Psychological Medicine, 1991, **21**, 825–830
Printed in Great Britain

EDITORIAL

Neural transplants as a treatment for Alzheimer's disease?[1, 2]

Embryonic neural tissues can survive transplantation into the brain, where the grafted cells grow, connect with the host brain, and can alleviate many of the functional consequences of experimental brain damage in laboratory animals (Björklund *et al.* 1987; Dunnett & Björklund, 1987). In the last three years these techniques have developed from the laboratory to the first clinical trials of neural transplants for the alleviation of neurodegenerative disease. These trials have been primarily conducted for Parkinson's disease, and over 100 patients around the world have now received embryonic tissue grafts in the brain. Although only few reports are yet available, there is sufficient information to conclude that in at least a few cases the grafts have survived and yield demonstrable benefit to the recipients (e.g. Lindvall *et al.* 1990).

Such advances in the context of Parkinson's disease lead to the inevitable speculation: might similar strategies be effective for other neurodegenerative diseases, in particular Alzheimer's disease? Laboratory studies have indicated that neural grafts can ameliorate deficits in several partial animal models of the human disease based on neurotransmitter and trophic factor replacement in aged animals and animals with lesions. These observations indicate that neural grafts can repair some specific neurodegenerative changes associated with Alzheimer's disease. However, whether they lead on to a viable therapy in patients will depend on whether these particular changes represent the fundamental deficit of Alzheimer's disease, or are merely phenomena secondary to other neurodegenerative events which remain unalleviated.

GRAFTS IN AGED ANIMALS

Like aged humans, aged rats and monkeys manifest many cognitive and behavioural deficits, which have been investigated in most detail in aspects of learning and memory performance. At the neuropathological level, changes akin to the senile plaques and neurofibrillary tangles of Alzheimer's disease are extremely uncommon in aged animals. By contrast, aged animals do show many of the neurochemical changes that are characteristic of aged humans, and which reach their most extensive decline in Alzheimer's disease (see Dunnett & Barth, 1991, for review). Thus, for example, aged rats and primates can manifest marked decline in brain levels of dopamine, noradrenaline and acetylcholine, and their associated synthetic enzymes and metabolites. In parallel, morphometric analyses have confirmed significant shrinkage and/or loss of cholinergic neurones in the basal forebrain of aged rats. In particular, interest in the cholinergic system has been stimulated by the explicit formulation of the 'cholinergic hypothesis of geriatric memory dysfunction', in which it was proposed that decline in this neurotransmitter system may be particularly implicated in the cognitive deficits of ageing and dementia (Bartus *et al.* 1982; Coyle *et al.* 1983).

Neural grafts can survive and grow in the brains of aged rats as effectively as in the brains of young adults. This was first demonstrated for grafts rich in serotonin neurones of the embryonic raphe (Azmitia *et al.* 1981), but subsequently has been well demonstrated for many other neurotransmitter systems, including dopaminergic, noradrenergic and cholinergic rich tissues (Gage *et al.* 1983*a*; Collier *et al.* 1988). In the case of cholinergic tissues, the grafts give rise to axonal

[1] The issues covered in this Editorial are based on a more detailed review article published in the *European Journal of Neuroscience* (Dunnett, 1990*a*).

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https://doi.org/10.1017/S0033291700029822 Published online by Cambridge University Press

outgrowth that makes morphologically normal synaptic contacts with the appropriate populations of target neurones in the host brain (Clark *et al.* 1986).

Such grafts have been demonstrated to reverse a wide variety of functional deficits in aged animals; (i) dopamine-rich nigral grafts implanted in the caudate-putamen of aged rats can ameliorate deficits in motor coordination and balance (Gage *et al.* 1983*b*); (ii) cholinergic-rich septal grafts in the hippocampus can ameliorate spatial navigation deficits in the Morris water maze (Gage *et al.* 1984; Gage & Björklund, 1986); (iii) cholinergic grafts in the hippocampus or neocortex can ameliorate short-term memory deficits in operant delayed matching and non-matching tasks (Dunnett *et al.* 1988); and (iv) noradrenergic rich grafts derived from the locus coeruleus region can ameliorate deficits in passive avoidance learning (Collier *et al.* 1988).

These studies have employed a variety of control procedures that indicate that the functional recovery is specific, requiring (i) the appropriate population of embryonic donor neurones, and (ii) implantation into appropriate target sites, for the particular function under test. The functional efficacy of such grafts indicates that age-related deficits in neurotransmitter function can be alleviated by cellular replacement of the appropriate population of embryonic neurones. Moreover, the transplantation paradigm provides a powerful experimental tool for elucidating the relationship between neurotransmitter decline and functional deficits in normal ageing (Gage *et al.* 1983*c*). This is because, in the natural course of affairs, many different neurotransmitter and behavioural changes decline in parallel, making it particularly difficult to establish convincing associations between the structural and functional levels. Neural transplantation permits selective replacement of identified populations of neurones one at a time in the aged brain, so that the observation of distinctive patterns of recovery can then provide a direct indication for a causative (rather than simply correlational) association between neurotransmitter integrity and particular functional capacities in ageing (Gage *et al.* 1983*c*).

