious, slowly replicating virus. The crucial

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evidence on the nature of the pathogen was finally found in tissue samples from hamsters that were infected with scrapie. Here in 1982 the research team led by American scientist Stanley Prusiner discovered an unusually robust protein that not even «molecular cleavers» (proteases) could touch.

Misfolded proteins recognised as cause

As it was discovered a short time later, this «prion protein» derives from a cellular protein that is found on the surface of the nerve cells. It only differs from this protein in its three-dimensional structure. As a result of misfolding, the changed prion proteins are deposited in brain tissue as insoluble, rod-shaped particles, which clearly causes damage to the nerves. According to the «prion hypothesis», which is widely acknowledged today, the misfolded protein – which is transmitted from a diseased organism or is spontaneously formed in the body, for example, as a result of a genetic defect – «imprint» its faulty three-dimensional structure on the «healthy» prion proteins. This leads to a kind of domino effect in which eventually more and more modified proteins gather in the brain.

Today's generally accepted «prion hypothesis» is supported by numerous biochemical and genetic studies, such as the observation by Adriano Aguzzi and other scientists at the start of the 1990s: Mice genetically modified so that they lacked an endogenous prion protein did not fall sick when they were exposed to infectious brain material.

Further research still needed

Although the BSE epidemic has now been kept at bay, it still makes sense to continue prion research – for example in order to identify possible modes of transmission and diseases risks, for which experiments in live animals are indispensable. For example, a study carried out over a period of several years in scrapie sheep by Aguzzi's team recently showed that prions are passed on to the next generation in the milk, if the mammary gland of the mother animals are inflamed because of a virus infection. The possibility can therefore not be excluded that modified prion proteins could thus find their way into the food chain.

Successful tests on infected hamsters

There is also a need for action in the further development of diagnostics. The detection of a prion disease in humans and animals has so far only been reliable in brain tissue samples if symptoms are already present. Tests that can provide such evidence in blood samples of humans who do not yet show any symptoms of diseases are being called for with particular urgency in Great Britain. There may possibly be more people infected with changed prion proteins than the 200 or so people, mainly in Great Britain, who are affected by or have already died from a new form of Creutzfeldt-Jakob disease. Epidemiological studies and experiments in animal models strongly suggest that this new variant of CJD was caused by the consumption of food from animals with BSE. There are some highly promising approaches that, similar to the PCR method, for example, reproduce the changed prion proteins in the blood test and can thus raise them above the limit of detection. These approaches have already been successfully tested in infected hamsters.

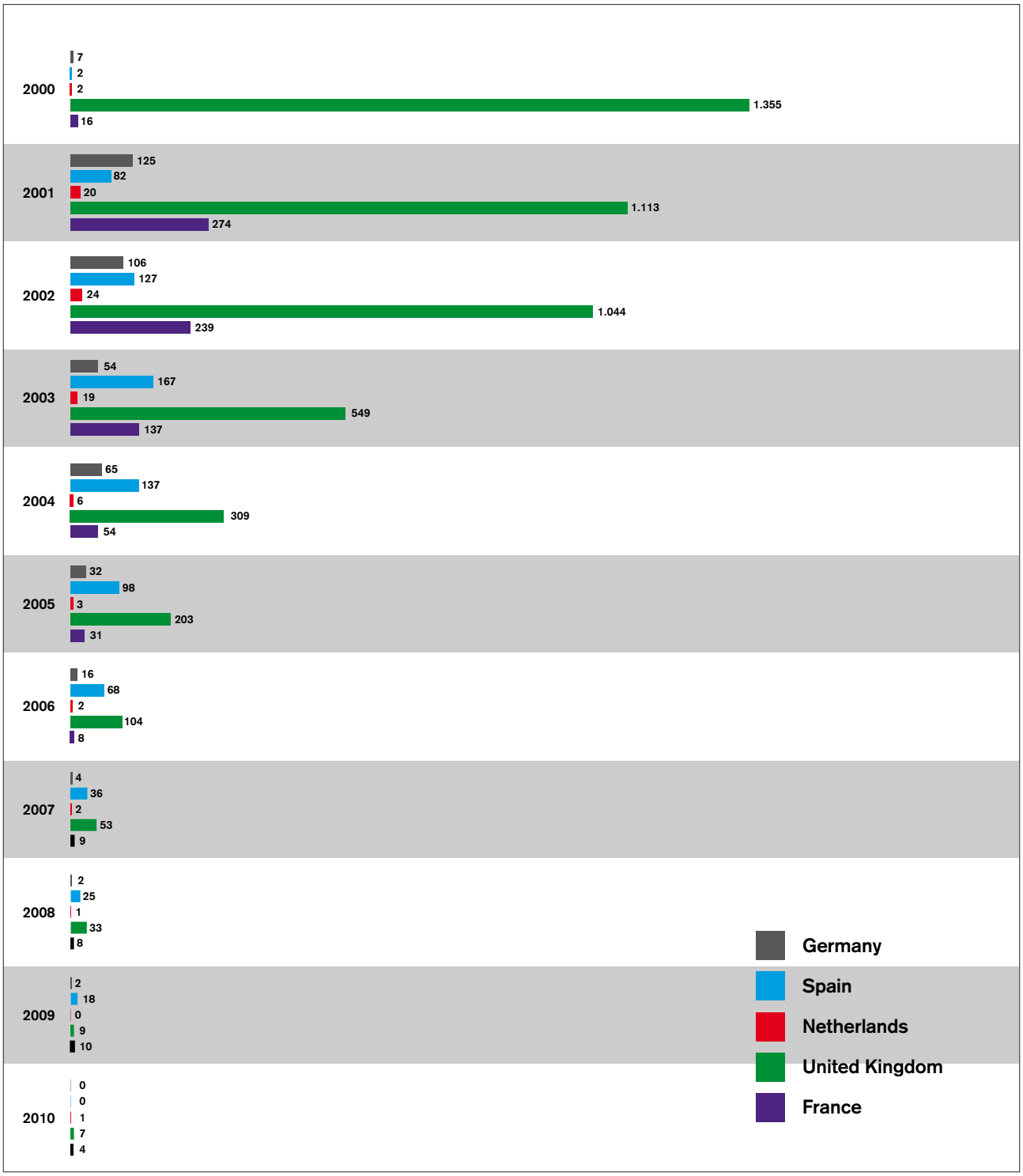

Fig. 2: Numbers of BSE cattle cases in selected European countries 2000 – 2010

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That fact that people are still becoming sick with CJD also motivates Adriano Aguzzi to continue with his prion research. «This is a rare but inexorably fatal disease that is a tragedy for patient and family members alike.» Studies in cell cultures, says Aguzzi, are extremely well suited to the discovery of substances, for example, that prevent the spread of changed prion proteins in the body. «But cells in culture do not suffer damage as a result of prion infection; so it is impossible to establish how the consequences of an infection are arrived at if we do not work with a complete animal», says Aguzzi.

To date it is still not known, for example, why it is precisely the prion proteins deposited in the brain that actually lead to the destruction of nerve cells. «Studies in animal models that explore this question could ultimately also help to better understand other more common diseases», says Aguzzi, since the clumping misfolded endogenous proteins in the course of the disease process is also a feature of Alzheimer's, Parkinson's and also type 2 diabetes. «We have very precise prion animal models here, with the help of which we can also carry out research on common diseases such as Alzheimer's », explains the Zurich researcher.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today, although researchers have for a long time conducted countless experiments with cells and tissues and, in the age of system biology, are also increasing our knowledge by means of computer simulation. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mausblick aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

IMPRESSUM

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