NEURODEGENERATION

Amyloid-β pathology induced in humans

People who died of the neurodegenerative condition Creutzfeldt–Jakob disease after treatment with cadaver-derived human growth hormone also developed some of the pathological traits of Alzheimer's disease. SEE LETTER P.247

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In the 1960s and '70s, researchers discovered that a rare but deadly human degenerative brain disorder called Creutzfeldt–Jakob disease (CJD) could be transmitted experimentally to animals and, under unusual circumstances, to other humans[1,2]. Since then, some have speculated that other neurodegenerative diseases might also be transmissible[1,3]. On page 247 of this issue, Jaunmuktane *et al.*[4] present evidence indicating that changes in the brain that are characteristic of Alzheimer's disease have been transmitted between humans. Transmission probably occurred through injections of contaminated, cadaver-derived human growth hormone (c-hGH) that was extracted from pituitary glands collected at autopsy.

Before 1985, an estimated 30,000 people — mostly children with growth deficiency — received injections of c-hGH (refs 2, 5). To obtain sufficient quantities of hormone for treatment, thousands of pituitary glands (a tissue found at the base of the brain) were pooled and homogenized, and c-hGH was then chemically extracted (Fig. 1). After disease incubation times ranging from 5 to more than 40 years, a small percentage of these people (up to 6.3%, according to country[2]) developed CJD. We now know that the CJD-causing contaminant in the pituitary extracts was the prion, a normally produced protein that becomes infectious and toxic by adopting an abnormal shape that similarly corrupts other prion proteins.

Another disease of protein misfolding — and the most prevalent form of dementia — is Alzheimer's disease[6]. The pathological hallmarks of the disease are insoluble aggregates of amyloid-β protein (Aβ) called plaques, which form between neurons; Aβ build-up in the blood vessels of the brain; and the abnormal deposition of tau protein in nerve cells (known as tauopathy). Several lines of evidence indicate that the misfolding and accumulation of Aβ is an early driver of Alzheimer's disease, and that this process precedes the onset of dementia by well over a decade[6]. But whether every person with extensive brain Aβ deposition will ultimately develop Alzheimer's disease is a focus of current research.

It is known that Aβ can aggregate in the brains of animals if their brains are injected with minute amounts of misfolded Aβ proteins known as seeds[7]. This indicates that Aβ deposition can be induced through a prion-like mechanism of corruptive protein templating[7]. By identifying a similar phenomenon in humans, Jaunmuktane and colleagues' study provides fresh support for this seeding concept in a clinically relevant setting.

The authors describe the findings of autopsies on 8 people who died of CJD at between 36 and 51 years of age, having been treated with c-hGH approximately 30 years earlier. In addition to the neurodegenerative changes typical of CJD, four of the subjects showed extensive Aβ deposition in the brain and two had sparse Aβ deposits. Such Alzheimer's-like changes are extremely rare at such a young age, and were not found in patients up to a decade older who died of prion diseases that were unrelated to c-hGH treatment. The authors also showed that the c-hGH-treated subjects did not have any of the known genetic risk factors for Alzheimer's disease. Moreover, they confirmed a previous report[8] that Aβ deposits occur in the pituitary glands of people with Alzheimer's disease, supporting the possibility that aggregates were induced by Aβ seeds in the c-hGH.

Although an observational study such as this cannot prove that the Aβ deposits in the patients' brains were caused by Aβ seeds, studies in genetically modified mice have established that aggregated Aβ can behave like prions[7,9]. Strikingly, when Aβ seeds were introduced into the abdomens of mice, rather than directly into the brain, Aβ deposition was more prominent in cerebral blood vessels than in Aβ plaques[10]. This finding mirrors the vascular Aβ accumulation observed by Jaunmuktane *et al.*, and reinforces the supposition that the Aβ seeds in the affected people travelled to the brain from elsewhere in the body.

How can future experiments strengthen the case for the prion-like seeding of Aβ in humans and better assess its implications? The original c-hGH extracts, if available, should be assessed for the presence of Aβ seeds using biochemical and animal-transmission experiments. Although age-matched control patients who died of prion disease had a much lower incidence of Aβ deposits than did the patients who died of CJD following c-hGH treatment, there remains a possibility that CJD itself can precipitate Alzheimer's-like pathology[11]. Understanding the mechanisms by which these different disease processes interact in the brain could help to explain the frequent coexistence of multiple degenerative brain diseases in the elderly[7].

