Cell Transplantation for Neurological Disorders

Toward Reconstruction of the Human Central Nervous System

Edited by

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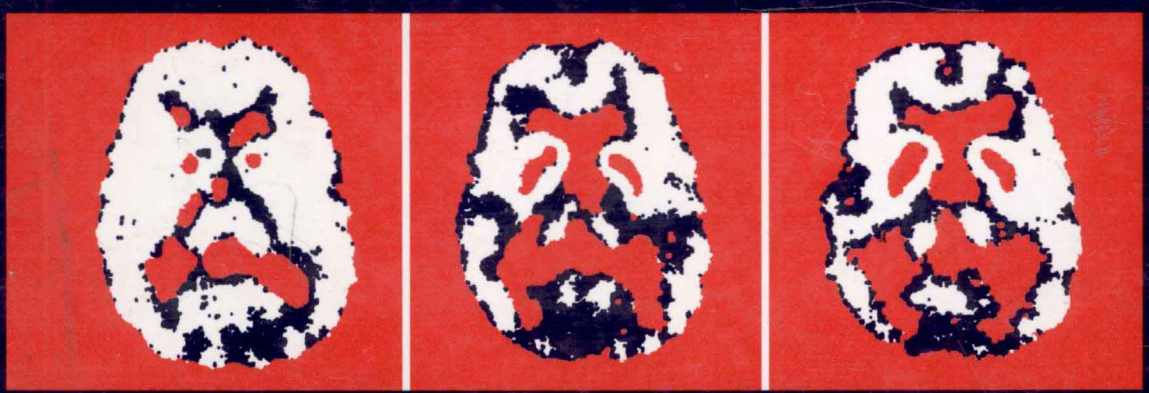
神经性疾病细胞移植治疗



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Foreword

NEURAL TRANSPLANTATION: *FROM LABORATORY TO CLINIC*

The history of neural transplantation for replacement of lost neurons and reconstruction of damaged circuitry in the mammalian CNS is short, and its clinical application is still in its infancy. Transplantation of neuronal tissue is a classic approach in neuroembryology, and this technique has been extensively used as an experimental tool for the study of neuroregeneration and repair in submammalian vertebrates. Work in amphibians and fish, which was carried out during the early part of this century, was the first to demonstrate the possibilities of neuronal replacement after damage in the central nervous system. This early work, which was performed above all by Matthey *(1),* Stone *(2),* and Sperry *(3)* in the visual system in salamanders and frogs, demonstrated that grafted neurons have a capacity to substitute both structurally and functionally for lost axonal connections, and that afferent and efferent connections can be established with a high degree of specificity between grafted neurons and the host brain (*see* ref. *4,* for review). The first attempts to apply neural grafting in animal models of neurodegenerative disease were made in the late 1970s *(5,6)* and since then, experimental work and clinical trials have developed in fruitful interplay between laboratory and clinic.

Parkinson's disease has come to serve as the primary test bed for the neural transplantation technique, for several reasons. One important reason is that Parkinson's disease affects primarily a circumscribed set of neurons in the brain (the mesencephalic dopamine neurons) whose main target, striatum, is anatomically well-defined and relatively accessible surgically. Moreover, and most importantly, there are well-characterized animal models, both in rodents and primates, that mimic the cardinal features of the disease. Results obtained in these animal models have repeatedly proved to have good predicative value with respect to the human disease.

Neural transplantation in Parkinson's disease is based on the idea that dopamine-producing cells implanted into the denervated striatum might be able to substitute for those mesencephalic dopamine neurons that have been lost as a consequence of the disease process. The grafted neurons are envisioned to function either by a "pharmacological" type of action, whereby the released dopamine is able to diffuse over sufficient distances to activate the denervated striatal receptors, and/or through functional reinnervation of the denervated target neurons by the outgrowing axons of the implanted neuroblasts, which allows the released dopamine to exert its action at defined synaptic sites. The idea that transplanted cells can function as "biological minipumps" has provided the rationale for using transplants of adrenal chromaffin cells, not only in Parkinson's disease (as discussed by Kordower et al. in Chapter 5), but also in patients suffering from chronic pain (as described by Sagen in Chapter 12). Similarly,

genetically engineered cells have been used as a source of therapeutic molecules; such cells may be applied either as transplants of naked cells or as implants of cells encapsulated in a semipermeable membrane, as discussed in detail by Emerich et al. in Chapter 13 and by Thode et al. in Chapter 15.

