# Opinion on the transplantation of nerve cells in the treatment of Parkinson's disease. Report.

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# Opinion

The ethical problems involved are of two orders:

1. One kind is related to the present state of knowledge;

2. The other to having recourse to embryos.

## Problems related to the present state of knowledge

The National Consultative Ethics Committee was informed of the results of such transplants, practised in several foreign countries over a number of years. With rare (unconfirmed) exceptions, these transplants have resulted only in minimal and usually transitory improvements, and in addition, only in a minority of Parkinson's patients. These improvements are disproportionately small, in comparison with the danger to patients resulting from surgical procedures required for the transplantation (frequent and severe postoperative complications, deaths).

This is why the Committee recommends that such therapeutic attempts not be undertaken in France, at least for the time being. In fact, it seems to the Committee that it is necessary to await the results of research presently underway, in particular on primates, to be able to judge whether such risky interventions are ethically acceptable. This research is investigating the nature of material to be transplanted (medullo-adrenal fragments, mesencephalic tissue from human fetuses, or possibly cultured dopaminergic cells), the biology of these transplants, and the long-term effects of different types of transplants in experimental Parkinson's disease studies.

## Problems related to having recourse to embryos

On the subject of possible recourse to tissue from human embryos, the Committee recalls that in a previous Opinion (1984), it recommended that the use of such tissue for therapeutic purposes be exceptional, in order to avoid any kind of pressure in favour of abortion. This recommendation remains valid, and all the more so since animal experimentation has shown that, in order to be able to join the host's nerve structure, embryonic neurons have to be transplanted at a particular stage of their development, which could lead to planned abortions.

The region of the human embryo's central nervous system, which is used for these transplants, contains only very few dopaminergic cells. It is by no means certain that using transplants, with so few constituents of potential benefit to Parkinson's disease patients, is really the technical solution with the greatest chance of success. Implantations including nothing but dopaminergic cells ought to be more effective, and this is why consideration is being given to preparing cultures of these cells.

In the two events, that technical difficulties associated with preparing such cultures are overcome, and that transplanting these cells leads to appreciable and sustainable improvement in experimental Parkinson's disease treatment of primates, the ethical objections mentioned above would lose their applicability. In any event, if a foetus is to be used as a source of dopaminergic cells, this can be done only in strict accordance with the recommendations made by the Committee in its 1984 Opinion.

# Report

Over the last fifteen years or so, many experiments involving transplantation of embryonic nerve cells have been conducted in various regions of the central nervous system (CNS) of adult animals, almost always rodents. They show that these transplants do not behave like foreign bodies, but can be integrated into the host's nerve networks. In animals with damage to certain CNS regions, these transplants manage to compensate for functional deficiencies. Even complete anatomic restoration has been achieved in animals deprived, through a genetic defect, of a particular type of neuron or of myelin sheaths surrounding certain nerve fibres.

There are considerable differences between these experimental models, and degenerative diseases of the CNS in man, in particular Parkinson's disease. Nevertheless, some experiments have gone so far as to transplant neurons (or neurosecretory cells) to patients suffering from this disease, in an attempt to improve their condition.

This presentation breaks down into three parts:

1. description of several transplant experiments with animals (rodents);

2. review of the therapeutic effects of transplants in Parkinson's disease;

3. ethical problems concerning the advisability of practising transplants in Parkinson's disease patients in France.

## Description of several transplant experiments with animals

A few preliminary remarks:

a) The great majority of nerve tissue transplants have involved neurons, whose activity " modulates" that of large populations of so called " integrator" neurons. The latter are parts of structures that process specific information (for example, neurons of the sensory pathways leading to the cerebral cortex, neurons of subcortical formations, that participate in preparation of the command signals of the locomotive apparatus). These modulator neurons, which are situated in the mesencephalon, are mainly aminergic (dopaminergic, noradrenergic, serotoninergic) and cholinergic neurons. Many neurological and psychiatric disorders can result from their dysfunction or degeneration.

b) Neuronal transplants do not develop in the CNS of host animals unless the transplanted neurons and the neurons of cerebral formations, where the transplantation is done, are matched.

c) Rejection reactions to transplants in the CNS are weak and relatively easy to control, because very few of the circulating immunocompetent cells (macrophages and lymphocytes) manage to penetrate the CNS. Nevertheless, such reactions do exist, probably because certain glial cells have immunocompetency properties; in the longer term, they are capable of putting transplant survival into question.

