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Selegiline in Parkinson's disease

No neuroprotective effect: increased mortality

See p 1602

In medicine, as in all other human activities, fashions come and go. In the field of Parkinson's disease, there has been an explosion of research on the possibility that nerve cells in the substantia nigra are dying because of excessive production of toxic free radicals.The "oxidative stress" hypothesis envisions dopamine undergoing oxidative metabolism to produce an excess of free radicals that gradually kill the dopaminergic neurons, which bear the brunt of the pathology of Parkinson's disease.[1] But there is no compelling evidence for this view[2]; at best damage by free radicals might represent the final common pathway to cell death, just as cessation of the heartbeat is an inevitable feature of corporeal death.

In its heyday, the free radical hypothesis fuelled enormous therapeutic trials for Parkinson's disease, based on the premise that if we could reduce formation of free radicals this would confer "neuroprotection" in chronic neurodegenerative disease. The largest of these trials was DATATOP (deprenyl and tocopherol antioxidant therapy for parkinsonism),[3] designed to see if an inhibitor of monoamine oxidase B, selegiline (deprenyl), or an antioxidant, tocopherol, might slow down the progression of Parkinson's disease. The DATATOP trial provided authoritative observations on 800 patients; it required a multicentre design with the collaborative participation of 169 investigators based in North America,[4] mostly in the United States. The results showed that patients taking selegiline fared better than those receiving placebo. The French selegiline multicentre trial[5] and other smaller studies corroborated this finding.[6,7]

However, an important problem of interpretation arose. Was the benefit from selegiline the result of neuroprotection or symptomatic improvement? Did the selegiline delay cell death in the substantia nigra, or did it alleviate symptoms by a dopaminomimetic effect that had nothing to do with the underlying pathology? Initially, either or both explanations seemed possible. But then an independent analysis of the DATATOP results indicated that the therapeutic effect of selegiline was transient and more in keeping with a symptomatic action.[8] Another critical re-examination cast further doubt on the idea of neuroprotection.[9] Follow up observations on the DATATOP cohort of patients showed that the benefit was of limited duration,[4] and new clinical trials by Yahr and his associates[10,11] increased the emerging scepticism concerning antioxidative therapy and neuroprotection. But some studies have continued to reinforce the earlier hopes of a neuroprotective effect.[12]

With this confusing background of conflicting conclusions, the Parkinson's Study Group of the United Kingdom publish their interim findings in this issue of the *BMJ*. They report a highly relevant and important new observation. The British trial was an open randomised study of 782 patients with Parkinson's disease studied longitudinally over a mean period of 5·6 years. There were three arms to the study: levodopa monotherapy, levodopa plus selegiline, and levodopa plus bromocriptine. The population studied was similar to that examined in the DATATOP trial, comprising patients with early, mild clinical features of Parkinson's disease. Far from finding any long term benefit from selegiline, the British group reported an increased mortality in the selegiline arm of the study.

The results with the levodopa plus bromocriptine arm are not provided in any detail. The report focuses on a higher death rate in the levodopa/selegiline arm versus the levodopa monotherapy arm. The hazard ratio was 1·57:1 (P=0·0152) meaning that mortality among patients receiving selegiline was about 60% higher than in those receiving levodopa alone. The open design is unlikely to have confounded the result because the prevailing environment of enthusiasm for neuroprotection would have been expected to work in the opposite direction and produce a bias in favour of selegiline. Thus 28 out of the 37 patients who withdrew from the levodopa monotherapy arm of the trial did so just as selegiline was becoming generally available, at a time when it was being energetically promoted because of the DATATOP report.

The new findings provide strong evidence against selegiline having a neuroprotective action, and they may perhaps be construed as evidence against the free radical hypothesis. They also refute an earlier claim by Birkmayer *et al* that selegiline decreases mortality in Parkinson's disease.[13] This claim was flawed by a retrospective design that paid no heed to the need for randomisation. Yet in spite of its serious weaknesses, the report of Birkmayer *et al* has been a prop for the free radical hypothesis. When a bandwagon is in motion, the baggage added to it is not usually subjected to critical scrutiny by impartial minds.

