BMJ
1840-1990

LONDON, SATURDAY 11 AUGUST 1990

Cell implantation in Parkinson's disease

More patients have probably been harmed than helped so far

The introduction of any new treatment is bedevilled by problems, and the story of implantation of dopaminergic neurones in patients with Parkinson's disease is no exception. Furthermore, the topic has been complicated by exceptional ethical issues. Though it now seems that successful engraftment may be possible, the optimal conditions, the precise indications, and the profile of side effects all need to be defined. Until these issues are clarified the procedure will remain experimental.

So far probably more patients have been harmed than have been helped, but the background to these first human studies was sound enough, and, with refinements, an addition to our current options for treatment could evolve over the next decade.

In 1979 two groups showed that when tissue rich in dopamine taken from the ventral mesencephalic region of embryonic donor rats was transplanted into adult rat striatum this corrected the behavioural abnormalities induced by a denervating lesion of the dopamine system.[1,2] Anatomical studies showed that the grafts were associated with outgrowth of fibres into normal projection areas.[3,4] Immunohistochemical methods showed the presence of tyrosine hydroxylase in the graft as well as neurotransmitters other than dopamine.[5] A graft could replenish on average one fifth of the normal striatal content of dopamine and in some cases half.[6,7] Ultrastructural studies showed the development of normal synaptic junctions, though abnormal contacts also occurred with other neurones in the striatum. The grafted neurones received a range of synaptic inputs that were similar, though not identical, to those seen normally. In rats damaged by 6-hydroxydopamine the grafts restored functional symmetry on spontaneous or amphetamine induced rotation and in sensory motor tests.[8,9] Animals given bilateral lesions fared less well, which suggests that there might be limitations to recovery.

Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates is a closer model for the human disease, but some natural recovery occurs, and this is a potential cause of confusion. The results of the (remarkably few) studies done in primates seem to parallel those seen in rats. Important issues that need to be resolved in research on animals include the need for immunosuppression and determining whether the graft works chiefly through the production of dopamine, the relevant synaptic connections, or the production of trophic factors. If it works through trophic factors the associated tissue components implanted might be vital, or growth factors might need to be introduced by other means. Controls on glial proliferation may be needed to avoid tumour formation or cells may need to be sorted to produce a purer source of dopaminergic cells. Cultured neuroblastoma cells or genetically engineered cell lines with dopamine or nerve growth factor phenotypes could function better and in the future replace the need for fetal tissue.

The first studies in humans used adrenal grafts. Such grafts work in rodents and can switch metabolism towards dopamine; and, as they were autografts, they reduced the immunological and ethical concerns. The Swedes used a stereotactic approach, placing small fragments of adrenal gland—predominantly the medulla—into one caudate. At six months the patients' conditions were thought to be unchanged.[10] Arguing that the loss of dopamine in Parkinson's disease is greater in the putamen than caudate and that the putamen is more important in terms of motor function, they then put two further grafts in the right putamen.[11] Minor improvements were seen, but they did not persist. A paper then appeared that claimed dramatic improvement in two patients who had received adrenal autografts.[12] This stimulated a surge of operations in various countries, principally the United States and China, which were often done in an uncontrolled fashion with limited data becoming available. Claims of improvement not easily explained by a destructive lesion are still being made, though it is also clear that patients have suffered substantial morbidity and some have died.[13] The few necropsy findings have shown minimal evidence of graft survival.

More recently the emphasis has shifted toward embryonic grafts. The critical age of the embryo is thought to be 7 to 12 weeks. About 60 000 dopaminergic neurones innervate the putamen; there are roughly 15 000 mesencephalic dopaminergic cells in an embryo. Clearly, one problem is ensuring survival of as many as possible of these cells; others include the number of donor embryos to be used and the optimal implantation site. Cell suspensions are easier to use than solid material. Some ethical issues have been agreed in Sweden and other countries (not always in advance). Tissue should be obtained only by standard suction procedures and should be tested for HIV, hepatitis, herpesvirus, and cytomegalovirus, which poses some technical problems—and some delay. The Swedish group made multiple assessments and kept medication constant for six months before and after transplantation.[18] F-fluorodopa positron emission tomography scanning was performed. Immunosuppression was given, and nigral cells were harvested from 8-10 week old embryos and placed in the putamen and caudate. There were

