almost synthesizing an isotropic solid with negative Poisson's ratio.

Materials with negative $\sigma$ are expected to have many interesting elastic properties. Since real isotropic materials with negative $\sigma$ are yet to be synthesized, one can only extrapolate from the results obtained with foams of negative $\sigma$. Such materials can be expected to have a large elastic resilience. Normal material are linearly elastic only up to 5% strain. But foams with reentrant units are linear up to 40% strain. These materials are also expected to have large energy absorption and fracture resistance. In the light of these facts we can look forward to a fertile field of study on the elastic properties of solids with negative Poisson's ratio.


RESEARCH NEWS


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Trends in experimental neural transplantation

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Neural transplantation is an exciting and rapidly growing field of research in neurobiology. Last decade has witnessed notable advances in this area. However, the initial hope, that neural transplantation could be a panacea for neurodegenerative diseases, has dwindled due to failure of the implants to survive on a long-term basis and also because the expected functional requirements have not been met. Experimental biologists have responded to these problems through newer approaches and there appears to be no wane in their enthusiasm. The major goals of neural transplantation to the mammalian brain are: (i) to explore the potential of grafts to alleviate symptoms of degenerative diseases, and (ii) to provide an experimental model to study the fundamental biology of the brain. The diverse topics in these areas have recently been reviewed.

The concept of transplanting glial cells into mammalian central nervous system to promote regeneration is an extension of the concept of the peripheral nerve-grafting experiments of Cajal and Tello at the turn of the century. Earlier, in 1890, Thompson had already demonstrated that brain grafting is possible. Yet there was a long gap before there was revival of interest in neural transplantation.

Potential of glial cell grafts. The resurgent studies explored the potential of grafts to alleviate symptoms of degenerative diseases. Two important objectives of the glial cell transplantation research are: (i) to understand the interactions of glia, schwann cells and axons during repair in the central nervous system (CNS), and (ii) to explore the theoretical possibility of glial transplantation as a therapeutic means to promote repair of demyelinating plaques in multiple sclerosis and enhance axon regeneration after spinal cord trauma. Significant contribution has been made by Blakemore and Franklin who, in a series of experiments, demonstrated the primary importance of type-1 astrocyte and also the role of cells of the O-2A lineage, the precursor of oligodendrocyte, in central myelination.

Application of genetically modified cells. A major breakthrough in grafting experiments is the application of genetically modified cells for intracerebral implantation. Two major groups of cells have been successfully used for gene transfer application to the CNS, viz. immortalized cells and primary cells. The advantages of genetically modified cells are that they can be 'customized' to produce discrete required factors and that, using autologous cells, the host immune responses can be minimized.

Genetically modified cells could find therapeutic applications, in genetic disorders like Huntington's chorea, where the disease phenotype can be corrected by introducing functional genes into mutant cells, and in non-genetic disorders of the CNS associated with deficits of specific neurotransmitter systems like Parkinsonism with dopamine depletion. In animal models of Parkinsonism, some of the behavioural abnormalities can be ameliorated with grafts of cells genetically modified to produce L-DOPA or dopamine.

An alternative approach is to deliver neurotropic factors like nerve growth factors (NGF) using genetically modified cells to specific sites like neurons undergoing degeneration. NGF has been shown to protect cholinergic neurons of the basal forebrain and neurons which are affected in Alzheimer's disease from injury-induced degeneration.

Transplantation to diseased and damaged retina. The accomplishments in CNS transplantation prompted several workers to explore the possibility of neural transplantation in other sites. The Royal College of Surgeons (RCS) rat, which is one of the most studied animal models for inherited retinal disease, provided the paradigm. In the dystrophic retinas of these rats, photoreceptor cells begin to degenerate during the third postnatal week. The photoreceptor cell layer, normally 8-10 cells thick, is reduced to two cells in thickness, by two months in these rats. Implantation of retinal pigment epithelial cells into the interphotoreceptor space in these retinas, effectively rescues the photoreceptor cells. It has also been shown that a single injection of a high concentration of basic fibroblast growth factor (BFGF)
FGF) into the vitreous humour or interphotoreceptor space of young RCS dystrophic rats causes a significant delay in photoreceptor cell degeneration. The successful transplantation of strips of intact photoreceptor cell layer into rat retinas has provided the impetus for studying the interaction of retinal pigment epithelial cells and photoreceptor cells, both in health and disease. There is also the exciting future prospect of treating patients afflicted with retinal disease such as retinitis pigmentosa and macular degeneration by transplantation.

