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50 & 100 YEARS AGO

50 YEARS AGO

"The English Climate" — In this engagingly written volume Dr. C. E. P. Brooks describes the climate of Britain in relation to the major factors controlling it as well as the various weather processes and seasonal vicissitudes which make it up... In the chapter on "Fog and Soot" much prominence is given to the disastrous 'smog' of December 1952. The heavy death-rate from bronchitis and pneumonia is apparently attributed in the main to sulphur dioxide and soot... No reference is made in this chapter to modern smoke-abatement practices and changed methods of domestic heating as bearing on the experience of the older generation that London fogs to-day have lost the sooty blackness of Victorian times.
From *Nature* 11 June 1955.

100 YEARS AGO

An article entitled "Some Candid Impressions of England" is contributed to the current number of the *National Review* by a "German Resident". The first fact which strikes the contributor is the indifference of Englishmen to their duties as citizens of a great Empire, and it seems to him, looking at English schools, that the mainspring of German success is here. He says:—"Our youths, like your youths, are human, and would be lazy if there were no penalty for idleness... I look at England and see the want of such an influence even in your public schools, which are good in a way, so far as they form character, but bad in that they neglect intellect."... The majority of our workers, he remarks, read little but the sporting Press, and care for little but betting and sport. It is pointed out that the Germans have destroyed in this generation the superstition that Germany makes only poor and cheap articles. "Our Mercedes motors and scientific and optical instruments are the best and most expensive in the world, and no English article of their class can for a moment compete with them."
From *Nature* 8 June 1905.

dimensional microcrystals that eventually proved to be suitable for high-resolution X-ray diffraction studies.

In the microcrystals, the peptide molecules are assembled into a structure that, remarkably, seems to possess the key features of the core of an amyloid fibril. Indeed, observations with electron microscopy suggest that the crystals result from the assembly of nanometre-sized components. The cross-β structure seen in the crystals is built up of pairs of β-sheets, so that side chains of amino-acid residues on the inner side of each pair of sheets are enmeshed with those of the residues of the other sheet to such a degree that water is excluded (Fig. 1). The outer faces of the pairs of sheets are hydrated and more distant from each other, implying that this less intimate interaction could be a crystal contact rather than a feature of the fibrillar state. The suggestion that the fundamental structural unit of a fibril could be just a pair of rather flat sheets is consistent with conclusions from studies of amyloid fibrils of several proteins, including insulin, by cryo-electron microscopy[10] — so adding further support to the supposition that the inherent fibrillar interactions have been captured in the crystalline molecular array.

One of the main objectives in prion research is to establish the relationship between specific structural features and biological properties such as infectivity. Ritter *et al.* (page 844)[5] set out to address this question using the 71-residue carboxy-terminal region of a prion, known as HET-s, from a filamentous fungus. This protein could not be crystallized, but, by using nuclear magnetic resonance techniques, four regions of the sequence were identified as being involved in β-sheet structure. Each region consists of 7–10 contiguous residues and, by judicious use of fluorescent probes, the amyloid core structure was again found to be a pair of β-sheets.

Following model-building and sequence analysis, Ritter *et al.* came up with a proposal for the arrangement of the polypeptide chain within the fibril core that shows marked similarities to the way the seven-residue peptide is arranged in the crystals studied by Nelson *et al.*[4]. Finally, by making a series of mutations designed to disrupt regions of the protein in turn, the amyloid core structure was indeed shown to be the key element required to maintain infectivity in living cells.

Further secrets about the way in which the biological properties of prions are linked to structure are revealed by Krishnan and Lindquist (page 765)[6]. They studied a much larger (250-residue) fragment of Sup35 that has all the characteristics of the natural yeast prion. Like Ritter *et al.*[5], in the absence of crystals they used a range of clever methods to probe the environment of individual residues; in particular, they used a fluorescence technique that enabled the relative proximities of different residues in the sequence to be defined. By analysing the large array of data

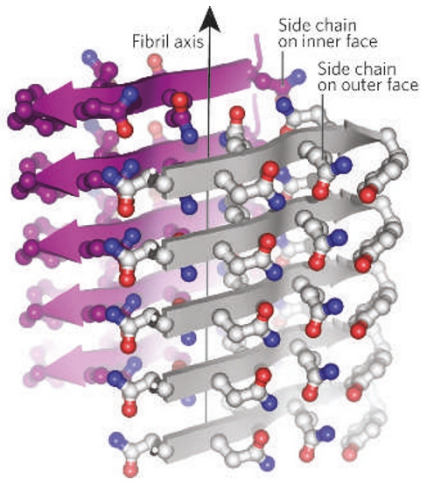

Figure 1 | Structure of the seven-residue peptide from the yeast prion, Sup35. The figure shows the double β-sheet arrangement observed in the three-dimensional crystal, which could represent the stacking of peptide molecules in an amyloid fibril. Here, the individual molecules form the β-strands (purple and grey arrows) that lie perpendicular to the fibrillar axis and are linked by hydrogen bonds to form a pair of β-sheets; addition of peptides to the edges of the sheets elongates the structure in the direction of the arrow and generates a fibril. On the inner face of each sheet, the side chains interact to such an extent that water is excluded. On the outer face, the side chains are hydrated in the crystal and would be exposed to solvent in the fibril. Longer polypeptides can form similar structures by folding back on themselves, with parts of the sequence being in the core structure and the rest forming turns and loops[10]. (Modified from Fig. 2a of ref. 4.)

collected in this heroic study, Krishnan and Lindquist identified two regions of the sequence, each some 15 residues long, that form the key intermolecular interactions in the fibrillar state of the prion. They were then able to show that the first step in the aggregation process involves the formation of a collapsed and disorganized 'molten' structure, in which nucleation can occur and allow the development of the fibrillar structure.

Krishnan and Lindquist's study[6] starts to get to the heart of the unique properties of prions, as it probes the mechanism that triggers their ability to self-propagate. One other aspect of prions that has stimulated much debate is the existence of 'strains', such that a given prion can be linked with a variety of self-perpetuating traits or forms of disease[8,11]. In this context, Krishnan and Lindquist made a striking discovery — they found that the specific residues making up the core of the fibrils are different when the fibrils are grown under different conditions, here simply a change in temperature of about 20 °C. It has already been shown that fibrils with distinctive characteristics can be seeded and propagated in much the same manner as crystals[12]. This new observation therefore suggests that different strains of prions could be linked to specific and self-