

Editorial: Reconstruction of Brains and Journals

This issue begins a new incarnation of the **Journal of Neural Transplantation and Plasticity (JNTP)**. New journals, new editorships, and major changes are often the occasion for the writing of editorials; this time, it is a new editorship and a clarification of purpose. With this issue, **JNTP** is re-dedicated to the publication of high-quality studies of neural transplantation and plasticity. **JNTP** will aim to become a leading journal in the field by maintaining high standards of quality and a clearly-focused mission.

The editors and publisher especially wish to thank Drs. Uri Yinon and Paul Sanberg for their prior service as editor-in-chief and interim editor respectively. Paul Sanberg has agreed to continue to serve as a member of the editorial board. Through their efforts, **JNTP** has become established and developed a record of consistent publication of quality papers.

THE MISSION OF JNTP

The mission of **JNTP** is to serve as a forum for studies on manipulating, promoting, or guiding neural plasticity. Neural transplantation, at the moment, accounts for a large part of this literature. Due to recent advances in molecular biology, it appears likely that intervention in brain circuitry through administration or manipulation of growth factors will in the near future at least equal transplantation as a major area of research. Other similarly promising methods of manipulating neural plasticity include, for example, altering the substrate for neural growth /2, 11, 50/, implantation of encapsulated cells /1, 70/ and polymers or gel matrices /71/, use of chronic drug-releasing polymers /3, 23, 40/, and genetic manipulation of neuronal cells *in situ* /24/. The niche for **JNTP** is to communicate studies of neural transplantation as well as neural plasticity, especially studies of neural plasticity that are relevant to experimental manipulation. This would include studies in areas such as effects of trophic factors, production of trophic or growth-inhibitory factors by brain /41/, recovery of func-

tion after lesions, including studies of reorganization of neural circuits /51/, effects of behavioral training /66, 68/ and drug administration /6, 12, 28/, survival or replacement of neuronal circuits, and enhancement or guiding of collateral sprouting or axonal regeneration, or studies which shed light on possibilities for such techniques.

In addition to its use as a means of manipulating brain function, neural transplantation has important applications as a basic research tool. The functional role of circuits in the brain has for the most part been defined by the consequences of their absence, following either experimental or accidental lesions. Neural transplantation is unique as a research tool in that scientists can begin to discern the functional contributions of newly constructed or permanently modified neural circuits. When used as a basic research tool, transplantation can help to explore the role of neuronal circuits by allowing for both removal (lesioning) and replacement (transplantation). Neural transplantation also serves as a method with which to study brain development, and can be a valuable tool for studying the processes of neuronal migration and segregation /59/ and the formation of synaptic connections. Studies on these topics would also be within the scope of **JNTP**.

POTENTIAL APPLICATIONS IN MODELS OF DISEASE

There is, of course, a hope that transplantation or techniques for manipulation of neural plasticity which have been developed in animal models will ultimately be useful to treat degenerative disease or injury in humans. For the most part, a rational and systematic development of appropriate animal models, and subsequently potential modes of therapy, for any disease requires that first the neuronal mechanisms and circuits which are involved be understood at least to some degree. Secondly, the relationships between these circuits and the disease itself must be found. Usually, this understanding can only be gained by basic studies of neuronal circuits in animals, followed by post-

mortem biochemical studies, histopathology, or potentially neural imaging studies of these circuits in living subjects. Finally, once a picture of the disease process has developed, clinical manipulation can be planned rationally. When clinical intervention is considered, ideally, transplantation will in time be only one of an array of methods which can be used to effect localized changes in the functioning of neuronal circuits. Intervention to alter neuronal plasticity might take many forms, including pharmacological treatments, localized administration of support matrices or growth factors, genetic manipulations, or behavioral training /20/.

Possibly the most direct form of manipulation of neural plasticity is to promote endogenous neurons to grow or form new connections. It may be possible to enhance the plasticity of mature neurons by genetic reprogramming, but it may also be possible to accomplish the same goal more simply by the administration of exogenous substances, generically "growth factors". The prototype growth factor, nerve growth factor (NGF), has been known and studied for decades /33/. NGF has a specific influence on peripheral sympathetic and sensory neurons and on central cholinergic neurons. Until recently, there have been relatively few studies of the effects of administration of NGF. In the past few years, however, possibilities for the use of NGF administration to enhance functional recovery from lesions, sparing of neurons following axotomy, and prevention of degeneration have begun to appear /29, 34/. The most likely avenues for potential therapeutic effects of NGF are in peripheral neuropathy and Alzheimer's disease. Advances in growth factor identification through molecular biology have led to the clarification of what has long been suspected, that an entire class of neurotrophins, growth factors with varying specificity for different neuronal populations, exists. In fact, numerous substances belonging to a variety of classes of proteins have neurotrophic activity under various circumstances. Availability of these proteins in pure form has greatly facilitated studies of effects of their administration. Neurotrophic factors can be employed in a variety of strategies; they can be administered directly to the brain, or peripherally in models of peripheral neuropathy, or they can

