Dementia

Can we afford to develop treatments for dementia?

S Lovestone

Can we afford *not* to develop treatments for dementia?

This issue and that of the *BMJ* (22nd June 2002), are dedicated to neurodegenerative disorders. We have come a long way in this field over the past two decades or so. Twenty years ago we knew only that Alzheimer's disease (AD) affected many elderly people, segregated in some early onset families, and was predominantly a disorder of cholinergic function. Now we have five years of postlicencing experience with the first drugs designed to rectify that cholinergic deficit[1] and our understanding of the molecular basis of AD is, if not complete, pretty much understood in outline. We know how the amyloid of plaques is produced in some detail and in the case of early onset familial AD we know why.[2] For late onset AD the influences on amyloid formation, aggregation, and deposition are less well understood, but we do know of some environmental influences such as head injury[3 4] and some genetic ones such as an as yet unidentified gene on chromosome 10.[5] We know about the aggregation of tau into tangles and, although the debate continues as to whether phosphorylation is primary or secondary,[6] some intriguing data indicate that it is this phosphorylation that underlies amyloid toxicity.[7 8].

All of this hugely exciting research is leading to better understanding of the relation between the different dementias. We know, for example, that tau pathology is at the root of the frontotemporal disorders and not just AD,[9] and that a complex relation exists between the previously distinct vascular dementia and AD.[10] We understand something of the molecular biology of Parkinson's disease and the accumulation of synuclein into Lewy bodies[11]—an understanding that is changing the way we think about the nosology of neurodegeneration.

Despite these advances, much remains unknown. The advances in the understanding of the molecular biology of AD have not yet been matched by understanding of the molecular pathology of either motor neurone disease or Parkinson's disease, although work on neurofilaments and superoxide in relation to the former and synuclein and parkin in relation to the latter holds promise. Two of the big unanswered questions regarding neurodegeneration are why then, and why there? Why are there disorders of such late onset and what underlies the neuroanatomical and cellular specificity of disease? What relates genotype to pathology to phenotype?

However, what really remains to be done is to cure the condition. New treatments such as the cholinesterase inhibitors for AD or riluzole for motor neurone disease have had a huge impact, although it has to be said the impact is often more on services than on patients as these are largely symptomatic treatments. The real goal is to generate disease modification treatment. For example, it was predicted from the amyloid cascade hypothesis that treatments that reduced β amyloid production or aggregation would be disease modifying. Subsequently, huge efforts have been expended in generating such compounds—inhibitors of amyloid secretases (predominantly β amyloid cleaving enzyme) and antifibrillogenic compounds have been generated. But what should we expect from such drugs? If the amyloid cascade hypothesis is correct, then we would expect these drugs to be efficacious most, and perhaps only, early in the disease process. Also, the amyloid cascade hypothesis postulates that amyloid pathology (in the broadest sense—it may be production or aggregation; intracellular or extracellular) precedes tangle formation. Furthermore, we know that tangle related pathology precedes dementia by some considerable time—perhaps decades. It follows that the amyloid approach to treatment of AD, on which so much is staked, may be effective only if used to delay pathological progression, if it is used years before the onset of dementia. The same holds true for other approaches. Non-steroidal anti-inflammatory drugs, for example, substantially reduced the risk of AD only when used for more than two years.[12]

This is a huge challenge for those funding clinical trials. It follows from the above that trials for these agents are likely to be very long term and consequently very expensive. There are ways to reduce the size of the problem by enriching for those at risk of dementia, using genetic factors or prodromal AD, for example. However, the evidence suggests that even in mild cognitive impairment (the most obvious prodromal syndrome) the damage has already occurred and pathology is extensive.[13]

We have come a long way, and this issue and that of the BMJ celebrate some of these advances. However, there are very considerable challenges for the future. Of these, trial design for disease modification and, perhaps more pertinently, trial funding are the largest. Given the huge costs of a disease, prevention trial funding may increasingly have to come from central, government sources, perhaps in conjunction with industry. The question is whether we can afford the trials that may be necessary for disease modification. Given the costs of neurodegeneration, the question perhaps should be: can we afford not to?

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