During the 15 years that have elapsed since the first Parkinsonian patient received a transplant of adrenal chromaffin tissue in 1982 *(7)*, the field has passed through two distinct phases. In the early clinical trials the patients received transplants of catecholamine-producing cells obtained from the patient's own adrenal medulla. As pointed out by Kordower et al. in Chapter 5, the choice of adrenal chromaffin cells was not primarily based on scientific considerations, and in retrospect it is clear that the poor survival of the grafted cells and the disappointing outcome in these trials could have been predicted from animal experimental data, and indeed, even from the results available at the time. Considering that many patients received this type of surgery, probably more than 1000 worldwide, it is unfortunate and regrettable that this procedure was adopted by many centers without proper consideration of its scientific basis.

The second phase of clinical trials has involved the use of immature dopamine neurons obtained from the mesencephalon of 6–8 wk aborted embryonic cadavers. These trials were initiated in 1987 *(8–10)*. Since then, over 200 patients with Parkinson's disease have received transplants of embryonic mesencephalic tissue, and time is now ripe to summarize the experiences obtained so far. In this timely volume, *Cell Transplantation for Neurological Disorders*, Widner, Hauser et al., and Peschanski et al. (Chapters 1–3) discuss the results obtained in three of the most influential ongoing clinical neural transplantation programs, and in the two subsequent chapters Snow and Kordower et al. summarize available data on long-term survival of grafted mesencephalic dopamine neurons in transplanted patients as assessed by either positron emission tomography (PET) or by immunohistochemistry of brain tissue obtained postmortem. Although the number of patients that have been studied in a systematic and rigorous manner (including PET analyses of transplant survival) is small, the results show clearly that embryonic dopamine neurons can survive and function for several years in the brains of patients affected by Parkinson's disease, similar to what has been observed in animals with toxin-induced parkinsonism. As a followup to these open-label studies, two NIH-sponsored double-blind controlled trials are now under way in the United States. Indeed, Peschanski et al. argue that the time now is ripe to initiate a phase III multicenter trial that would involve 20–30 centers worldwide in order to clarify the reliability and overall usefulness of embryonic mesencephalic grafts as a therapy for late-stage Parkinson's disease.

I think most of us agree with the view of Dunnett *(11)* and Lindvall *(12)* that the clinical studies carried out so far provide a "proof of concept" rather than a practical therapy for widespread application. Our experience from the early trials using adrenal medullary transplants has told us that it is essential that the reliability and therapeutic value of a new procedure be clearly demonstrated before it is spread to a larger number of nonspecialized hospitals. Moreover, as emphasized by Peschanski et al., it is important to ensure that a neural transplantation protocol can be carried out by well-trained but not specialized clinical teams in a large number of hospitals before it can be accepted as a viable therapy.

The principal argument against the idea of a large-scale multicenter study is that the neural grafting technique is in a stage of active development and that it is still not good

enough, and not reproducible enough, to justify a test on that scale. In this volume, Dunnett and Everitt (Chapter 8) discuss the limitations of the currently used procedures and point out that the requirement for large supplies of fetal tissue of a defined age, safety status, and rapid availability imposes such serious practical constraints that neural transplantation, however effective, is unlikely to become a widely available therapy.

Several outstanding issues thus remain to be solved, not only in order to find ways of improving the yield, viability, and growth capacity of embryonic dopamine neurons, but also in order to find alternative sources of cells for transplantation that may be more easily accessible and also ethically less problematic than the fresh tissue from aborted embryos currently used. Interesting possibilities are offered by xenogeneic cells, summarized by Isaacson et al. in Chapter 10, and by immature neural progenitors or cell lines that are grown in large numbers in cell culture, as discussed by Thode et al. in Chapter 15. The use of survival-promoting and growth-stimulating neurotrophic factors may also prove important as adjuncts to neural transplants. All these emerging possibilities show that neural transplantation will remain a highly dynamic research field in the years to come. Indeed, it is likely that some of the most important breakthroughs are still waiting around the corner.