perhaps be used to enhance the effects of neuronal tissue transplants. There are complex issues associated with methods of administration of proteins to living organisms. Possibilities for administration include chronic injection, administration through various kinds of chronic infusion pumps, incorporation into gels or slow-release matrices, and elicitation of expression of growth factors by endogenous /24/ or transplanted /14, 54/ cells.

The second major form of manipulation of neural plasticity is neural transplantation. The "prototype" disorder for neural transplantation, Parkinson's disease, is in that position because the nature of the affected neuronal circuits is largely known. Conceptually, the goals of transplantation research in Parkinson's disease, both clinically and in animal models, are clear: replacement of the dopaminergic afferentation of the neostriatum. Most of the efforts in this area have been concentrated on three tissue sources, each with quite different origins: These include: (a) transplantation of fetal substantia nigra into the striatum or lateral ventricles /4, 17, 19, 65/, (b) the use of adrenal medulla as an alternate source of catecholamine-producing cells /21, 63/ with possible trophic effects as well /5, 45, 48/, and (c) the use of catecholaminergic cell lines /1, 15, 30/. There have been a substantial number of human clinical trials of both adrenal medulla and substantia nigra transplantation /16, 27, 35-37/. Some relatively modest improvements have been observed in most of the clinical trials. Limitations of clinical trials of adrenal medulla grafts have included a gradual loss of improvements /43/, a high frequency of side-effects including death, as well as psychological disturbances and dementia /38, 44/, and inconsistent graft survival /47/. For clinical trials of embryonic SN grafts, the results are generally promising, especially regarding the apparently smaller frequency of side effects. Nevertheless, the degree of improvement seen in human subjects after SN grafts is generally modest, and so far not qualitatively greater than the effects of adrenal medulla grafts. Improvements in the performance of transplantation procedures may arise, for example, from advances in surgical technique /9, 10/ or improvement of the performance of grafts through the administration of growth factors /62/ or co-transplantation of tissues

which may secrete growth factors /8, 22, 32, 67/. Efforts to develop new sources of dopamine-producing cells, through immortalization /7, 25, 55/ or other genetic alteration of cells /15, 30/, derivation of cells from tumors /39/, and perhaps the use of cells generated from the brain through other techniques /49, 52, 53/ are also guided by the same goal, of finding improved methods of replacing the dopaminergic system.

Additional possibilities for application of transplantation and administration of growth factors in models of disease are likely to emerge over the course of time. For neural transplantation, two other notable possibilities have recently emerged, in particular chronic pain syndromes /56, 57/ and Huntington's disease /26, 31, 64, 69/. Interesting possibilities have also been raised in connection with application of transplantation to more complex animals models /42/. Although possibilities for applications to other clinical disorders are more remote, research is being conducted in a number of different areas. For example, studies on transplantation in the visual system and in models of cortical injury are represented by papers in this and other recent issues of *JNTP* /13, 46, 58, 60/. Peripheral neuropathies are at present the most immediate candidates for clinical application of growth factors for similar reasons, e.g., because the goals of potential therapies are clear. Such a clear picture is available for few other disorders. Nevertheless, there are other potential avenues for clinical applications. Clinical trials of NGF administration in Alzheimer's disease are currently being conducted. It is probable, however, that some neuronal degenerative disorders will have properties which are not amenable to manipulation according to any existing concept. For these, the properties of the disorder, once found, may indicate new therapeutic possibilities. It is entirely possible that techniques for manipulating brain plasticity, in any form, will find application for diseases (e.g., schizophrenia) which are as yet not at all understood.

The issues of application of therapy to humans are complex and have not been considered systematically /18, 61/. It is generally acknowledged that degree of risk and invasiveness bears a direct relationship to the amount of justification and degree of confidence in the procedure which

should be required. For example, there are certainly some avenues for manipulation that can be employed following brain injury, even without any understanding of the neural circuits involved. The most notable of these is behavioral training. It is well established that behavioral training can do a great deal to aid recovery following CNS damage /66/, yet the reasons why the training works and the nature of the brain damage to be treated are not yet understood. Where more complex or invasive procedures are required, a more thorough rationale is certainly needed. As yet there are no systematic procedures for considering rationales for clinical procedures such as brain tissue transplantation. *JNTP* hopes to become a major forum for communication of information related to manipulation of neural plasticity through transplantation and other techniques. This will include, in addition to original research papers, scholarly discussion of issues related to the applicability and justification for potentially invasive techniques.