signs of slight, but not clinically important, improvement.[14] In the same year (1988) a report from Mexico of combined substantia nigra and adrenal medulla implant in two patients said that the patients showed some improvement two months after surgery. In Britain two transplantations were performed using fetal tissue of 14-16 weeks' gestation implanted without immunosuppression into the right caudate nucleus.[15] Surprisingly, an immediate response was reported that was then apparently sustained, though the condition of some patients in a larger series later deteriorated.

Earlier this year the group from Sweden and London reported their experience with a single patient after a unilateral implantation into the putamen.[16] Immediate improvement was not seen, but from the second month the time that the patient spent in "off" periods was much reduced, and this was associated with improvement in rigidity and mobility. As had been found previously improvement was not solely on the contralateral side. An important finding was the evidence of graft survival with increased tracer uptake in the putamen that was not thought to be secondary to a breach in the blood-brain barrier. Further studies will look at the need for immunosuppression and for growth factors. Whether the underlying disease will in the end destroy the graft is an issue. Treatment with deprenyl or other purported neuroprotective agents may enhance survival of grafts.

Possibly we are close to another treatment for the symptoms of late stage Parkinson's disease. The efficacy of the technique has to be defined, however, and careful follow up is crucial to determine whether the improvement is maintained. We also need to know that the graft cannot undergo uncontrolled growth, that changes in mental state do not become obtrusive, and that abnormal synaptic connections do not cause problems. Many other fundamental questions have to be answered—and they may be better investigated in rats or primates. Firm standards have been set for the assessment and choice of patients, and all results must be reported, preferably from a few centres performing prudent clinical studies that are assessed by positron emission tomography and that have close relations with research teams working with animals.

The neurodegenerative diseases are rapidly and rightly becoming one of the most important health issues of our time. Properly funded and conducted studies are needed on all new treatments, including implants, and those should run in parallel with the development of preventive and neuroprotective measures. In the long run an organised approach of this kind will be far cheaper than chaotic development of an expensive surgical "half way technology" approach—but it will need capital investment now.

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Trials and tribulations in speech therapy

At a guess we need more therapists

Patients who lose the ability to communicate through language after a stroke or other neurological catastrophe need help, as do those with swallowing disorders caused by conditions such as motor neurone disease.[1] Such help can come from speech therapists. Randomised controlled trials of speech therapy in patients with aphasia after stroke, however, have cast doubt on the efficacy of some speech therapy methods. Unfortunately this has in turn prompted the rejection by some therapists of randomised trials as a valid method of assessing their skills.

Lincoln and her colleagues from Nottingham attracted much misunderstanding with their randomised trial.[2] They found no difference after six months in communication ability between patients who had had no speech therapy and those who had had "routine therapy" for only two hours a week. This finding does not imply that all speech therapy is useless, but clearly that available in Nottingham at the time (and probably elsewhere in Britain) was of little benefit.

Wertz *et al* reported a crossover study in which the control patients received no therapy for 12 weeks then formal speech therapy for 12 weeks.[3] The treatment group received 12 weeks' therapy from either speech therapists or volunteers and then no therapy for 12 weeks. After 12 weeks there was a significant improvement in the treated group over the control group but no significant difference between those treated by speech therapists and those treated by volunteers. In the second 12 weeks the control group caught up with the treated group so that after 24 weeks there was no difference between them. Therefore, the speech therapy, which was more intensive than in Nottingham (eight-10 hours), was doing something. Unfortunately, there was no group receiving no treatment at all for 24 weeks to test whether therapy was more than speeding up natural recovery.

To try to separate the therapists' effect from the effectiveness of their therapies Hartman and Landau randomly assigned 60 patients to either formal speech therapy or "only"