Preface

As actuaries confront life insurance companies in the developed world with their tables of life expectancy over the next decades, some very important positive and negative points emerge from their projections. One of the most striking, is that our children's children will live to be centenarians. Bravo, what enormous progress we have made in extending the longevity of the human race! But this progress has been won at what cost? Given the present correlation between the incidence of debilitating neurodegenerative diseases, like Alzheimer's and Parkinson's diseases, with increasing age, how can we contemplate a situation, where we have only extended our life expectancy, in order to confront the probability that we will be struck down by diseases which will virtually reduce our existence to little more than an advanced vegetative state. In stark terms, what this means is that we must be just as concerned about the quality of life of our ageing population as about their life expectancy. The recent statistics published in the Archives of Neurology of estimates of the incidence of Alzheimer's disease in the US population do not make encouraging reading. They suggest that from around 4-5 million at present, this will increase to around 13 million by the year 2050, much higher than previous estimates. This is essentially due to the rapid ageing of the American population. We can anticipate that, while the rise will also be important in Europe, it will be less pronounced, because the European population is already much older than that of the US. One only needs to talk with a 'carer' for someone with advanced debilitating neurodegenerative disease, to realize that the consequences extend far beyond the individual affected patient.

What this means in concrete terms, is that we must pursue, with the greatest urgency the following three objectives: (i) endeavour to find out what are the causes of these age-related neurodegenerative diseases, (ii) seek to find therapeutic measures which will slow down the onset of these disorders and (iii) ultimately, find ways and means of preventing them – to quote the Chinese proverb 'poor doctor cures, good doctor prevents'.

In this book our objective has been to give an overview of many of the neurodegenerative diseases which currently plague humankind. We have tried in most cases to define the biochemical actors in the disease (proteins or peptides), and to describe their normal, and where possible, their pathological conformations. Then, we have outlined the characteristics of the disease, with frequent emphasis on the role of metal-induced oxidative stress (Table 1) in the disease process, often resulting in the production of intracellular aggregates of the target proteins or peptides. These latter are often characterized by their accumulation in morphologically characteristic inclusion bodies containing proteins, specific to the particular disease. These include β-amyloid plaques and neurofibrillary tangles in Alzheimer's disease, Lewy bodies in Parkinson's disease, prion protein (PrP) plaques in prion diseases and

Table 1: Some neurodegenerative disorders with possible metal-associated pathology

Disorder	implicated Metal	implicated Metalloproteins or enzymes
Alzheimer's disease	Copper, iron, zinc	Aβ, APP
Parkinson's disease	Iron	α-synuclein, neuromelanin, lactoferrin, ferritin, melanotransferrin, ceruloplasmin, divalent cation transporter
Creutzfeldt-Jakob disease	Copper, iron	Prion protein
Familial amyotrophic lateral sclerosis	Copper, zinc deficiency	Superoxide dismutase 1
Friedreich's ataxia	Iron	Frataxin, aconitase, mitochondrial proteins
Multiple sclerosis	Iron	Not known
Wilson's disease	Copper	Ceruloplasmin deficiency, Wilson's protein
Hallervorden-Spatz syndrome	Iron	Vitamin B5 metabolism
Huntington's disease	Iron, calcium	Huntingtin

nuclear inclusions in Huntington's as well as in other neurodegenerative diseases. The formation and subsequent accumulation of these insoluble protein aggregates in neurons must in some way reflect an incapacity of the cell to correctly respond to their formation and to eliminate them. The degradation of cellular proteins takes place by one of two pathways. They may degraded by proteolytic enzymes within the intracellular compartments known as lysosomes – this appears to be a relatively non-selective process. However there is a second, cytosolic-based and energy (ATP)-dependent proteolytic system which is independent of the lysosomal system. Proteins that are selected for destruction by this are first marked by covalently linking them to ubiquitin, a small protein that is both ubiquitous and abundant in eukaryotes, indeed it is the most highly conserved protein known. The ubiquinated protein is degraded in an energy-dependent process within a large multiprotein complex, known as the proteosome. And it is this process which seems to be dysfunctional in many neurodegenerative diseases.

Finally we discuss the progress that is being made in understanding the pathogenesis of the diseases and the identification of targets for their treatment. As a recent article has pointed out, the pharmaceutical industry is frequently in the process of looking for Cinderella after the ball – in other words, they have a glass slipper (a low molecular weight molecule) which exerts an enormous effect on a disease process (the unfortunate Prince), but they do not know to which cellular protein (the glass slipper) it fits. As we gain a greater understanding of the mechanisms which are involved in the oxidative and other stress factors that provoke degeneration of nervous tissue and the often debilitating diseases that are their consequence, we will hopefully also find effective therapeutic approaches, which will not only improve their treatment once they have been diagnosed, but also enable the effective delay of their onset.

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