In conclusion, the controversy over the role of selegiline in the management of Parkinson's disease can perhaps now be put behind us. The main weight of the evidence does not support a neuroprotective action. The argument that antioxidant therapy inhibits damage by free radicals is

correspondingly weakened. As often occurs in biomedical science, answering one question poses another. We now have to decide whether the long term use of selegiline is causally related to the increased mortality reported in this week's *BMJ*, and if so, what is the mechanism?

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The future of breast and ovarian cancer clinics

No longer just research—now a clinical need

In a general practitioner's list of 2000 people 40 to 50 will have a first degree relative with cancer, 10 of which relatives will have developed cancer under the age of 50 years. A few of these people will have a strong inherited predisposition to some common cancers, such as breast and ovarian cancer.[1] Mutations in the recently identified BRCA1 gene are associated with extremely high lifetime risks of cancer of the breast (87%) and ovaries (44%).[2] These mutations account for an estimated 10-30% of all women diagnosed with breast cancer under the age of 45,[3,4] an important group as they contribute a large proportion of the years of life lost to breast cancer

Individuals should have access to accurate information about their risk, and those at high risk want access to effective screening.[5] But our ability to identify women at high risk has come at a time when no consensus exists over the most appropriate management of these women. Mammographic screening for breast cancer is of uncertain effectiveness in young women[6,7]; and it remains uncertain which screening strategy is most appropriate for ovarian cancer.[8] At national and district level, NHS commissioners have been justifiably reluctant to allocate substantial resources to untested and unproved screening programmes.[9]

The need for information and counselling for women at risk has been met largely by ad hoc cancer genetics clinics funded by research agencies. Several clinics were established in regional centres in the early 1990s.[10] They have dealt with an increasing number of women with a family history of cancer, mainly referred by general practitioners. In 1994 more than 1000 new referrals were made to familial breast cancer clinics in Scotland. However, as the clinics are funded independently, limited progress has been made in standardising policies or practices and in coordinating research at a national level. The future of these clinics remains uncertain, posing an important problem as many women have been told of their increased risk of cancer and enrolled in screening programmes that may be terminated through lack of funding.

The future for these clinics could be secured if the clinical and research needs were clarified. NHS commissioners need to recognise that cancer genetics is no longer of interest only to researchers. Women who are at very high risk of breast or ovarian cancer (or those who are extremely anxious about their perceived risk) need accurate risk estimation and counselling services. Where cancer genetics services do not exist, experience suggests that these women will attend services for women with symptomatic breast disease, which may not have expertise in the rapidly changing field of cancer genetics. For the small minority of women who are truly at high risk the NHS could also provide gene testing when it becomes available. Commissioners should ensure that the client group is clearly defined, that national guidelines on risk assessment and screening criteria are developed and agreed, and that storage and handling of data are satisfactory. They should then provide a core service for these people with recognised needs.

One possible model for an NHS regional cancer genetics service would entail the appointment of two specialist genetics nurses with training in oncology. The nurses would be supervised by a physician specialising in cancer genetics, with appropriate input from surgical specialists for clinical examinations and close links with oncology colleagues. The genetics nurse specialists would also carry out home visits, help primary care staff to provide counselling and follow up services in the community, and help to develop clinical guidelines for general practitioners, including when to refer women to regional cancer genetics services.

Of several possible models, none has so far been adequately evaluated. At the moment no formal training programmes in cancer genetics exist,[11] although several centres have the expertise to run such programmes and, in collaboration with the royal colleges, to set up subspecialty training in cancer genetics. While the role of screening in young women at high risk remains unresolved,[12] it may be prudent for the cancer genetics centres not to provide screening unless they are collaborating in a multicentre trial to evaluate the effectiveness of the screening programme.

Building on the basic infrastructure of these established centres, collaborative research could then tackle the many outstanding research questions. What, for example, is the possible role of testing for a specific gene? How effective are screening programmes or intervention strategies in women at high risk? Meaningful progress will only be made by multicentre collaboration. Research funding should support centres that agree to follow nationally agreed guidelines and collaborate in common research protocols to address these questions. An important opportunity will have been lost if the