

Safety and risk in practice

Parkinson's disease, foetal tissue and placebo surgery

Attempts to examine possibly beneficial new forms of treatment for Parkinson's face a complex series of ethical, legal and moral issues. It is clear that the disease itself involves a disorder of cells in the substantia nigra. The cells cease to produce dopamine, and they cannot be revived. The basic method of treatment during the last thirty years has been pharmacological, primarily with L-Dopa, which provides in effect an external source of dopamine to the brain. This treatment, however, has considerable limitations, including the induction of dyskinesias; other drug treatments, old and new, cannot at present be regarded as more than supportive. The problem in assessing any form of treatment is the variable course of the disorder, but a secondary difficulty is that the reaction to any therapy may set in late and be of variable duration and extent. It is a typical situation in which large scale studies, prolonged observation and placebo control are called for.

A number of surgical approaches to treatment have been introduced or are in the course of study [1], but here too the same difficulties arise – as well as some additional ones. Thalamotomy, involving destruction of some thalamic tissues, can correct a disabling tremor in the upper limbs, but the results are not dependable and destructive surgery, once performed, cannot be undone. Much the same holds good for pallidotomy, carried out on the globus pallidus, which sometimes corrects disorders of balance, movement and slow tremor. Something of the benefit seen with destructive surgery can be attained in certain individuals with the placement of electrodes which stimulate selected areas of the brain; an advantage here is that invasion is minimal, nothing is destroyed and that the electrodes can if necessary be removed.

With none of these treatments constituting anything like a breakthrough, the next experimental treatment in line is the introduction into the relevant areas of the brain of foetal brain cells, taken from the products of therapeutic abortion. Both in animal studies and in humans, these cells have shown the ability to integrate into the patient's own brain tissue and recommence the secretion of dopamine, though results are still variable. At this point a whole series of dilemmas arise. One is ethical and even religious – can material from an aborted foetus properly be used, even to benefit a living patient? Setting that objection for the present purpose aside, some problems related directly to physical risk remain. Firstly, it is possible that the cells may induce an allergic reaction in the recipient. Secondly, if one seeks to avoid such a reaction by administering an immunosuppressant drug, such as cyclosporin, one is faced with the adverse effects of this substance. Thirdly there is the surgical risk of implantation, though in fact a burr hole suffices, which does not even penetrate the inner cortex of the skull bone, the cells from that point being injected using a needle. And then, finally, one has the need for placebo-controlled investigations in order to arrive at the same assessment of reliability and risk which is needed before a drug therapy can be considered for routine use; on present evidence the efficacy of the method is variable, the exact technique still uncertain and possible long-term entirely obscure. But placebo treatment in this case will involve both the drilling of burr holes and the administration of an anaesthetic, neither of which are entirely without risk; obtaining volunteer consent to participation in such a study is clearly more tricky than in drug studies where the placebo is likely to comprise little more than colored chalk. A patient whose Parkinsonian symptoms are so stubborn that surgery or transplantation need to be considered at all may

be less than anxious to risk ending up being randomized to receive placebo. There is a (very little) evidence that the placebo surgery itself could have an effect in a minority of patients, though early work on Parkinsonism does not suggest that the placebo effect is likely to be helpful in practice.

At this moment, the ethical and religious objection to the use of foetal cells stands in some countries entirely in the way of developing this approach further, but in others work continues and the medical risks are being accepted in one way or another – very understandably so, in view of the potential gains to at least some patients incapacitated by Parkinsonism. One writer who, after a careful analysis of all the arguments, essentially rejects the approach is Peter A. Clark of the (Catholic) St. Joseph's University in Philadelphia (“...placebo surgery in controlled trials using fetal tissue for Parkinson's disease should be stopped immediately...”) [2], though in such a complex analysis it is difficult to know how heavily the religious and ethical argument weighed in arriving at his judgement; and even this author thinks the question might in due course be re-evaluated. One relatively large study with a positive outcome is that by Freed in Denver and Fahm in New York, published in 1999 [3], in which some two thirds of patients reacted relatively well, with evidence that the transplants had taken and were producing dopamine. But Clark argues that the design for the research using placebo surgery is flawed, especially since the mechanical effects (of stereotactic needle insertion) could themselves influence the outcome. He points also to a statement dating from March 2001 on the negative outcome of work using pig foetal material in human subjects [4]; he also cites a later statement by Freed that in a proportion of the patients in the Denver study the transplants proved to be excessively effective in producing dopamine, resulting in extremely distressing movements [5].

Commenting on Clark's review, Weijer from Canada [6] generally accepts that something less contentious than sham surgery (with burr holes) much be found into provide valid controls further studies of these approaches to Parkinsonism, but it is not clear that he seems able to point to a valid alternative at the present time. It seems very likely that this work will continue in many centres across the world, but the ethical discussion goes on, and may assist in overcoming at least some of the objections which can be raised to current work.

