Preimplantation diagnosis with the polymerase chain reaction

Scientifically possible, not widely available

DNA amplification by the polymerase chain reaction is one of those brilliant ideas that in retrospect seem obvious.¹ It depends on a well known peculiarity of DNA replication: if the two strands of DNA are designated (+) and (−) strands to synthesise a (+) strand on a (−) strand template you need not only the polymerase enzyme and the DNA monomers but also a short primer segment of the (+) strand. DNA synthesis works by extending the primer. By supplying only one specific primer in vitro DNA synthesis can be made to begin always at a certain sequence. If (+) and (−) strand primers are supplied that recognise sequences a short distance apart on the template and are arranged so that synthesis runs from each primer towards the other the sequence between the two primers can be selectively copied. The copies may themselves serve as templates for further copying—so that in theory the amount of target DNA doubles with each round of copying.

In the laboratory this is achieved by mixing the DNA template, primer sequences, DNA monomers and polymerase and controlling the reaction by changing the temperature. At 95°C the two strands of DNA separate; at 60°C the primers anneal to their complementary sequences; and at 70°C the special high temperature polymerase extends the primers. Thirty cycles take two to three hours to complete and give a millionfold amplification.

The technique is transforming molecular genetics. It is simple, fast, highly specific, and unbelievably sensitive. Most of the tests at present done with Southern blotting may be done much more simply with the polymerase chain reaction. A radioactive probe is no longer needed to locate the DNA fragment of interest: after amplification it is abundant enough to be seen as a fluorescent band in an electrophoretic gel. Already the polymerase chain reaction is being applied routinely to the prenatal diagnosis of cystic fibrosis and other single gene disorders using material obtained by chorionic villus biopsy at eight weeks' gestation.^{2,3} Several groups have shown that the starting material for the polymerase chain reaction may be as little as one molecule.^{1,4} Such sensitivity makes possible many new ventures: the genotype of individual subjects may be determined from a single hair or a dried bloodspot; extremely rare RNA transcripts or a single virus may be detected within cells; and single cells may have their sex determined⁵ or—as described by the group at St Mary's on p 22—may be examined for genetic abnormalities. If the single cell is derived from a preimplantation embryo the method can be used for uniquely early prenatal diagnosis. How useful will this be?

Couples would have a choice between natural conception followed by chorionic villus biopsy and in vitro fertilisation with preimplantation diagnosis, using the polymerase chain reaction in each case. Couples opting for chorionic villus biopsy would have to be prepared for a termination of pregnancy in the first trimester; in those opting for in vitro fertilisation the woman would have to undergo follicle stimulation, monitoring of the ovarian cycle, egg retrieval, and embryo replacement, with a considerably less than even chance of success.⁶ The option of in vitro fertilisation would circumvent some, but not all, of the qualms of those who find abortion a difficult choice. Couples will need help to make these choices, and this is best done within an integrated clinical, laboratory, and counselling service.

With expert support many couples may decide to take the obstetrically less complex path of chorionic villus biopsy. This might be a relief to hard pressed teams offering in vitro fertilisation. At least 1000 pregnancies annually in Britain carry a one in four risk of producing a child affected with cystic fibrosis, and if population screening to identify them becomes feasible demand for in vitro fertilisation could overwhelm the existing services. In 1987, 5592 embryo transfers were performed in Britain; most were transferred in private facilities,⁶ and waiting lists for NHS treatment extend for many years.

Until the technology of in vitro fertilisation becomes much simpler adding this procedure to existing prenatal diagnosis programmes seems daunting. Coutelle *et al* mention, however, women who have been sterilised after the birth of an abnormal child, who subsequently wish to have more children (p 22). For these women, who would already be enrolled into in vitro fertilisation programmes, adding the polymerase chain reaction as a diagnostic step would be simple and beneficial.

ANDREW P READ

Senior Lecturer

DIAN DONNAI

Consultant Geneticist

Department of Medical Genetics,
St Mary's Hospital,
Manchester M13 0JH

- 1 Saiki RK, Gelfand DH, Stoffel S, *et al*. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 1988;239:487-91.
- 2 Kogan SC, Doherty M, Gitschier J. An improved method for prenatal diagnosis of genetic diseases by analysis of amplified DNA sequences. *N Engl J Med* 1987;317:985-90.
- 3 Williams C, Williamson R, Coutelle C, Loeffler F, Smith J, Ivinson A. Same-day, first trimester antenatal diagnosis for cystic fibrosis by gene amplification. *Lancet* 1988;ii:102-3.
- 4 Li H, Gyllenstein UB, Cui X, Saiki RK, Ehrlich HA, Arnheim A. Amplification and analysis of DNA sequences in single human sperm and diploid cells. *Nature* 1988;335:414-7.
- 5 Handside AH, Pattinson JK, Penketh RJA, Delhanty JDA, Winston RML, Tuddenham EGD. Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1989;ii:347-9.
- 6 Voluntary Licensing Authority for Human In-vitro Fertilisation and Embryology. *Fourth Report*. London: Voluntary Licensing Authority for Human In-vitro Fertilisation and Embryology, 1989.

