with age can be seen as a threat (given population projections) or as an opportunity—a delay in the onset of these conditions by, say, 5-10 years would dramatically reduce their incidence and therefore costs. Individuals have realised that if they are lucky enough to side step or survive cancer and vascular disease the next threat is neurodegeneration in its various guises. But have governments realised this? Secondary postponement of disability is possible and it is impressive and fast moving in Parkinson’s disease and modest in Alzheimer’s and motor neurone disease.

The key characteristics of these conditions are that progressive degeneration occurs as a primary event long before symptoms develop and that it is selective, at least initially, for a particular neuronal pool. Other groups of neurones could join—for example, sensory end organ failure—and there is overlap with what we arbitrarily accept as ageing. In the future these diseases will be increasingly defined by the proteins involved. Improved diagnostics will hopefully change terminology and reduce the need to second guess pathology, thus increasing the accuracy of classification from the start. Eventually the mechanisms through which particular proteins cause toxicity would be elucidated, as will genetic and environmental risk factors. Primary preventive strategies could then emerge and ultimately (as in the case of polio and vaccination) these diseases will be defined by their solutions.

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**Treating neurodegenerative diseases**

*What patients want is not what doctors focus on*

Parkinson’s disease is an excellent example of the challenges of caring posed by people with neurodegenerative disorders. It is insidious in onset, inexorably progressive, of unknown cause, incurable, yet amenable to management with pharmacological and other interventions. With the ageing of the population the prevalence of Parkinson’s disease and other such disorders is projected to increase in the years ahead. Thus all doctors must be prepared to provide diagnostic and management strategies for this growing population of patients. Medical practitioners must understand the expectations of patients and their families and introduce these perspectives within the framework of scientific understanding and evidence based practice. Conventional medical education has set a tradition of practice based on science, basic and clinical, cemented by a period of postgraduate training in the conventional apprenticeship mode. This has ensured that practices are generally competent and safe and grounded in the best available information. But is this approach consistent with the mission of professionals to build partnerships with patients by means of strategies for care consistent with the knowledge, attitudes, and values of a public most of which is educated.

Do most people believe, for example, that the quality of life of patients with neurodegenerative disorders depends primarily on the severity of disease and the effectiveness of pharmacological interventions? Without a detailed examination of evidence or a familiarity with the risks associated with treatment, patients may have an outlook that differs from that of professionals with respect to health related factors conducive to a better quality of life. Moreover, protocols for the care of patients are likely to derive more from the research interests and focus of investigators than the daily burdens of the people who have the illness.

There is a growing consensus that a lack of congruence exists between what patients and doctors value in terms of the impact of disease on quality of life and what should be done about it. In Parkinson’s disease, there is robust evidence in favour of this divergence of perspective which may represent a potential barrier to the effectiveness of protocols for care, guidelines for management, and the most effective and efficient use of health resources. When face to face interviews with more than 1000 patients with Parkinson’s disease and carers were carried out in six countries only 17.5% of the variation in perceptions of health related quality of life could be explained by the severity of disease and the effectiveness of drug treatment. Such evidence necessarily represents a wake-up call for those health providers who believe that these factors are most important for prognosis and require a large share of professional effort.

During these interviews, patients were also given the opportunity to complete specially developed questionnaires and validated instruments to identify other domains of care of equal or greater importance which affect the quality of their life. These domains had been identified in pilot studies by the investigators. The salient responses that accounted for approximately 60% of health related quality of life were respondents’ mood, satisfaction with the explanation at the time of...
Neurodegeneration in the age of molecular biology
Abnormal protein folding holds the key to specific treatment

Clinicians still think of neurodegenerative disorders in terms of nonspecific, 19th century style palliation. For a few disorders, we can temporarily relieve symptoms by pharmacological or surgical manipulation of the neurotransmitters emitted by the degenerating neurones. In the past decade, thinking about these disorders has been reordered by the discovery that most of them feature excessive protein misfolding and intracellular protein aggregation. This insight could permit us to interrupt the process of neuronal loss itself.

Tau, an important component of cytoskeletal physiology, is the protein that aggregates most commonly in neurodegenerative diseases, both in terms of number of disorders and numbers of patients affected. It forms the neurofibrillary tangles of Alzheimer’s disease, Pick’s disease, progressive supranuclear palsy, frontotemporal dementia, corticobasal degeneration, postencephalitic parkinsonism, and a handful of others.

Next most common, at least in terms of population prevalence, is β-amyloid, principal component of the amyloid plaques of Alzheimer’s disease. Another protein with epidemiological importance is α-synuclein, which forms the aggregates of Parkinson’s disease, dementia with Lewy bodies, multiple system atrophy, and others. Tau and α-synuclein may even interact to increase the risk of Parkinson’s disease.

The mechanisms by which protein aggregates impair cell function and survival are slowly becoming known. One advanced example is α-synuclein. The normal function of this small protein, still unclear, includes protecting neurotransmitter-laden vesicles and helping to transport them from cell body to synapse. The classic pathogenetic hallmark of Parkinson’s disease is the Lewy body, a layered, radially arranged fibrillary aggregate of some two dozen chemical components, chief among which, found in 1997, is α-synuclein. It seems, however, that Lewy bodies themselves do not damage neurones. Rather, an early stage of aggregate consisting of fewer than 30 α-synuclein molecules, a “protoaggregate” or “oligomer,” is probably the offending species. It may exert its toxic action by creating pores in lipid membranes. One result is leakage of dopamine from vesicles into the cytoplasm. Free dopamine, aside from its direct oxidative toxicity, exacerbates the pathogenetic process by inhibiting the further aggregation of the protoaggregates into Lewy bodies. By sequestering the protoaggregates, the Lewy bodies may provide a protective function. The story for the other neurodegenerative disorders may be variations on the theme of protoaggregates producing toxicity and mature aggregates providing a means of sequestering them.

Underlying this story for most neurodegenerative disorders is abnormal protein folding. This exposes hydrophobic regions, permitting aggregation. The cell’s principal means of disposing of abnormally folded proteins is the ubiquitin-proteasome system. Protein aggregates themselves can impair the function of that system, probably by a simple clogging mechanism. At least one