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Safety of home births: The evolving scene

The last two decades of the twentieth century have in a series of countries seen a substantial move back to home birthing with a qualified midwife in attendance. It is probably correct to say that it should never have been eclipsed in the first place; midwives – qualified or otherwise – have managed the vast majority of births since the beginning of the world, done it in the home and have generally done it very well. The way in which deliveries had over several generations been forcefully moved into the

sphere of hospital procedures was certainly not due to the shortcomings of professional midwifery; to a considerable extent it undoubtedly reflected the attitude of a medical profession which had come to view pregnancy as a disorder, delivery as a surgical rather than a physiological and family event, and (in the extreme view) the midwife as little more than a nursing assistant who was good enough to hand the forceps to the obstetrician when so commanded.

The renaissance of home birthing has naturally been surrounded by safeguards; the obstetric delivery room is still likely to be the best place to deliver where pregnancy is attended by any complication which might render special measures necessary. In addition, there are many parts of the world where domestic housing is so cramped or of such poor quality that even the birthing room of a simple country health post is preferable. In addition, where distances are so great or communications so poor that last-minute referral to a hospital is hardly feasible, one is likely to be particularly stringent in excluding from home delivery those pregnancies where there could be even the slightest prospect of complications. Finally, in those countries where the profession of midwifery had been relegated to the shadows for a considerable time it can still be impossible to create a sufficient network of qualified professionals over a short period.

The safety of home midwifery itself is hardly in doubt, nor is the fact that it is efficient and cost-effective – a relevant consideration in a time of rising hospital costs. There have been positive studies of home delivery outcomes in the Netherlands [1], the United Kingdom [2], the USA's Washington State [3] and New Zealand [4]. The series has now been extended by a relatively small but meticulously conducted follow-up in Canada's British Columbia [5]. Canada presents a particular challenge because of the prolonged and fargoning marginalization of midwifery, a trend which has only recently been thrown into reverse. Quebec and Ontario approved home birthing once more in 1994, and British Columbia in 1998. The last of these is an especially enterprising step because of the province's geography and the prevalence of difficult weather conditions which can derange ambulance services. However, the regulations of 1998 made detailed provision both for ensuring midwifery standards and for the criteria which would be applied in deciding for or against domestic birthing; the choice between home and hospital birthing is made by the pregnant women herself in consultation with her midwife.

The British Columbia team of physicians and midwives were able to examine the outcome of 862 planned home births attended by midwives, and to compare the results with those recorded in 571 hospital deliveries attended by midwives and 743 attended by physicians. All home births in the province over a period of two years were included in the series, and women in the three groups were similar, though those in the home birthing group were on average slightly younger.

Women who gave birth at home had fewer procedures during labour (epidural analgesia, induction, pharmacological augmentation of contractions, episiotomy) as compared with women who gave birth in hospital; hospital births attended only by a midwife showed results very similar to those seen in home deliveries. 21.7% of the women opting for home delivery ultimately had to be transported to hospital (16.5% during labour), for example because caesarian section proved advisable; however the chance of caesarian section in home deliveries was only a third of that in planned hospital births. The risk of a series of complications affecting the infant (low Apgar score, perinatal mortality, meconium aspiration, transfer for specialised neonatal care) was low but very similar in all groups. For a number of other measures, the series was too small for statistically valid comparisons to be made.

In part, of course, results like this reflect something of a self-fulfilling prophecy; the very reason why many births took place at home was that these were pregnancies in which the anticipated risks at the time of delivery were very low; a favourable outcome with little need for special procedures was therefore to be expected unless the fact of domestic delivery introduced any new risks. However the findings, which are tabulated in detail, provide further sound reasons to believe that home birthing is safe and that in

a very high proportion of pregnant women it is appropriate. The demedicalization of normal birthing has very clearly arrived.

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Ventilation of operating theatres – costs, risks, and uncertainties

As with most other forms of risk in medical and surgical practice, there is a price to be paid for reducing the risk of post-operative infections; the question is bound to arise repeatedly which of the pre-, per-, or postoperative measures that are currently taken – or could be taken in the future – are really cost effective. Some long-established practices – such as the wearing of surgical masks and the use of rubber gloves during surgery – have become regarded as so self-evident that no one would wish to test their value today in a controlled study. Other measures, including steps to reduce contamination of the air entering the operating theatre, have become widely used but with a very variable degree of stringency. How important is the quest for pure air in the theatre, and what costs are justified?

It is evident that one could easily go further than is strictly necessary – and at considerable expense – since within the operating theatre the inflow of air is only one of the possible sources of contamination; the personnel (and the patient) are themselves significant sources of bacteria, disseminated from exposed hair and skin but also during speech and breathing.