Psychiatric aspects of Parkinson's disease

Dementia, depression, and rarely psychosis

Parkinson's disease commonly has psychiatric complications, which may be disabling. Cognitive impairment occurs in two forms: dementia, which affects about a tenth of patients,^{1,2} and frontal-subcortical dysfunction (a more discrete deficit of the frontal lobes), which may affect up to two thirds.¹

Patients with Parkinson's disease have a higher risk of developing dementia than an age matched control group,² but the risk applies mainly to those who develop the disease after the age of 60.^{2,3} The basis of dementia in Parkinson's disease is controversial. A combination of pathological change in both substantia nigra and the cortex may lower the threshold for developing dementia.⁴ At the extremes Alzheimer's disease may complicate Parkinson's disease,⁵ and parkinsonism occurs in about two thirds of patients with Alzheimer's disease.⁶ Some recent evidence suggests, however, that the characteristic Lewy body disease of Parkinson's disease may be more diffuse,⁷ occurring in the neocortex as well as the brain stem. This may be an additional, underdiagnosed explanation for dementia in Parkinson's disease.⁸ Frontal-subcortical dysfunction may arise from deficits in the dopaminergic connections from the caudate nucleus and midbrain to the frontal cortex.⁹ There is no firm evidence that

it presages dementia, but it may cause slight forgetfulness, repetitiveness, and reduced initiative or creativity.¹⁰ It may commonly be detected by a simple word fluency test.¹

Depressed mood affects about two fifths of patients with Parkinson's disease.¹¹ The metabolism of serotonin in the brain is sometimes disordered in Parkinson's disease and may increase susceptibility to severe depression.¹² More common is a milder depression that is associated with motor disability¹³; also important are the strategies used by the patient to cope with the illness and the availability of practical support.¹⁴ Vulnerability to depression is increased at times of rapid deterioration in motor symptoms,¹⁵ but in one study the patient's own perception of disability predicted depression better than did objective measures of neurological impairment (DS Glosser *et al*, paper to the ninth international symposium on Parkinson's disease, Jerusalem, 1988).

Recognising these psychiatric complications of Parkinson's disease raises practical implications. Firstly, dementia in Parkinson's disease is not always intrinsic to the disease and must be assessed comprehensively to exclude reversible causes, including depressive pseudodementia, whose treatment may improve both motor and cognitive function. Dementia aggravates disability from Parkinson's disease¹⁶ so that the diagnosis is important. Frontal-subcortical dysfunction shows an unpredictable response to levodopa¹⁷ but may vary with the degree of internal planning of behaviour required for a given task.¹⁸ Hence there is a potentially fruitful but as yet unexplored job for clinical psychologists.

Severe depression may underlie an apparent failure of motor symptoms to respond to levodopa. Tricyclic antidepressants are effective, although constipation and postural hypotension may be troublesome. An alternative is electroconvulsive treatment, which may also improve motor symptoms.¹⁹ Early control of worsening motor symptoms may prevent depression.¹⁵ A strategy for treating milder depression begins by taking seriously the patient's own estimation of disability. The next step might include cognitive treatment to modify maladaptive coping behaviours, a support group to enhance self esteem, and reappraisal of practical and paramedical support (occupational therapy, speech therapy, and physiotherapy) to counter helplessness and encourage independence. For example, providing a simple chair raise may be dramatically effective. Sadly, these simple needs often go unmet.^{20 21}

Psychotic disturbance is usually caused by antiparkinsonian drugs. The treatment is to withdraw anticholinergic drugs and then lower doses of levodopa or dopamine agonists, or both. A neuroleptic drug may be given, but parkinsonism is aggravated and long term use of such drugs leads to tardive dyskinesia, which may be mistakenly attributed to antiparkinsonian drugs. Electroconvulsive treatment may benefit resistant cases²² and if successful may avert the difficult judgment of whether the patient is better off mentally well but immobile.

