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?

DONALD B CALNE
Director

Neurodegenerative Disorders Centre,
Faculty of Medicine,
Vancouver Hospital and Health Sciences Centre,
Vancouver, BC,
Canada V6T 2B5

1 Fahn S, Cohen G. The oxidant stress hypothesis: evidence supporting it. *Ann Neurol* 1992;32: 804-12.
2 Calne DB. The free radical hypothesis in idiopathic parkinsonism: evidence against it. *Ann Neurol* 1992;32:799-803.
3 Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989;321:1364-71.
4 Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993;328:176-83.
5 Allain H, Cougnard J, Neukirch HC. Selegiline in de novo parkinsonian patients: the French selegiline multicenter trial (FSMT). *Acta Neural Scan* 1991;136:73-8.
6 Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989;245:519-22.
7 Myllyla VV, Sotaniemi KA, Vuorinen JA, Heinonen EH. Selegiline as initial treatment in de novo parkinsonian patients. *Neurology* 1992;42:339-43.
8 Schulzer M, Mak E, Calne DB. The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992;32:795-8.
9 Ward CD. Does selegiline delay the progression of Parkinson's disease. A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994;57:217-20.
10 Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease. *Arch Neurol* 1989;46:1280-3.
11 Brannan T, Yahr MD. Comparative study of selegiline plus L-dopa-carbidopa versus L-dopa-carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995;37:95-8.
12 Olanow CW, Hauser RA, Gauger L, *et al.* A longitudinal double blind controlled study of the effect of deprenyl and levodopa on the progression of signs and symptoms of Parkinson's disease (the SINDEPAR study). *Ann Neurol* (in press).
13 Birkmayer W, Knoll J. Riederer P, Youdim MBH, Hars V, Marton J. Increased life expectancy resulting from addition of l-deprenyl to Madopar treatment in Parkinson's disease: a long-term study. *J Neural Transm* 1985;64:113-27.

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

current system of autonomous centres with short term funding is allowed to continue.

HARRY CAMPBELL
Senior lecturer

Department of Public Health Sciences,
Edinburgh University,
Edinburgh

JAMES MACKAY
Senior registrar

ICRF Department of Medical Oncology,
Western General Hospitals NHS Trust,
Edinburgh

MARY PORTEOUS
Consultant

Department of Clinical Genetics,
Western General Hospitals NHS Trust,
Edinburgh

1 Department of Health. *Advances in the genetics of common diseases: implications for the NHS.* DoH: London, 1995. (Report of workshop, May 1995.)
2 Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, Breast Cancer Linkage Consortium. Risks of cancer in BRCA1 mutation carriers. *Lancet* 1994;**343**:692-5.
3 Easton D, Ford D, Peto J. Inherited susceptibility to breast cancer. *Cancer Surveys.* 1993;**18**: 95-113.
4 Weber BL. Susceptibility genes for breast cancer. *New Engl J Med* 1994;**331**:1523-4.
5 Biesecker B, Boenhke M, Calzone K, Markel DS, Garber JE, Collins FS, *et al.* Genetic counselling for families with inherited susceptibility to breast and ovarian cancer. *JAMA* 1993;**269**:1970-4.
6 Forrest AP, Alexander FE. A question that will not go away; at what age should mammographic screening begin? *J Natl Cancer Inst* 1995;**87**:1195-7.
7 Evans DER, Fentiman IS, McPherson K, Ashbury D, Ponder BAJ, Howell A. Familial breast cancer. *BMJ* 1994;**308**:183-7.
8 Philip J. Is screening for ovarian cancer worthwhile? *Journal of Medical Screening* 1994:**1**;206-7.
9 Advisory Council on Science and Technology. *A report on medical research and health.* London: HMSO, 1993:21.
10 Ponder BAJ. Setting up and running a familial cancer clinic. *Br Med Bull* 1994;**50**:732-45.
11 Mackay J, Crosbie AEC, Steel CM, Smart GE, Smyth JF. Clinical and ethical dilemmas in familial ovarian cancer. In: Sharp F, Blackett A, Leake R, Berek J, eds. *Ovarian cancer 4.* London: Chapman and Hall, 1995.
12 Hoskins KF, Stopfer JE, Calzone KA, Merajver SD, Rebbeck R, Garber JE, Weber BL. Assessment and counselling for women with a family history of breast cancer: a guide for clinicians. *JAMA* 1995;**273**:577-85.