QUALITY STANDARDS FOR *JNTP*

JNTP will endeavor to publish research of high quality, specifically in terms of methodology, experimental design, clarity of logic, careful formulation of conclusions, appropriate statistics, and research fundamentals. Issues such as coding of samples, blind testing, random assignment of animals to groups, use of appropriate control groups, and quantification of histological and histochemical data where appropriate will be especially emphasized. Editorial board members and referees will be asked to pay particular attention to these factors.

To give some concrete examples of what will be asked of the referees: For behavioral studies, appropriate control groups will be expected and experimental designs will be examined for the ability to support the stated conclusions. Studies which are based on changes in histological and histochemical parameters induced by experimental manipulations (as opposed to descriptive histology) will usually be expected to provide appropriate quantitative data or other forms of objective data presentation. Referees will be asked to assess whether these data were collected in con-

trolled and carefully designed experiments. Conclusions will be examined to determine whether they can be supported by the choice of control groups and experimental design. For clinical studies, where it is often impossible to employ controls or large numbers of subjects, experimental design issues such as baseline testing, frequent assessments, quantitative measurements of outcome, and attention to problems such as separate testing during "on" and "off" phases (in Parkinson's disease) are even more important. In other cases, such as studies of primates, where practical realities limit the experimental design, authors will be expected to point out these limitations in their conclusions.

Although manuscripts describing new and exciting findings are certainly desired, these will be published only if they also meet similar criteria of quality. In fact, specialized studies which extend upon, clarify, or refute an earlier study are especially sought after as candidates for publication in *JNTP*. It is also important to note that quality is not necessarily synonymous with completeness, length, or even thoroughness. Short papers, and brief communications are solicited as well. Papers that carefully address a single, restricted aspect of a problem are encouraged provided that, within their own limits, the work presented is of similar high quality. Technical reports and papers describing new methods are also encouraged.

The journal is interested in publishing scholarly reviews, commentaries, and letters questioning issues related to neural transplantation and methods of manipulating neural plasticity. Commentaries and letters which question conclusions of earlier studies or research areas, raise issues of experimental design, either advocate or question opportunities for human application, or address controversial issues in neural transplantation and plasticity are solicited. *JNTP* is particularly interested in reviews which examine the conclusions and designs of earlier studies in detail. In general, review papers should offer new conclusions, integration, or re-interpretations of other studies. Reviews which simply abstract or enumerate previous experiments are not desired. Reviews may be submitted without prior arrangement with the editor-in-chief, although prior consultation may increase the likelihood of acceptance.

The field of neural tissue transplantation and manipulation of neuronal plasticity has become one of the central specialties in neuroscience. *JNTP* aims to become a first choice forum for communication of research and controversy in this area.

William J. Freed
and
The Editorial Board of
*JOURNAL OF NEURAL
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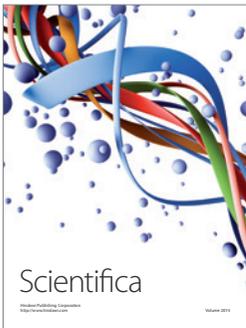
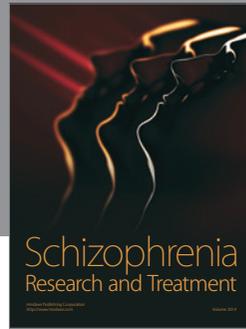
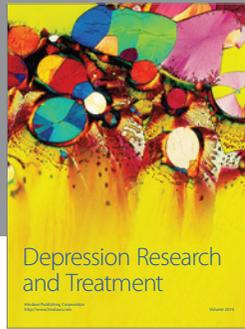
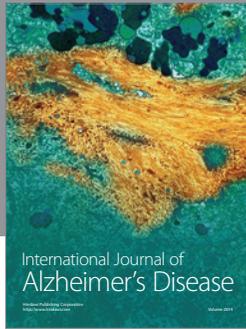
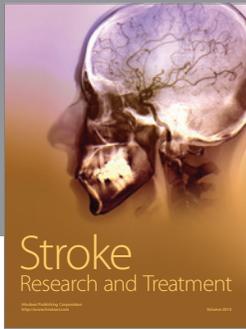
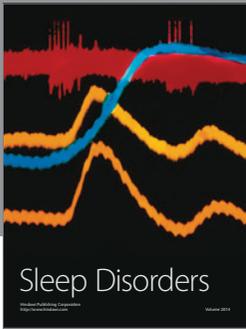
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