Finally, what are the wider prospects of the intracerebral transplantation technique? Several potential applications are discussed here: Embryonic striatal neurons in Huntington's disease (Chapters 6, 7, and 10); neurotrophic factor-secreting cells in several types of neruodegenerative diseases, particularly Huntington's disease, Alzheimer's disease, and ALS (Chapter 13); fetal cells or cell lines in cerebral ischemia (Chapter 11); adrenal chromaffin cells in patients suffering from chronic pain (Chapters 12 and 13); and glial cells in myelin disorders (Chapter 14). Clinical trials using embryonic striatal transplants in patients with Huntington's disease, and chromaffin cells in patients with chronic pain, are already under way. The future development of these various new approaches will depend on a close interplay between basic science and clinical application. The experience from the Parkinson's disease field clearly shows the importance of basing clinical trials on solid experimental data. Moreover, since the clinical relevance and the validity of available animal models in many cases are unclear, it is essential that progress toward clinical application be cautious, even excessively careful. Any new application of the intracerebral transplantation technique will inevitably raise important questions about the procedure by which results from the laboratory can be transformed into clinical trials. To what extent should clinical trials be supported by animal experimental data? How far should animal experimentation be carried before any clinical trials are attempted? Basic neuroscience research will not only help us to better understand the mechanisms underlying neurodegenerative disease processes, but also provide us with new possibilities for the treatment of neurodegenerative diseases. In this era of rapid developments, it is important to emphasize that true knowledge is obtained only through the application of rigorous scientific methods. Any "fast" route to clinical trials will inevitably compromise this basic principle. The development of new ways to manipulate the diseased brain has made it increasingly important to discuss how animal experimental work and clinical research can work together in order to promote the development and application or scientifically based experimental therapies. *Cell Transplantation for Neurological Disorders* will provide a good start: Here, the interested reader will find excellent intro-

ductions and insightful discussions of the problems, challenges, and possibilities in this fascinating field.

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Anders Björklund

Preface

The field of neural reconstruction has reached a critical threshold. Fetal nigral grafts have been transplanted into patients with Parkinson's disease. Preliminary evidence of clinical efficacy has been demonstrated in several reliable centers. Presumed graft survival as demonstrated by fluorodopa PET scanning has been observed by multiple groups. Histological proof of robust graft survival has been observed in three patients from two centers. Two separate placebo-controlled safety and efficacy trials are underway in order to evaluate clinical efficacy in definitive clinical studies.

The purpose of *Cell Transplantation for Neurological Disorders* is therefore to evaluate the variables that will become critical as the field matures. A review of the elegant preclinical data relevant to Parkinson's disease is outside the scope of this clinically oriented book. For those interested in reviewing this literature, we have included some useful references at the end of the preface.

Neural reconstructive techniques may also be useful for other diseases besides Parkinson's disease, including Huntington's disease, pain, demyelinating diseases, stroke, spinal cord injury, and epilepsy, among others. *Cell Transplantation for Neurological Disorders* focuses on those diseases for which clinical trials are either ongoing or likely to occur within the near future. Furthermore, the majority of chapters discuss the utilization of unmodified cell types, including embryonic neurons derived from humans or pigs, as well as adrenal cells. The clinical use of gene therapies, cell lines grown in vitro, and trophic factors are being investigated in multiple laboratories and are reviewed here as well.

Space limitations prevent the publication of chapters by all groups involved in neural reconstruction worldwide. For example, at least 18 groups have transplanted fetal nigral tissue in patients with Parkinson's disease as of this printing. We have therefore selected representative groups that are either recognized internationally for their expertise or whose novel and previously unpublished observations warrant contribution to this volume.

It is difficult to compare results between groups because of differences in methods of grafting and clinical analyses, as well as in levels of expertise. Therefore, the editors have requested that all authors focus on their rationale for clinical trial designs rather than rewrite specific data that have been clearly documented elsewhere.

The first chapter by Dr. Widner and colleagues reviews the landmark clinical data and experience in the Lund program with embryonic neural tissue transplantation in idiopathic Parkinson's disease, and includes rationales for the techniques used in this program. Accounts of the effects obtained in three patients with MPTP-induced parkinsonism are also included. The role of an ongoing neurodegenerative disease process affecting the grafted cells is discussed.

Dr. Hauser and colleagues summarize the followup data from their patients who received bilateral fetal transplants for the treatment of Parkinson's disease. These authors also describe the rationale for their transplant parameters, including target localization within the postcommissural putamen, use of bilateral transplants, and restriction of donor ages. Clinical and PET data from this group, in combination with autopsy data derived from this series (presented in the chapter by Kordower and colleagues) prove that clinical benefit in patients and increased fluorodopa uptake on PET scan are the result of graft survival and host reinnervation. Immunological issues with relation to allograft survival in humans (as demonstrated in this series) are also discussed.