Reconstruction of cerebellar circuits. An additional field of pursuit is reconstruction of cerebellar circuits. Neuronal networks in sensory and motor systems are organized in a point to point manner. A successful neural grafting requires reestablishment of the anatomo-functional integrity of the impaired circuits. Repair of neural network after neural grafting has been extensively studied in the cerebellum of adult Purkinje cell degeneration (pdc) mutant mouse, an animal model for hereditary degenerative ataxia, using embryonic Purkinje cells.

The embryonic cells selectively invade the deprived cerebellar cortex and migrate to their proper domains. They also become integrated synaptically within the pcd cerebellar cortex by inducing axonal sprouting of specific population of lost neurones. Information carried to the cerebellar cortex through extracerebellar afferents is processed by the cortical circuits and must be transferred to post-cerebellar nuclei. Thus, to obtain functional recovery, it is essential that the grafted Purkinje cells generate a new corticonuclear projection. In the transplant models, corticonuclear projection is achieved only rarely and remains a stumbling block. The limiting factor is not the axonal elongation of the grafted cells, but it is the adult nature of the host cellular milieu.

Survival and innervation of spinal cord grafts. The survival and innervation abilities of embryonic motor neuron transplants to the spinal cord have also been studied. Experimental studies reveal that embryonic spinal grafts prevent cell death of axotomized neurones in the nucleus ruber of neonatal rats, reduce the severity of gliotic scars in chronically lesioned spinal cord of adult rats and encourage axonal elongation for long-descending axons as well as intrinsic connections in severed spinal cords of immature animals. The goal in spinal transplantation is to replace the loss of spinal motor neurones as occurs in spinal muscular atrophy, amyotrophic lateral sclerosis and poliomyelitis. Attempts are also being made to compensate the loss of supraspinal inputs and `realize the performance' of existing spinal cord circuitry in hosts by transplants which produce appropriate neurotransmitters. Transplantation in primates. Most of the work with respect to neural transplantation has been carried out in rodents.

Clinical application has mandated experiments in primates. Primate studies also provide an opportunity for more detailed assessment of the behavioural characteristics, to measure the more complex and cognitive functions that may be affected by transplantation and also the optimum techniques for transplantation which may vary from species to species. The transplant experiments in monkeys suggest that implantation of foetal dopamine-rich tissue into animals with experimentally induced Parkinsonism can be of therapeutic benefit and pronounced behavioural recovery can be achieved with very modest increase in the level of dopaminergic activity in the caudate nucleus. The ability of neuronal grafts to restore cognitive abilities has been studied in marmosets. Transplantation of acetylcholine-rich foetal tissue into the hippocampus after bilateral surgical transection of the fornix (which carry the cholinergic projection of the hippocampus) improves visuospatial tasks. Histological studies demonstrated that the grafts stained densely for acetylcholinesterase activity and there was substantial fibre outgrowth into the surrounding host tissue.

Contribution to neuropathology. Parallel to the knowledge gained in neural transplantation biology, there have also been signal contributions in this field to neuropathology and fundamental neurobiology.

The experimental technique of grafting hippocampal tissue rekindled interest in studies on the trisomy-16 mouse, a potential model for understanding the pathophysiology of Alzheimer's disease. The lethal effect of this aneuploidy in utero had thwarted the efforts of previous investigators in studying the neuropathology in Alzheimer's disease, since it required long-term survival of CNS tissue. Long-term survival is now achieved by grafting hippocampal tissue dissected from 16 to 18-day-old embryos of trisomic mice, to the cortical cavity in young host Carworth Farms Lane-Petter (CFLP) mice. These trisomic grafts survive for 4-6 months and can be assessed using histological and immunocytochemical methods for defects associated with Alzheimer's disease. There are suggestions that in this mouse model it will be possible to capture the primary defect in Alzheimer's disease and also to develop a means to ascertain the memory impairments. Thus an animal model to correlate specific neuropathology to dementia of diverse aetiology and to try out treatment modalities would be available.

Impact on understanding of circadian pacemaker. In the field of fundamental neurobiology a significant benefit of neural transplantation research has been in the analysis of the mammalian hypothalamic circadian pacemaker.