For a long time, well-equipped operating theatres have used positive pressure ventilation with filtered or otherwise purified air. The purification may be basic or sophisticated; simple filtration can eliminate particles as small as 3–10 μm ; it is however possible to use filters with pores of only 0.3 μm , resulting in essentially bacteria-free air; the term “High Efficiency Particulate Air” (HEPA) is applied to air where the contamination is less than 10 CFU/m³. One can also control the nature of the airflow: “Laminar Air Flow” provides parallel streams of incoming air, so directed that air which has been contaminated inside the theatre does not continue to circulate around it and is eliminated as soon as possible. These more advanced systems are used in a proportion of western hospitals. Do the results justify the costs? It has after all been calculated that at the present day it will cost some \$50,000 to equip a theatre with a HEPA air supply, and the running costs are considerably higher than those of a simpler system.

Surprisingly, questions like these have not been satisfactorily answered on the basis of thorough studies of the benefits which can be expected. Official committees, for example in Norway and Germany, have set standards for the quality of the air in operating theatres, but it is not easy to see on what data these are based [1,2]. The Norwegian guidelines require a contamination level below 100 CFU/m³ for general surgery, and a level below 10 CFU/m³ for surgery where wound infection carries a particularly high risk (e.g., in the cardiovascular or neurological field); these standards appear to be based on the basis

of work and recommendations by Lidwell and his group dating back to the eighties [3], but the latter are far from watertight. One working group which recently examined the world literature in great detail could in fact find not a single reliable study [4]. One well-planned study from the Mayo Clinic relating to hip replacement was never published in full [5]. In the working group's view, current recommendations are based on beliefs and hypotheses and not on facts. Despite the numerous factors determining the risk of post-operative infection, the influence of air quality in the theatre is an issue which could be studied systematically, and which deserves more attention than it has so far received.

References

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The Alzheimer vaccine – what went wrong?

The controversy as to whether it will ever be possible to provide vaccination against Alzheimer's disease unavoidably continues following the complications which disrupted the trial of a potential vaccine in the USA [1].

Created by Ireland's Elan Corporation with international consultant support and with America's Wyeth participating in clinical work, the vaccine (known as AN-1792) contains A β , the peptide which many scientists believe fires off Alzheimer by forming amyloid plaques in the brain. It had already proven to remove plaques of the same or similar type which had been induced in transgenic mice [2], and it seemed to be capable of preventing cognitive defects and possibly even reversing them [3]. After that a Phase II clinical study was started up, to which 375 patients with mild to moderate Alzheimer were recruited. In January 2002 further administration of the vaccine was stopped because four patients showed signs – headache, stiff neck, moderate pyrexia – which suggested inflammation of the central nervous system. By the end of February a further 11 cases were showing symptoms, and two patients suffered ischaemic stroke and the study was stopped. Clinically, far from showing any cognitive improvement, affected patients showed aggravation of their confusion and their difficulty in performing simple everyday activities. No infection was traced, though CSF levels of protein and lymphocytes were raised; there was no correlation between antibody titres and symptoms. The patients with complications showed no further deterioration after the study was stopped and some showed improvement.

A clue as to what had happened might be provided by Morgan's work in pharmacology at the University of South Florida, though that is not undisputed. Again using middle-aged transgenic mice he found that administration of A β vaccine temporarily (from the fifth to the ninth month) raised levels of the enzyme CD₄₅ in the hippocampus. A rise in CD₄₅ is believed to point to activation of the brain's phagocytic microglia, which among other things phagocytose antibody-bound issue; it is considered characteristic of inflammation. The fact that the rise was temporary, Morgan argued, might indicate that the mice were becoming tolerant to the vaccine. It has been pointed out however that Morgan was not using old mice, and that there was no evidence of cognitive failure accompanying the supposed inflammatory reactions.

Various other approaches to vaccination (or even means of passive immunization) are being devised at a number of centres, but a burning question is whether the use of $A\beta$ has any future or not. Sceptics had in advance argued that it amounted to immunizing subjects to a naturally occurring human peptide, and was therefore only inviting trouble, unless the peptide has no “normal” function in the body and therefore can be eliminated without risk. Others assert that $A\beta$ is encapsulated within the plaques and could be released in harmful amounts if they are dissolved. Yet others point out that in Alzheimer the defect involves not plaque formation but also intracellular tauopathy – a tangle of material composed of the protein tau which is now thought to be one of the main causes of neuronal degeneration; in their view there is no point in curing the plaques if the tauopathy persists.

Optimists are not likely to abandon the effort at present. An intranasal trial of $A\beta$ vaccine is planned, as is an effort to identify and screen out those individuals at particular risk from vaccination. Companies, as well as U.S. health agencies, are planning to invest further in efforts to counter Alzheimer, but what has so far happened with $A\beta$ vaccine suggests that one is still far from an effective – and safe – approach [4].

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