**A. Transplants followed by functional recovery**

- In the rat, transplantation of embryonic dopaminergic cells to the corpus striatum, deprived of part of its dopaminergic allocation by section of a nigro-striatal pathway, causes the disappearance of motor and posture disorders resulting from the section (Bjorklund).
- In paraplegic rats, after transverse section of the spinal marrow in its lower thoracic part, the transplantation of embryonic noradrenergic neurons to the underlying marrow causes locomotor reactions to reappear, while serotoninergic neurons do the same for vesical and genital reactions (Privat).
- Memory and learning deficiencies, observed after section of cholinergic septi-hippocampal fibres, are reduced following transplantation of cholinergic embryonic neurons to the hippocampus (Gage).
- Transplantation of hypothalamic neurons to the median eminence re-establishes the fertility of mice, when they are sterile for lack of hypothalamic gonadorelins of genetic origin.

**B. Transplants leading to anatomic recovery**

- Because of a genetic defect, the Purkinje cells (neurons located in the cerebellar cortex) of a certain strain of mouse degenerate completely after birth, which leads to locomotor ataxia. In these mice, the transplantation of embryonic cerebellar cells is followed by their migration to the cerebellar cortex, their complete maturation and the reconstitution of specific interneuronal circuits with functional synapses (Sotelo, Crepel).
- In mice, in whom the myelin sheath of certain nerve fibres is abnormal or even absent, whether because of a genetic defect, or after administration of lysolecithin, the myelin sheaths are reconstituted after transplantation of embryonic tissue or of glial cells (oligodendrocytes) in culture (Gumpel, N. Bauman). Transplants of tissue from the peripheral nervous system have also been attempted, for example, sciatic nerve transplantation to promote the regrowth of nerve fibres of a sectioned optic nerve (Aguayo). Transplants of embryonic muscle cells to damaged striated muscles are capable of reconstituting normal muscle fibres (Fardeau).

## Review of the therapeutic effects of transplants in Parkinson's disease

To our knowledge, no transplants have so far been practised in Parkinson's disease patients, except in certain foreign countries. In the great majority of cases (no doubt several hundred), the strategy has been to compensate for the dopamine deficiency of the corpus striatum, resulting from degeneration of nigro-striatal neurons (neurons located in the black substance that innervates the corpus striatum), by transplanting medullo-adrenal fragments taken from the patients themselves to the corpus striatum. It is only in a very small number of cases (a few dozen), that dopaminergic embryonic cells taken from the mesencephalon of human foetuses have been transplanted. The transplantation of medullo-adrenal fragments has been practised much more frequently, because these autotransplants do not lead to rejection reactions, and also because they do not give rise to ethical problems of the same gravity, as those associated with the use of human fetal tissue.

The chromaffin cells of the medullo-adrenal gland, once activated by the preganglionic cells that innervate them, release noradrenalin, and also adrenalin, in variable quantities depending on the species. These amines act on a very large number of organs through the

blood stream. Chromaffin cells are potentially capable of releasing very small quantities of dopamine, a precursor to noradrenalin. The hypothesis (possibly a bit simplistic, and not yet tested by prior experimentation) was that chromaffin cells, transplanted to the corpus striatum of Parkinson's disease patients, would release enough dopamine, even in the absence of any afferent innervation. Using these cells could be justified by the fact, that motor and posture disorders in rats, after section of the nigro-striatal neurons on a single side, are corrected fairly well by the transplantation of medullo-adrenal fragments to the corpus striatum.

The first transplants were done in Sweden in 1982 (Backlund, Bjorklund and Olson) on four patients. Suffering from Parkinson's disease for several years, they presented on and off periods, that is, periods during the waking state, during which anti-Parkinson medication (mainly L-DOPA) was, respectively, effective and ineffective. The implantation sites were the head of the caudate nucleus (two cases) and the putamen (two cases). The observed improvements were very modest: increase over several weeks of the duration of on periods, and possibility of reducing L-DOPA doses for a certain period of time; these results remained unnoticed by the public at large.

It was the publication in 1987, in the New England Journal of Medicine, of observations made in Mexico by I. Madrazo et al., that elicited substantial interest among neurologists, and raised much hope among Parkinson's disease patients. It was in fact reported in this article that two patients, treated by transplantation of fragments of one of their medullo-adrenal glands to the right caudate nucleus, presented distinct clinical improvement just a few days after the transplant; this improvement progressed rapidly, to the extent that rigidity and akinesia almost disappeared several months after the transplant, and trembling diminished considerably.

There was an attempt to explain the inconsistency between the results of the Swedish and Mexican teams by differences in patient age (much younger in Mexico than in Sweden), and in operating technique (in Sweden, stereotaxic injection to the striatum of a cellular suspension; in Mexico, open micro-surgery, allowing for the insertion of medullo-adrenal fragments into a cavity of the caudate nucleus head, so that the transplant was in contact with intraventricular cephalorachidian fluid).