The suprachiasmatic nucleus (SCN) of the hypothalamus is considered to be the site of pacemaker cells that generate circadian rhythmicity in mammals. The most telling evidence that the SCN contains the pacemaker cells comes from the transplantation studies. By transplanting SCN into animals whose own nucleus has been ablated and by using donors and hosts with genetically different circadian characteristics, it is possible to recognize unambiguously the donor rhythm expressed in a transplant recipient. The reappearance of the rhythm indicates not only the survival of the grafted tissue but also that pacemaker cells that generate circadian rhythm were included in the grafts. Though the central role of SCN in circadian rhythm has been proved beyond doubt, questions which are sought to be answered by transplantation techniques are the identity of the circadian pacemaker cells within the SCN, the pattern of communication between these cells as well as between these cells and the rest of animal.

Alternative approaches in the use of whole tissue grafts include studies in which the SCN is manipulated prior to
transplantation, either by cellular disassociation or by selective elimination of specific cell types. By transplantation of tissue cultures that contain immunocytochemically defined cell populations, the tissue specific for the expression of rhythmicity in the host may be defined. Genetic alteration prior to transplantation of the cultured SCN cells using replication-deficient viral vectors, is a novel approach which might throw light on mammalian pacemaker function at a cellular and molecular level.

**Stumbling block to clinical application.**

The hindrance to wide clinical application of neural transplantation in humans is the absence of long-term survival of functionally competent grafted tissue. The failure of grafts is attributed to the immunological response of the host to neural grafts.

Central nervous tissue is different from the majority of peripheral tissue with respect to immune status. Though brain was considered as a privileged tissue as far as immune response is concerned, observations such as rapid rejection of neural tissue transplanted beneath host kidney capsule, suggested that neural tissue behaves like an orthotopic skin graft and that it is immunogenic, though there may be differences of degree. Experiments also show that there is no prior deficiency of immune response in the efferent arch, but the afferent arch might rather be compromised in some way. Recent studies have shown that there is a higher rate of failure of take up of foetal nervous tissue transplant in rhesus monkeys compared to rats. The graft in monkeys was found in these studies to be invaded by both T and B lymphocytes and macrophages. MHC type II molecules were demonstrated not only in the endothelial cells of blood vessels of the grafts and the surrounding brain but also in astrocytes and microglial cells. Grafted neurons were found to undergo progressive degenerative changes after an initial healthy survival period of several months. This premature ageing of the graft has been attributed to immune rejection.

Review of available data reveals that CNS may represent an immunologically privileged site indeed but the privilege is far from absolute. Some form of immunosuppression has been advocated in the therapeutic regimen when allo-grafts are used. While solid tissue fragments and cell suspensions of neural tissue are immunogenic as a whole, the individual cell types within the graft themselves could be immunogenic to different degree. There are claims that neural allograft rejection can be completely surmounted by preselecting a subpopulation of embryonic epithelial cells for grafting. This can be achieved with the use of immunobead separation on the basis of major histocompatibility (MHC) expression. The neuronal precursor cells which did not express MHC class I antigen in vitro when treated with interferon-γ (IFN-γ) were successfully maintained in the brain parenchyma in a mouse model where whole neural grafts were normally rejected. This observation obviously offers the possibility of grafting enriched neuronal cells population across allogenic and perhaps even xenogenic histocompatibility barriers, without the need to immunosuppress the recipients.

**Use of neuronal stem cells.** Yet another novel pursuit in transplantation research focuses on the identification and manipulation of neuronal stem cells. Techniques that allow the culture of primary foetal cells and their expansion in vitro prior to grafting promise greater versatility compared with fresh tissue in two ways. Firstly, they might allow an increase in the number of cells available for transplantation. Secondly, during the short period in culture the graft cells might be manipulated to express genes with useful functional effects.

To conclude, in neural transplantation, the game is just beginning.


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**Complete nucleotide sequence**

**T. Ramakrishnan**

Several laboratories in the world have been ambitious project to sequence the entire human genome. The magnitude of the task can be judged from the fact that the longest sequence—on one of the yeast chromosomes consisting of 315 x 10^6 bases—has recently been published (Nature, 1992, 357, 38) and has been hailed as a landmark in the sequencing of entire genomes. Yeast has 16 pairs of chromosomes and the sequencing of the smallest of them is the result of the collaboration of 35 laboratories in 17 countries. Compare this achievement with what has to be done with regard to the human genome which consists of 23 pairs of chromosomes, the smallest of which—chromosome 21—has 150 x 10^6 bases. Daniel Cohen at CE Ph, Paris is in the final stages of sequencing this chromosome. In March 1992, 12 x 10^8 bases from three contiguous stretches of the genome of the nematode Caenorhabditis elegans was published in Nature. Within the next four years the nucleotide sequence of C. elegans and the bacterium Escherichia coli should be complete as well as a few of yeast (Saccharomyces cerevisiae) chromosomes and one or two...