The question remains whether fetal tissue transplantation can be reliably performed outside specialized institutions. Dr. Peschanski and colleagues have outlined some of the requirements necessary to begin a multicenter Phase III study to evaluate this issue. Given the millions of patients with Parkinson's disease worldwide, this type of study becomes critical if neural transplantation is to be used worldwide. The chapter also contains a review of the existing evaluation protocol, CAPIT, and proposes changes in this protocol. We hope this chapter will stimulate discussions leading to the international consensus necessary to organize such a vast study.

The chapter by Dr. Snow provides a concise review of the use of PET scanning and other radiologic techniques utilized to evaluate patients with Parkinson's disease who have received fetal nigral transplants.

Kordower et al. review autopsy cases of dopaminergic transplants, including those derived from adrenal and fetal nigral sources. They trace the decade-long evolution of clinical trials that evolved from largely unsuccessful attempts to more recent autopsy cases that show robust graft survival. This chapter demonstrates how closely the preclinical animal experiments predicted clinical and histological outcomes of early transplant trials. The authors review the case reports confirming that the mechanisms of action of fetal nigral grafts in patients with Parkinson's disease are related to graft survival and host reinnervation and are not secondary to trophic effects on the brain. Finally, the authors conclude that fetal nigral grafts represent the current "gold standard" against which future neural reconstructive strategies must be compared.

Dr. Sanberg and colleagues review the preclinical experiments that have led to the postulation that fetal tissue transplantation may be a useful therapy for the treatment of patients with Huntington's disease. The anatomical and pathological issues related to clinical deficits in Huntington's disease are more complex than those seen in Parkinson's disease. This partly accounts for the protracted time between the earliest discoveries of graft survival and behavioral improvements (performed in the early 1980s) and the onset of scientifically sound clinical trials (which are currently underway in a few centers). Of note, what is now called the embryonic "ventricular eminence" has historically been called the "striatal eminence." However, at least twelve primordial brain nuclei or cell types develop within this region. This realization has led to progressively refined subdissections of the ventricular eminence. Dissection of the lateral ganglion eminence has led to successful striatal grafts in rodent models, but there are no published reports to date that have been able to reproduce these findings using human fetal xenografts. It is for this reason that most centers that are currently performing fetal tissue transplants for the treatment of Parkinson's disease have not

also initiated transplant programs for the treatment of Huntington's disease. However, this is a technical obstacle that will be overcome in the near future; to date six centers have initiated similar transplant programs (*see* ref. *4*).

The chapter by Dr. Kopyov et al. presents the Good Samaritan program's rationale for beginning their clinical trials using transplants of human lateral ganglionic eminence tissue. The case report in this chapter is that of a patient with many atypical symptoms of Huntington's disease with marked variability in clinical symptomatology between the two baseline studies. Nevertheless, this preliminary case report documents the rationale and methods for the first attempt to subdissect the human ventricular eminence and transplant the lateral ganglionic eminence into patients with Huntington's disease. We must await peer review publications of a more extensive series before firm conclusions regarding clinical outcomes, PET scan changes, encephalomalacia in needle tracts, potential graft overgrowth, and other transplant-related issues can be well delineated.

In spite of the exciting developments in the field of fetal nigral transplantation, Parkinson's disease has not been "cured." Although there are many tissue source-related issues, one of the main problems is that nigral transplants only reconstruct the pathological anatomy of the brain in a simple fashion at this time. The pathological changes associated with movement disorders such as Parkinson's and Huntington's diseases are very complex, and strategies to cure diseases involving the striatal system need to become more sophisticated. In this context, the chapter by Drs. Dunnett and Everitt is important. This chapter summarizes what is currently known about the organization of the striatum, including afferent and efferent connections, as well as the striosome–matrix compartmentalization. Understanding of the way these circuits are aberrant in both Parkinson's and Huntington's diseases is critical to the improvement of reconstructive strategies using cellular therapeutic strategies.

The immunology chapter by Dr. Widner describes the anatomical and physiological barriers of the brain as a transplantation site and the various factors thought to contribute to the brain's being an immunologically privileged site for transplants. Animal experiments defining the limitations of immunological protection of grafts are discussed, as are the clinical implications relevant to human fetal allograft trials.