The announcement of an effective treatment for Parkinson's disease by transplantation, disseminated very widely by the media, raised much hope among Parkinson's disease patients, who often insisted themselves on being operated. As a result, many teams of surgeons, especially in the United States, in Great Britain, China, Spain, Italy and Cuba, started to practise medullo-adrenal autotransplantation, following the example of the Mexican surgeons. Unfortunately, the spectacular results reported by these neurosurgeons were not confirmed, and initial expectations quickly gave way to disappointment.

The overall evaluation, based on about fifty cases, and reported to the last international Parkinson's disease congress (Jerusalem, 1988), is negative: in only one third of operated patients was there a lengthening of the on phases, accompanied sometimes by a slight reduction in the quantity of administered L-DOPA, but these beneficial effects generally did not persist beyond several months; two thirds of the patients did not present any improvement at all. On the other hand, these procedures resulted in quite a number of postoperative complications (cerebrovascular, pulmonary, abdominal, and neurological, such as dyskinesia and mental confusion), as well as several deaths.

Just recently (1989), the results of a study carried out in several North American centres on 19 Parkinson's disease patients (Goetz et al.), treated by medullo-adrenal transplantation, were published. These groups of neurosurgeons and Parkinson's disease specialists set themselves the explicit objective of comparing their results with the first results of the Mexican team, by applying an identical operating technique. The operated Parkinson's disease patients were of all ages, with some of them below the age of forty. Significant lengthening of on " periods" was observed, but it was not possible to reduce the doses of anti-Parkinson medication. Motor activity during " on periods" did not present significant

improvement; however, choreal movements were attenuated. These authors, while assessing their results as encouraging, conclude that they are quantitatively very different from those reported by the Madrazo team, for they did not determine " excellent improvement of most clinical signs" . In this series of operations, there was also a rather large number of postoperative complications, and one death.

Postmortem examination of the brains of transplanted Parkinson's disease patients has shown, that medullo-adrenal transplants are usually completely atrophied and sclerotic, and consequently incapable of exercising the expected dopaminergic effect on the striatum. In several cases, axonal collateral budding was observed in the neighbourhood of the transplant. If this budding is produced from nigro-striatal fibres that are still intact, and supposing, in addition, that it is accompanied by increased dopamine release by each of these fibres, then one could attribute to it the slight improvements that have been observed. One would also have to know whether this budding results from a trophic action, specifically connected with the nature of the transplant.

The results of transplantations of embryonic tissue from human fetuses, taken from the ventral part of the mesencephalon, which encloses the cellular bodies of nigro-striatal neurons, have not been published in extenso, to our knowledge; but the scanty preliminary information that is available hardly differs from that pertaining to adrenal autotransplantations. Nevertheless, it is advisable to wait for some time before evaluating their action, in case re-innervation of striatal neurons does develop in the longer term.

Given the present state of affairs, great prudence with regard to medullo-adrenal or embryonic tissue transplantation would seem to be the order of the day, especially since it is known that the condition of certain Parkinson's disease patients can improve spontaneously, for periods of variable duration, and since placebo type effects are always difficult to exclude.

## Ethical problems concerning the advisability of practising transplants in Parkinson's disease patients in France

To our knowledge, it would seem that intracerebral transplants in Parkinson's disease patients have not been practised in France, the reserved attitude of French biologists and clinicians, who specialize in the nigro-striatal system, doubtless contributing to some extent to this state of affairs.

This is why it seems to us that two questions could be submitted to the National Consultative Ethics Committee : the one requiring a speedy answer, and the other with perhaps not the same degree of urgency.

1. In the immediate term, and even though the Committee's opinion on this question has not been sollicited, would it not be advisable that the Committee recommend, if this does not fall outside its competence, that attempts to treat Parkinson's disease by transplantation not be undertaken, at least for the time being, in our country? For if one weighs the serious postoperative risk for patients of these procedures, against their uncertain, small and generally transitory benefit, one cannot help but share the view of most foreign medical and surgical teams having gained some experience with such transplants, namely, that it is not appropriate, given the present state of our knowledge about transplant biology, to continue these therapeutic experiments.

This attitude in no way signifies, that embryonic nerve cell transplants have no future in the treatment of Parkinson's disease (or of other morbid conditions of the nervous system), but only that it is, at present, contrary to the interests of the patient to practise medullo-adrenal or embryonic mesencephalic tissue transplantation.

The results of experimental animal research on the biology of transplants, with a view to

determining their survival, their mode of action (direct or indirect, specific or non-specific), and their restorative ability, will have to be known, before these therapeutic attempts are, possibly, undertaken or resumed. Such research is possible, in particular by studying the long-term effects of transplants on experimental Parkinson's disease in primates, following the destruction of nigro-striatal dopaminergic neurons by a neurotoxic substance, namely methyl-phenyl-tetrahydro-pyridine (MPTP). Initial observations are encouraging (Redmont and Roth), but observations over a longer term are necessary.

