*European Journal of Neuroscience, Vol. 2, pp. 567–587* 

# REVIEW

# Neural Transplantation in Animal Models of Dementia

S. B. Dunnett
Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK

*Key words:* ageing, Alzheimer's disease, neural transplants, rats, monkeys, cortex, hippocampus, acetylcholine, noradrenaline, serotonin, amyloid, senile plaques, neurofibrillary tangles

## Abstract

Neural transplantation provides a powerful novel technique for investigating the neurobiological basis and potential strategies for repair of a variety of neurodegenerative conditions. The present review considers applications of this technique to dementia. After a general introduction (section 1), attempts to replace damaged neural systems by transplantation are considered in the context of distinct animal models of dementia. These include grafting into aged animals (section 2), into animals with neurotransmitter-selective lesions of subcortical nuclei, in particular involving basal forebrain cholinergic systems (section 3), and into animals with non-specific lesions of neocortical and hippocampal systems (section 4). The next section considers the alternative use of grafts as a source of growth/trophic factors to inhibit degeneration and promote regeneration in the aged brain (section 5). Finally, a number of recent studies have employed transplanted tissues to model and study the neurodegenerative processes associated with ageing and Alzheimer's disease taking place within the transplant itself (section 6). It is concluded (section 7) that although neural transplantation does not offer any immediate prospect of therapeutic repair in clinical dementia, the technique does offer a powerful neurobiological tool for studying the neuropathological processes involved in both spontaneous degeneration and specific diseases of ageing. New understandings derived from neural transplantation may be expected to lead to rational development of novel strategies to inhibit the neurodegenerative process and to promote regeneration in the aged brain.

## 1. Introduction

A century has passed since the first attempts at transplantation of neuronal tissue into the mammalian brain (Thompson, 1890), although the technical conditions for achieving reliable survival and growth of the grafts have only been established in the last two decades (Björklund *et al.*, 1983; Das and Altman, 1971; Lund and Hauschka, 1976; Olson and Seiger, 1972; Stenevi *et al.*, 1976). The neural transplantation paradigm provides a powerful technique for the study of brain organization, development and function, and several recent symposia attest to the rapid increase of transplantation studies in the field of neuroscience (Azmitia and Björklund, 1987; Björklund and Stenevi, 1985; Dunnett and Richards, 1990; Gash and Sladek, 1988).

It is now well established from biochemical, electrophysiological and behavioural studies that neural grafts can indeed have a functional influence on the host animal. Earlier studies evaluated such claims in the context of potentially simple neuronal systems, including implants of hypothalamic and other cell populations that may exert neurohormonal or neuroendocrine influences on the host brain (e.g. Freed *et al.*, 1981; Gibson *et al.*, 1984; Huang *et al.*, 1987) or catecholaminergic and cholinergic neurons which provide a relatively diffuse innervation of their normal brain targets (Björklund and Stenevi, 1979; Dunnett *et al.*, 1982a, 1983; Freed *et al.*, 1980; Perlow *et al.*, 1979). More recently, the success achieved in these earlier studies has led to the consideration of the functional effects of neural transplantation in more complex connected circuits of the host brain, including the neostriatum (Dunnett *et al.*, 1988d; Isacson *et al.*, 1986), hippocampus (Kimble *et al.*, 1986; Woodruff *et al.*, 1987), neocortex (Bragin *et al.*, 1987, 1990; Dunnett *et al.*, 1987a; Labbe *et al.*, 1983) and retino-tectal pathway (Coffey *et al.*, 1990; Craner *et al.*, 1989).

