Getting out of shape

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Two greatly debilitating illnesses — Alzheimer's disease, which is largely associated with ageing, and variant Creutzfeldt–Jakob disease (vCJD), which is linked with the recent bovine spongiform encephalopathy (BSE) epidemic in Britain — have had a huge impact on public consciousness. Despite their very different origins, these diseases are closely related to each other and also to the 20 or so other 'amyloidoses' — so called because they involve the aberrant deposition of proteins in the form of amyloid fibrils or plaques. Other diseases in this group, which are less publicized but no less devastating to those affected, are Parkinson's disease, type II (late-onset) diabetes and rare conditions such as familial insomnia.

Amyloidoses thus include some of the most feared and costly diseases in the Western world. Alzheimer's may very soon be the most prevalent and socially disruptive illness in the ageing populations of all developed countries. It is remarkable, therefore, that most of these diseases were virtually unknown until relatively recently. Indeed, the first detailed description of an amyloid pathology was made less than 100 years ago, when Alzheimer identified the form of dementia that bears his name. As with many other diseases, Alzheimer's disease is usually sporadic, although there are less common hereditary forms that can afflict relatively young people — Alzheimer's most famous patient was in her early 50s.

The first form of a transmissible human amyloid disease was recognized only in the 1950s, when the fatal condition kuru, which was affecting people in Papua New Guinea, was found to be the consequence of ritualistic cannibalism. Shortly afterwards, a similar 'transmissible spongiform encephalopathy' (TSE) emerged, this time in Europe and the United States, when a form of CJD struck individuals who as children had been treated with growth hormone extracted from human cadavers. And, of course, the consequences of the BSE catastrophe in the 1980s threaten many more people. Although a widespread epidemic of vCJD as a result of eating infected beef seems unlikely, about 100 people have already died of this truly dreadful illness. As other animal species besides cows and sheep are now known to be infected with similar conditions, including deer and elk in parts of North America, further tragedies may be waiting to unfold.

As mentioned above, all of these diseases, whether sporadic, familial or transmissible, are associated with deposits in tissue of proteins that are normally soluble. The deposits, depending on the disease, can be in the brain, in skeletal tissue or in other organs. The amount of protein involved ranges from scarcely detectable quantities to kilograms. Affected tissues are often found to be riddled with thread-like fibrils, sometimes assembled into plaques, with a single predominant protein component that is characteristic of each disease (for example, the prion protein in TSE). This observation led to the idea that the structures of the soluble forms of the proteins involved have an unusual ability to convert to an alternative conformation, which can then assemble into the thread-like structures. A major puzzle was that although the proteins involved have different structures in their soluble forms, the fibrils look remarkably similar, suggesting that the molecular structures in the aggregated forms are essentially the same.

While investigations of the emerging amyloid diseases were taking place in medical schools, research into the nature of protein structures was developing in chemistry and physics departments. In the 1930s it was discovered that many proteins can exist in two forms: a globular, soluble state and a fibrous form, which is often produced at extreme temperatures or pH values. As the globular forms were usually those with biological activity, virtually all attention was focused on them. Indeed, the observation of alternative forms of proteins (except in the case of the prion protein) was not linked to amyloid diseases until very recently, following accidental discoveries that 'ordinary' proteins can form fibrils in vitro that are indistinguishable from those extracted from patients. Moreover, with sufficient patience and cunning, conditions could be found in which seemingly any protein could form amyloid fibrils. This observation suggested that the ability to form such fibrils is 'generic' to proteins, although the propensity to form such structures under given circumstances can vary greatly from one protein to another.

Why does this alternative form of protein structure exist? And why have 'new' diseases associated with it apparently emerged only recently? Both of these questions can be addressed by considering the nature of biological evolution. We each produce about 50,000 different proteins, but this number is only a minute fraction of the countless ways in which the 20 different amino acids can be linked together to give polypeptides of the length that is typical in living organisms (about 300 residues). Natural proteins are therefore a very special group of polypeptides with remarkable properties that have emerged over several billion years of evolution. One factor in increasing the competitive ability of an organism is the efficiency of its information transfer, which is largely achieved by rapid molecular diffusion. Cells are very densely packed with molecules that can communicate rapidly with each other. The fact that proteins do not normally interact inappropriately or even precipitate in such crowded environments is a triumph of evolutionary design.

The astonishing complexity and variety of natural proteins is determined by the unique way in which the various side chains of the constituent amino acids pack together. In amyloid fibrils, however, the structure of the polypeptide chain is dominated by hydrogen bonding between the atoms of the main chain that results in the formation of extended β-sheets, rather than by the specific interactions of the side chains that dictate the structures of globular proteins. In fact, the generic fibrillar forms of proteins can be regarded as the intrinsic 'polymer' structure...
The ability of proteins to change conformation is the essence of the amyloidoses — in these diseases, the proteins have converted into the ‘primordial’ structure rather than remaining in their evolved states.

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