2. If research of this type, as well as long-term clinical observations of Parkinson's disease patients, to whom human embryonic tissue has already been transplanted, were to demonstrate the effectiveness of these transplants, the second question which the Committee would have to answer, and which one can obviously start to study right away, is whether or not the commonplace use of nerve tissue taken from human embryos gives rise to objections of an ethical order. In a 1984 Opinion given by the National Consultative Ethics Committee, it was specified that: " The use of embryonic tissue for therapeutic purposes (transplants) is justified, provided such use is exceptional in nature, and is supervised by an ethics committee. The condition of exceptionality is necessary, in order to avoid such use constituting pressure in favour of abortion on a massive scale, and becoming a widespread, routine technique."

In Sweden, the prevailing opinion seems to be that brain fragments taken from a fetus, under legally determined conditions, may be transplanted with the authorization of the woman having decided to terminate her pregnancy, or having aborted spontaneously.

In Great Britain, the Ministry of Health has just authorized research on fetal tissue, available as a result of induced abortion, and stresses the fact, that there has to be a clear distinction between the mother's consent to the abortion, and the consent for subsequent use of tissue taken from the fetus.

In the United States, the participants in a meeting held in 1986 at Case Western Reserve University, considering that " foetal tissue transplantation will doubtless hold out much promise, and will render great service to the victims of severe neurological disorders" , concluded that the retrieval of foetal tissue is comparable to taking organs, for therapeutic purposes, from adult human cadavers. Nevertheless, recognizing that the two situations are not identical, they recommended that there be complete separation of decisions concerning foetal tissue acquisition, and those concerning their transplantation; that anonymity between donor and recipient be respected absolutely; that any family relationship between donors and recipients be excluded; that in-depth information be provided as to the grounds for the planned use, and that patients be informed of any risk involved.

In the United States (where the federal government has prohibited, at least on a provisional basis, any human fetal tissue research funded by the National Institutes of Health), the use of non-viable foetuses, after spontaneous abortion, is being envisaged for therapeutic transplantation; this potential source of embryonic tissue is not very abundant, and is also not quite compatible with the planning that transplantation requires.

Animal experimentation has in fact shown, that embryonic neurons do not continue their normal development within the nervous system of adult recipients, unless they are already differentiated without being completely developed, that is, before their dendritic marking appears, and before their axon genesis starts. In the case of dopaminergic neurons of the ventral mesencephalon of the human embryo, the period when these cells are in this particular phase occurs around the ninth week of the embryo's life.

Therefore, tissue must be retrieved from foetuses of a specific age, and it is not difficult to imagine the possible consequences of this constraint: planned pregnancies and induced abortions on appropriate dates.

Even before adopting an ethical position as to tissue retrieval under such conditions, it must be realized that in the embryo's ventral mesencephalon (where dopaminergic cells are to be

found) less than two percent of the cells are dopaminergic, and that the effectiveness of transplantation of embryonic tissue, with such a paucity of dopaminergic cells, is far from having been demonstrated.

For reasons of technical efficacy, it would seem preferable to try to obtain cultures of embryonic dopaminergic cells. If the transplantation of such cells, at the appropriate stage for their possible development in the host's brain, were to turn out to be an effective treatment of experimental Parkinson's disease in monkeys, then one could envisage the creation of banks of human dopaminergic cells, prepared from samples taken from human fetuses. It seems to us, that their use would not encounter the same ethical difficulties, as the transplantation of tissue retrieved from human embryos of a given age.

In conclusion, would it not be opportune that the Committee:

1. Recommend to French neurosurgeons that they not undertake medullo-adrenal autotransplantation, or transplantation of human embryo mesencephalic tissue, in patients with Parkinson's disease, because of the danger of such procedures, which is incommensurate with the doubtful and uncertain benefit that can be expected?

(It would be specified explicitly, that this recommendation might only be provisional in nature. If progress is achieved on the nature of the elements to be transplanted, and on the biology of transplants, and especially if it is demonstrated, on Parkinson models close to Parkinson's disease itself, that certain transplants can be effective, this recommendation would obviously be annulled.)

2. Re-affirm its position as to the ethical aspects of procedures based on the use of human embryos?

It could do so immediately, or only after possible technical progress would have demonstrated the utility, for Parkinson's disease patients, of transplants of dopaminergic cells taken from human embryos (mesencephalic tissue from an approximately nine-week foetus, or possibly embryonic cell cultures).

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