Aβ seeds are long-lived in the brain, and may be even more resistant to degradation than are prions[12]. Given the build-up of Aβ in the pituitary glands of people with Alzheimer's disease, and the relatively high prevalence of the disease in the general population, batches of c-hGH are more likely to have been contaminated by Aβ seeds than by prions, which could

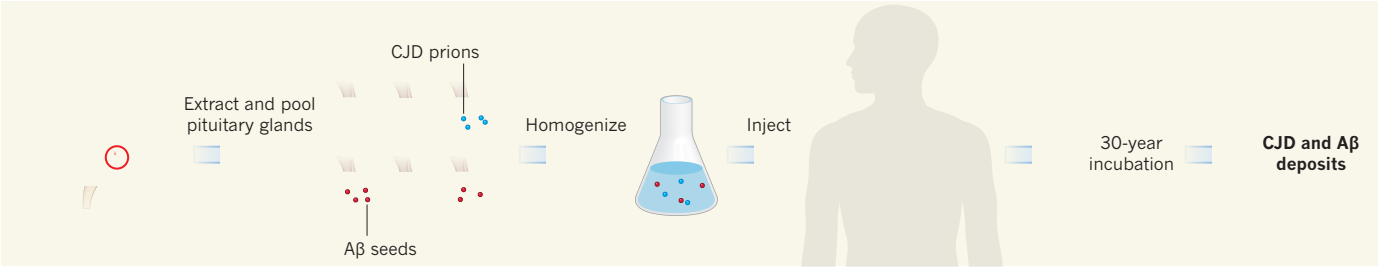

Figure 1 | Contamination of growth-hormone extracts. Before 1985, people in need of growth-hormone treatment were treated with cadaver-derived human growth hormone (c-hGH). To prepare c-hGH, the pituitary gland at the base of the brain was extracted at autopsy. Of the thousands of glands extracted, a few contained prions from people with the neurodegenerative condition Creutzfeldt–Jakob disease (CJD). Jaunmuktane *et al.*[4] report that some of the glands probably also contained seeds of amyloid-β protein (Aβ), possibly from people with Alzheimer's disease. The pooled glands were homogenized and the c-hGH was then extracted and injected into patients. After approximately 30 years, some recipients died of CJD, owing to a build-up of prions. The authors show that some of these people also had Aβ deposits in the brain, suggestive of incipient Alzheimer's disease.

mean that more recipients received injections containing Aβ seeds. However, it is important to stress that the subjects of this study died of CJD, not of Alzheimer's disease. Whether those with Aβ lesions would eventually have manifested clinical Alzheimer's disease cannot be known with certainty.

Continued surveillance of surviving c-hGH recipients will be essential to determine whether they are at unusually high risk of developing Alzheimer's disease. An earlier study[8] suggests that, as of 2008, c-hGH-treated patients in the United States are not more likely to develop Alzheimer's disease than people in the general population, although an incubation period of 30 years or more is possible. Interestingly, the subjects in the current study lacked tauopathy, an essential feature of Alzheimer's disease[6]. Whether tauopathy would have emerged over a longer incubation period is unknown.

This transmission of Aβ pathology occurred in the uncommon context of long-term c-hGH therapy. So far, there is no indication that Alzheimer's disease can be transmitted between people under ordinary circumstances. Furthermore, the replacement of c-hGH by genetically engineered growth hormone has eliminated the risk that growth-hormone treatment will inadvertently transmit brain disorders between humans. However, it is conceivable that the human transmission of Aβ seeds can occur under other conditions, which must now be carefully defined. Jaunmuktane and colleagues' findings should stimulate new research in this direction, and, more generally, will inspire further investigation into the mechanisms that govern the formation, transmissibility and toxicity of misfolded protein seeds in neurodegenerative diseases. ■

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ATMOSPHERIC SCIENCE

Sea-spray particles cause freezing in clouds

Ice clouds in marine regions at high latitudes might form in warmer and drier air than was previously believed because of freezing induced by airborne particles that contain organic materials from ocean surface waters. SEE LETTER P.234