Delayed childbearing

Fertility declines at 30 and is almost gone by 40

See p 1647

Women perform best at childbearing when they are young, just as they do in gymnastics and marathon running. Aristotle recommended that "marriage be set for girls at 18, for men at 37 or somewhat less" because these were the ages thought to produce the finest children. In the days when life expectancy was low, it was clearly prudent to begin a family while still young. But the price of early marriage was usually a train of pregnancies that did not halt until infertility, menopause, or death intervened. With the advent of efficient contraception, we became biologically a new breed. Women could choose whether to have children—and when.

For the first time in recorded history, the number of births for every thousand British women in their early 30s has recently exceeded that in women in their early 20s. The rate in older women is climbing too.[1] The trend towards later maternity is strongest among women with better educational qualifications as they increasingly postpone child rearing to pursue their careers. In addition, some women who have already reared a family wish to have another child with a new partner. This "greying" of reproductively active women is not so dramatic that differences are obvious in the waiting rooms of antenatal clinics, and the shift is less obvious in, say, Yorkshire than in the south east of England. But it amounts to an important and widespread social change, and women planning to start a family late do well to weigh the biological consequences.

For reasons still far from clear, human evolution has allowed the female reproductive system to age faster than other parts of the body. Menopause at mid-life is the most striking sign, yet it is only the full stop at the end of the fertility chapter. Decline sets in much earlier. Some of the clearest evidence has been recorded in the Hutterites, a sect of anabaptist refugees from Europe who settled in North America over a century ago. Although its fertility has fallen in recent years, the community has the highest age specific fertility in the world. This is because it forbids any form of fertility control while enjoying a high standard of living and health care. In the 1950s women in the sect were delivering an average of 11 babies each, and the peak age for fertility was 30 years of age. Interestingly, half the women had delivered their last child by 40,[2] when only 1% would be expected to be postmenopausal. Several explanations can be offered for this early onset of infertility, but we now suspect that physiological aging of the ovary is most important.

In studies of gynaecologically normal European women using artificial insemination because their husbands had azoospermia, fertility was found to begin falling by the age of 30.[3,4] After this age it took longer and longer to achieve a viable pregnancy until the chances in the late 40s were vanishingly small. According to studies of in vitro fertilisation or gamete intrafallopian transfer, the oocyte seems to be the main limiting factor.[5] Remarkably high pregnancy rates can be achieved when eggs are transferred from younger to older women,[6] and successful pregnancy long after the normal age of menopause shows that the egg rather than the uterus is the Achilles' heel of human reproduction.[7] Given eggs from young donors, no age is too old for pregnancy—at least in theory for those in good health. This is hardly the point, however, because women contemplating pregnancy in their 30s or 40s want to know their chances of success with their partner alone. Apart from the menopause, there is no obvious biological turning point in the reproductive lifespan, but if forced to state a critical age, we would say that the amber light should come on at 35. By this time, a woman will take twice as long to conceive as she would have 10 years earlier. The health and survival of her unborn child are usually her prime concerns, but despite the reassurances of prenatal screening and an overall decline by some 70% in fetal death rates,[8] the risks for both mother and child remain stubbornly higher than for younger women.

Age changes cannot be reversed. Oocytes disappear faster from the ovary after the age of 37[9] and are more susceptible to aneuploidy and possibly to mitochondrial mutations too.[10] The inexorable upswing of statistics looks alarming but success often comes with patience and late pregnancies usually have a happy outcome. We must remember, however, that deferring fertility is a gamble. Journalists and broadcasters are probably in a better position than doctors to raise public awareness of this underacknowledged fact of biology. The effects of aging cannot be dismissed as only matters for elderly people.

ROGER GOSDEN
Professor of reproductive biology

ANTHONY RUTHERFORD
Consultant gynaecologist

Clarendon Wing,
General Infirmary,
Leeds LS2 9NS