Both ethical and technical issues affect the ability to obtain the large quantities of human fetal tissue necessary to treat millions of patients worldwide with neurodegenerative diseases. Dr. Isacson and colleagues review many of the issues important to the use of cross-species neural transplants for the treatment of patients with Parkinson's and Huntington's disease. The field of neural transplant immunology is evolving rapidly, and the field of cross-species transplant immunology is in preliminary stages at this time. This chapter is interesting from several perspectives. It would be reasonable to expect that xenografts would contain so many foreign surface antigens that rejection would be nonspecific and robust. The authors present a compelling review, however, that points to the role of major histocompatibility antigens in neural xenograft rejection. The authors also review evidence that hyperacute rejection, which is the major obstacle for transplantation of xenografts in the periphery, is absent in neural xenotransplantation. Methods for immune modulation, including immunosuppression as well as MHC-I masking, are discussed. The authors also review laboratory studies of cross-species nigral and striatal transplants. Experiments described

in this chapter have formed the basis of ongoing clinical trials using cross-species transplants of porcine nigral and striatal cells in patients with Parkinson's and Huntington's diseases, respectively. Unfortunately, these clinical trials are still in sufficiently preliminary stages that they cannot be reported in this volume.

The field of neural transplantation for the treatment of cerebral ischemia is not as developed as similar research for the treatment of Parkinson's and Huntington's diseases. Borlongan and colleagues describe many of the current animal models for cerebral ischemia, particularly stroke models confined to lesions in the striatum rather than in the cerebral cortex. Although striatal infarcts constitute a minority of all strokes, the epidemiological significance of this type of infarct is dramatic and warrants further investigation. This chapter summarizes both the use of fetal striatal cells as well as a terminally differentiated teratocarcinoma cell line in the treatment of adult models of stroke. Although research is in the preclinical stage at this time, this chapter was included because of the likelihood that clinical trials will be initiated in the near future.

Neural reconstruction may utilize grafts that reinnervate the central nervous system. However, cellular therapies may also be used as a way to deliver pharmacologically active agents. This is the case in the chapter by Dr. Sagen, who reviews the preclinical and clinical use of adrenal medullary allografts to modulate pain. These cells were chosen since they secrete both opiate peptides and catecholamines, agents that reduce pain when administered directly into the spinal subarachnoid space. The epidemiology of pain syndromes clearly makes this potential therapy important.

The chapter by Dr. Emerich and colleagues reviews the use of transfected cell lines producing various beneficial factors encapsulated within biologically compatible polymer capsules. A theoretical discourse on porous membrane properties is included, and examples on the applications of the technique are given for animal models of Parkinson's, Alzheimer's, and Huntington's diseases, as well as amyotrophic lateral sclerosis. The technique has also been used clinically, as exemplified in the treatment of pain in cancer patients.

The chapter by Dr. Duncan reviews current attempts to transplant myelinating cells to remyelinate the central nervous system after damage or genetic defects of the myelination process. The models and cell sources used, as well as their relevance to human diseases, are discussed.

Dr. Gage and colleagues describe techniques for gene transfer using both ex vivo and in vivo approaches. These techniques have been utilized mainly in animal models of Parkinson's disease, but also in models of other neurodegenerative disorders. The chapter reviews the benefits and limitations of existing viral vector systems, the genes that have been introduced, and the cells used as vectors. The authors also discuss various strategies for obtaining functional effects secondary to pharmacologically active constructs, including L-dopa producing fibroblasts, and neuroprotective/trophic constructs such as induction of neurotrophic factor production.

Drs. Vawter and Gervais provide an elegant discussion of many of the important ethical issues surrounding the use of fetal tissue for transplantation purposes. Many of the ethical discussions advanced here have formed the basis for the United States Federal laws that regulate this field. However, current Federal law applies only to fetal tissue research supported by Federal funds. These authors correctly point out the necessity for widening the scope of the provisions to include research done outside the

scope of Federal funding. The strength of ethical arguments rests in their ability to persuade. We anticipate that many of the ethical proposals advanced in this chapter will lead to multiple discussions within ethical, scientific, and legislative bodies.

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This book is dedicated to our families: Susan, Danny, Andy, and Jonathan Freeman, and Pia Widner. It is also dedicated to the brave patients who have volunteered to participate in our clinical trials.

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