GRAFTS IN ANIMALS WITH BASAL FOREBRAIN LESIONS

To the extent that degeneration of individual identified populations of central neurones contribute to the functional deficits in Alzheimer's disease, then explicit lesions of these populations in young animals may also provide viable models to study alternative approaches to therapy. This strategy has been particularly apparent in the recent development of basal forebrain lesions as a model to permit evaluation of cholinergic drugs for potential application in dementia. So, also, there is now a large literature surrounding the capacity of neural transplants to restore many of the functional deficits associated with lesions targeted on the cholinergic system and other neurotransmitters that were relevant in the ageing studies described in the previous section.

The most extensively studied transplantation model of dementia has been the capacity of cholinergic-rich septal grafts to alleviate the effect of cholinergic deafferentation of the hippocampus, typically made by transection of the fimbria-fornix (FF) fibre bundle. Septal grafts survive transplantation to the FF lesioned hippocampus, provide a new cholinergic innervation, and restore deficits in T maze alternation, working memory in radial mazes and spatial navigation in water mazes (Dunnett *et al.* 1982; Low *et al.* 1982; Daniloff *et al.* 1985; Nilsson *et al.* 1987; Segal *et al.* 1987; Ikegami *et al.* 1989). The recovery observed in these studies is only partial, and the cholinergic reinnervation appears to be a necessary but not a sufficient condition for recovery to be observed (Dunnett *et al.* 1982). This is not surprising, given that the lesions typically deafferent the dorsal hippocampus of all other subcortical connections (including noradrenergic and serotonergic inputs) in addition to the loss of cholinergic afferents. The importance of these other connections is demonstrated by the observation that combined grafts of both septal and raphe tissues implanted into the hippocampus are more effective than single grafts of either tissue alone (Richter-Levin & Segal, 1989; Nilsson *et al.* 1990).

Similar patterns of recovery have been observed following transplantation of cholinergic tissues into the neocortex following basal forebrain lesion (Dunnett *et al.* 1985; Fine *et al.* 1985; Sinden *et al.* 1990). However, here the relevance to the cholinergic hypothesis of dementia should be treated

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with great scepticism because of the now apparent lack of specificity of the model: the lesions produce as great a destruction of cortical outputs descending via the globus pallidus as they do of ascending cholinergic afferents to the neocortex, and they induce attentional and other non-cognitive impairments rather than memory dysfunction *per se* (Dunnett, 1990*b*).

GRAFTS TO DELIVER TROPHIC FACTORS

Notwithstanding the functional successes that have been achieved with grafting discrete populations of neurones to neo- and allo-cortical sites of host animals with subcortical lesions, it remains likely that the primary pathological deficits in human dementia are cortical. The neuropathological hallmarks of senile plaques and neurofibrillary tangles in Alzheimer's disease are associated with neuronal cell loss in the neocortex, and associated enlargement of the ventricular spaces and cortical sulci (Tomlinson *et al.* 1968, 1970; Terry *et al.* 1981). Although they were not generally concerned with models of dementia, a number of transplantation studies have been concerned with the issue of whether cortical cell loss can be functionally replaced by neuronal transplants.

It might be supposed that the complexity of cortical circuits is such that no cellular transplantation could ever be expected to reconstruct damaged circuitry sufficiently to yield recovery on cognitive functions associated with association neocortex. This presumption was challenged when Stein and colleagues demonstrated recovery in a T-maze delayed alternation task in rats with prefrontal cortex lesions following transplantation of embryonic cortical tissue into the lesion cavity (Labbe *et al.* 1983; Stein *et al.* 1988). This remarkable observation has been replicated in other laboratories (Kesslak *et al.* 1986*a*; Dunnett *et al.* 1987), and similar effects have since been reported on the recovery of a variety of other tasks following transplantation of embryonic cortical tissues (Haun *et al.* 1985; Stein *et al.* 1985; Bermudez-Rattoni *et al.* 1987; Kolb *et al.* 1988; Escobar *et al.* 1989).

Such dramatic recovery on complex learning tasks, when taken together with the observed formation of afferent and efferent connections between cortical grafts and the damaged host brain, make it tempting to suggest that the grafts induced recovery by the functional reconstruction of damaged cortical neural circuitries. However, this conclusion turns out to be premature. For functional efficacy, the timing of the lesion, transplantation and testing is critical with no more than a few days separating each stage of the experiments (Kesslak *et al.* 1986*a*; Dunnett *et al.* 1987; Kolb *et al.* 1988; Stein *et al.* 1988), before any connections have had time to develop. Indeed, recovery may subsequently wane once graft-host connections do become established (Dunnett *et al.* 1987). These observations suggest that the cortical grafts stimulate or secrete neurotrophic substances that promote functional recovery in the host brain. This is corroborated first by the observation that actually removing the cortical grafts does not abolish the recovery to which they give rise (Stein, 1987), and second by the fact that a similar pattern of recovery can be induced by implantation into the prefrontal lesion cavity of glia cells as an alternative source of presumed trophic molecules (Kesslak *et al.* 1986*a*, *b*).