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The oceans cover two-thirds of Earth's surface and are almost entirely, and rather uniformly, composed of water and inorganic salts[1]. The remaining fraction of a per cent of ocean water contains organic material. This has a variable concentration in space and time[2] and is largely uncharacterized, but might be a key component in driving ice formation in the atmosphere. On page 234 of this issue, Wilson *et al.*[3] report that organic material concentrated in the topmost millimetres of the ocean has the essential crystal-forming properties needed to freeze water and form ice clouds in the atmosphere — a process called ice nucleation. The findings might help to refine predictions of future climate.

Ice formation in clouds is central to precipitation processes because it affects whether, when and where rain, snow or ice falls out of clouds. Climate models calculate the timing and location of ice clouds and the associated precipitation partly on the basis of the particle types and concentrations that are thought to be present in the atmosphere. For example, air temperature must drop to almost −40 °C, and the humidity relative to that at which ice can form at that temperature must be well above 100%, for water to freeze in the atmosphere when no ice-nucleating particles are present[4,5]. But different types of particle can promote freezing when the air is not as cold or as humid as that — by contact with, or immersion in, supercooled water droplets (that is, liquid droplets cooled to below the ideal freezing temperature), by condensation of water onto particles or by direct deposition of ice from water vapour on the particles (Fig. 1).

Wilson *et al.* provide evidence that marine particles could support ice-cloud formation at locations (or at times of the year) where dust is too sparse to freeze ice efficiently. To do this, they sampled surface seawater using a variety of

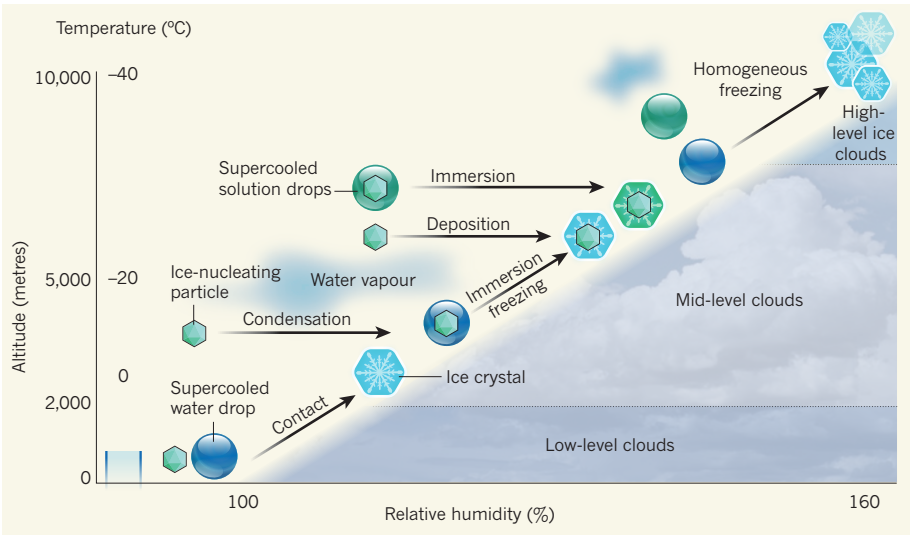

Figure 1 | Ice formation in clouds. The predominant processes for ice formation in the atmosphere depend on temperature (which changes with altitude) and the relative humidity with respect to that at which ice can form. In low-level mixed-phase clouds (composed of water droplets and some ice particles), freezing may occur most effectively when supercooled water droplets come into contact with ice-nucleating particles (INPs). In mid-level mixed-phase and ice clouds, water vapour condenses on INPs, or INPs become immersed in water droplets, after which ice crystals form. Ice crystals can also form when INPs are immersed in supercooled drops of solutions (of salts or of organic compounds, for example), or by direct deposition of ice on the particles. High-level ice clouds include ice that forms 'homogeneously' when supercooled droplets freeze or water vapour crystallizes in the absence of INPs. Wilson *et al.*[3] report that particles from the ocean surface can act as INPs. (Figure adapted from refs 4 and 5.)