R C BALDWIN

Consultant Psychiatrist for the Elderly,
Department of Psychiatry,
York House,
Manchester Royal Infirmary,
Manchester M13 9BX

E J BYRNE

Lecturer in Health Care of the Elderly,
Queen's Medical Centre,
Nottingham NG7 2UH

- 2 Mayeux R, Stern Y, Rosenstein R, *et al*. An estimate of the prevalence of dementia in idiopathic Parkinson's disease. *Arch Neurol* 1988;45:260-2.
- 3 Godwin-Austen RB, Lowe JS. The two types of Parkinson's disease. In: Rose, FC, ed. *Parkinson's disease: clinical and experimental advances*. London: John Libbey, 1987:79-82.
- 4 Quinn NP, Rossor MN, Marsden CD. Dementia and Parkinson's disease—pathological and neurochemical considerations. *Br Med Bull* 1986;42:86-90.
- 5 Hakim AM, Mathieson G. Dementia in Parkinson's disease: a neuropathological study. *Neurology* 1979;29:1209-14.
- 6 Pearce J. The extrapyramidal disorder of Alzheimer's disease. *Eur Neurol* 1974;12:94-103.
- 7 Yoshimura M. Cortical changes in the parkinsonian brain: a contribution to the delineation of "diffuse Lewy body disease." *J Neurol* 1983;229:17-32.
- 8 Byrne EJ, Lennox G, Lowe JS, Reynold G. Diffuse Lewy body disease: the clinical features. *J Neurol Neurosurg Psychiatry* (in press).
- 9 Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. *Brain* 1986;109:845-83.
- 10 Lees JA, Smith E. Cognitive deficits in the early stages of Parkinson's disease. *Brain* 1983;106:257-70.
- 11 Mayeux R, Williams JBW, Stern Y, Cote L. Depression and Parkinson's disease. In: Hassler RG, Christ JF, eds. *Advances in neurology*. Vol 40. New York: Raven Press, 1984:241-250.
- 12 Mayeux R, Stern Y, Williams JBW, Cote L, Frantz A, Dyrenfurth I. Clinical and biochemical features of depression in Parkinson's disease. *Am J Psychiatry* 1986;143:756-9.
- 13 Gotham A-M, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. *J Neurol Neurosurg Psychiatry* 1986;49:381-9.
- 14 MacCarthy B, Brown R. Psychosocial factors in Parkinson's disease. *Br J Clin Psychol* 1989;28:41-52.
- 15 Brown RG, MacCarthy B, Gotham A-M, Der GJ, Marsden CD. Depression and disability in Parkinson's disease: a follow-up of 132 cases. *Psychol Med* 1988;18:49-55.
- 16 Mutch WJ, Dingwall-Fordyce I, Downie AW, Paterson JG, Roy SK. Parkinson's disease in a Scottish city. *Br Med J* 1986;292:534-6.
- 17 Gotham A-M, Brown RG, Marsden CD. Levodopa treatment may benefit or impair "frontal" function in Parkinson's disease. *Lancet* 1986;ii:970-1.
- 18 Brown RG, Marsden CD. Internal versus external cues and the control of attention in Parkinson's disease. *Brain* 1988;111:323-45.
- 19 Yudofsky SC. Parkinson's disease, depression and electroconvulsive therapy: a clinical and neurobiological synthesis. *Compr Psychiatry* 1979;20:579-81.
- 20 Mutch WJ, Strudwick A, Roy SK, Downie AW. Parkinson's disease: disability, review and management. *Br Med J* 1986;293:675-7.
- 21 Anonymous. Parkinson's disease patients and their social needs. *Br Med J* 1982;285:900.
- 22 Hurwitz TA, Calne DB, Waterman K. Treatment of dopaminomimetic psychosis in Parkinson's disease with electroconvulsive therapy. *Can J Neurol Sci* 1988;15:32-4.

Greening the NHS

A plan to make the NHS more environmentally friendly

This year seems to be the year when environmental destruction has come to matter in Britain. One in eight people voted for the Green party in the European elections last month, and the various political parties are now vying to be the greenest. Given this impetus coming from the top of the political structure is it not time for the NHS to become more environmentally conscious? One of the main objectives of the NHS is to help people to remain healthy, and if environmental degradation continues unchecked it will start to have serious adverse health effects in the next century.

Many health authorities and NHS workers have already taken small but important steps to tackle some of the environmental problems that the health services are helping to create—for example, by collecting waste paper. Such projects may be started by individuals or groups throughout the NHS, and we have developed a table that will help staff start the process of greening the NHS. It is, however, not enough for individuals to take such actions. The scale of our environmental problems also requires units, districts, regions, and the departments of health to take policy decisions in favour of the planet, and the table also suggests what they may do.

The prospects of appreciable global warming and climactic disruption in the twenty first century are becoming increasingly likely. Such warming is caused by the greenhouse gases of the stratosphere, among the most important of which are carbon dioxide and nitrogen oxides.¹ Both these gases are produced when hydrocarbons are burnt to release energy. Carbon dioxide is fortunately recycled by plants, but one of the most important areas of the planet for such recycling—the tropical rain forests—is being cut and burnt. The NHS may

1 Oyebode JR, Barker WA, Blessed G, Dick DJ, Britton PG. Cognitive functioning in Parkinson's disease: in relation to prevalence of dementia and psychiatric diagnosis. *Br J Psychiatry* 1986;149:720-5.