The possibility that one mechanism of graft function can be to provide deficient trophic factors has recently received renewed attention with the observation that central cholinergic neurones are dependent upon nerve growth factor (NGF) for trophic support, and the extension of the cholinergic hypothesis that Alzheimer's disease may involve a deficiency in such support (Hefti, 1983; Hefti & Weiner, 1986). Thus, chronic intracerebral infusions of NGF can inhibit the progressive atrophy of septal cholinergic neurones both in response to experimental axotomy and in natural ageing (Hefti, 1986; Williams *et al.* 1986; Fischer *et al.* 1987; Kromer, 1987). NGF does not cross the blood-brain barrier so that its sustained delivery by mechanical infusion systems raises substantial technical problems. This raises the possibility that transplantation of NGF secreting tissues may provide an alternative means of chronic delivery of this or other trophic molecules in physiological concentrations to selected CNS targets at will.

The viability of grafts to deliver NGF was first investigated in a different context. Following the observation that NGF promotes survival of adrenal chromaffin cells grafted to the neostriatum (Strömberg *et al.* 1985) the seural nerve was successfully cotransplanted as a stable source of NGF

https://doi.org/10.1017/S0033291700029822 Published online by Cambridge University Press

to promote adrenal survival (Hansen *et al.* 1990; Watts *et al.* 1990). An even richer source of NGF is the mouse submaxillary gland. Although a preliminary study of cotransplantation of this tissue with adrenal medulla provided little evidence for any promotion of differentiation of chromaffin cells (Freed *et al.* 1985), subsequent research has indicated that intraventricular implantation of the mouse submaxillary gland can substantially increase survival of axotomised cholinergic neurones of the septum and diagonal band following fimbria-fornix transection (Springer *et al.* 1988).

Probably the greatest scope for achieving sustained delivery of physiological levels of NGF lies in recent developments of molecular biological techniques for the manipulation of cells for transplantation. Preliminary success has been achieved in the transfection of fibroblasts with the NGF gene, and the engineered cells have been demonstrated to be capable of secreting NGF (Ernfors *et al.* 1989; Gage *et al.* 1990), and to have biological activity both in the rescue of axotomized septal cholinergic neurones (Rosenberg *et al.* 1988; Gage *et al.* 1990) and in the promotion of chromaffin cell differentiation *in oculo* (Ernfors *et al.* 1989; Olson *et al.* 1990).

NEURAL TRANSPLANTS AS A TREATMENT FOR ALZHEIMER'S DISEASE?

It is apparent that neural transplantation strategies have been effective in reversing the deficits associated with cholinergic deficiency both in lesioned and aged animals. This has been achieved by using the grafts firstly as a source for trophic support to promote intrinsic cell survival and inhibit progressive degenerative events, and secondly as a source of replacement cholinergic neurones once irreversible degeneration has taken place. More limited advances along the same two fronts have taken place with regard to other subcortical afferent systems implicated in cortical cognitive function, including noradrenergic and serotonergic systems. Thus, to the extent that Alzheimer's disease involves a primary degeneration in subcortical regulatory systems, the prospects of developing a rational therapy along similar lines to the replacement of dopaminergic neurones in Parkinson's disease would appear optimistic.

However, the fundamental issue is whether the cholinergic hypothesis is valid – it appears increasingly likely that at least in its strong form it is not. For example, there is considerable circumstantial evidence to support the view that the classical cortical pathology is primary to the disease process. For example, whereas experimental cortical damage can readily induce secondary retrograde atrophy of subcortical afferent neurones, including basal forebrain cholinergic cell groups, which can be rescued by cortical cell replacement (Sofroniew *et al.* 1983, 1986), the only study indicating experimental induction of secondary cortical degeneration following subcortical basal forebrain lesions (Arendash *et al.* 1987) appears to be artefactual (Thal *et al.* 1990).

If the symptomatology of Alzheimer's disease does turn out to be attributable to cortical degeneration then the task of extensive cellular replacement and reconstruction with neural transplants appears altogether more daunting. The normal processing subserved by the neocortex is intimately dependent upon its intrinsic columnar organization and its efferent connectivity with other cortical and subcortical areas. Although the replacement of multiple cellular populations should be quite feasible, the precision of internal reorganization and connectivity cannot be restored by grafting of relatively crude agglomerations of embryonic neurones, as achieved using present transplantation techniques.

Thus, in the absence of knowledge about the aetiology or primary neuropathology of Alzheimer's disease it is not yet possible to answer the question posed in the title. Current transplantation techniques developed in experimental animals make it quite feasible to repair and reconstruct cholinergic cell loss, or loss of other subcortical diffuse regulatory systems, producing substantial functional benefit to the host animal. There is no reason why similar principles should not also apply to patients with a primary cholinergic deficiency. However, if the dementia of Alzheimer's disease is attributable to a fundamental deterioration in the integrity of cortical circuitries, then functional reconstruction by cellular replacement is beyond the scope of present neural transplantation techniques.

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https://doi.org/10.1017/S0033291700029822 Published online by Cambridge University Press

My own research in this field is generously supported by grants from the Mental Health Foundation and the Medical Research Council.

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