In parallel with the development of a wide range of model systems for the functional evaluation of neural grafts has come the realization that the grafts may exert their effects via a variety of different mechanisms (Björklund *et al.*, 1987; Dunnett and Björklund, 1987; Freed *et al.*, 1985b; Gage and Buzsaki, 1989; Gash, 1987). In particular, Björklund *et al.* (1987) have provided one conceptual framework for analysing such effects, and identified at least six mechanisms by which grafted neural tissues might influence neural activity (and behaviour) of the host animal: (i) non specific or negative consequences of the implantation surgery; (ii) trophic actions on the host brain; (iii) diffuse release of

*Correspondence to:* S. B. Dunnett, as above

*Received and accepted 5 March 1990*

hormones or neurotransmitters; (iv) reinnervation of elements in the host brain by the grafts; (v) establishment of reciprocal graft-host connections; and (vi) complete integration of the graft into the host circuitry (see section 4.2 for further details). Evidence for each of these different mechanisms has been acquired in different model systems (see Björklund *et al.*, 1987 for examples). This hierarchical division is inevitably an oversimplification, because each of the mechanisms may vary in extent and several different mechanisms may be operative to influence the functional capabilities of any individual experimental animal. Therefore, rather than seeking to identify what is the general mechanism of graft function, it becomes necessary to consider each individual model system (i.e. the interactions between experimental lesion, graft tissue, host environment and functional test), and ultimately each individual animal, if we are to fully understand how grafts exert their functional effects.

The present review considers recent experimental studies on neural transplantation in animal models of ageing and dementia. Dementia is characterized by a progressive deterioration of cognitive functions in later life, with memory impairment as an early pronounced feature. Different forms of dementia are associated with distinctive patterns of neurodegeneration in the brain. By far the commonest types are Alzheimer's disease and multi-infarct dementia, each with a characteristic profile of degeneration in the cortex and hippocampus (senile plaques and neurofibrillary tangles, and ischaemic lesions, respectively; Corsellis, 1976; Tomlinson *et al.*, 1970). Although the distinct types can only be differentiated with confidence based on post-mortem analysis of the brains (Corsellis, 1976; Khachaturian, 1985), it has proved possible to establish clinical criteria for the diagnosis of 'senile dementia of the Alzheimer type' with a reasonable degree of reliability (McKhann *et al.*, 1984).

In addition to the classical neuropathological signs of Alzheimer's disease, distinctive changes have more recently been described in identified neurotransmitter systems of the brain. This includes not only neuronal populations intrinsic to the the cortex [e.g. corticotrophin releasing factor (CRF)] but also particular subcortical populations that project to the neocortex and hippocampus, including the cholinergic neurons of the basal forebrain, serotonergic neurons of the raphe nucleus and noradrenergic neurons of the locus coeruleus (Bondareff *et al.*, 1982; Mann and Yates, 1983; Rossor and Iversen, 1986; Tomlinson *et al.*, 1981; Whitehouse *et al.*, 1982; Yamamoto and Hirano, 1985). These latter neuronal populations of the 'isodendritic core' have attracted particular interest because the relatively diffuse regulatory control that they provide may be more amenable to rational therapeutic manipulation (e.g. with drugs) than the precisely organized neuronal circuits intrinsic to the cortex and hippocampus.

Parkinson's and Huntington's diseases are also associated with dementia (for reviews see Brown and Marsden, 1988; Cummings, 1986; Huber and Paulson, 1985), and many studies have considered neural transplantation in animal models of these diseases. However, the primary interest in these studies has been directed towards transplantation in the basal ganglia and modification of related motor functions (Björklund *et al.*, 1987; Brundin and Björklund, 1987; Dunnett *et al.*, 1985a). Here, we focus on those studies directed at modelling in animals the cognitive impairments of ageing which reach their most profound level of debility in the senile dementias, in particular Alzheimer's disease.

Alzheimer's disease does not occur explicitly and there exists, as yet, no truly valid animal model of the disease. Nevertheless, specific aspects of the clinical neuropathology are observed in the brains of aged animals (Price *et al.*, 1988; Wisniewski *et al.*, 1970, 1973) and other aspects can be induced in animals by a variety of experimental treatments (Arendash *et al.*, 1987; Bartus *et al.*, 1983; Dunnett and Barth, 1990; Fisher and Hanin, 1986; Olton and Wenk, 1987; Price, 1986; Price *et al.*, 1988; Sarter, 1987; Smith, 1988; Wenk and Olton, 1987). Attempts have been made to repair the damage with drugs or transplantation in some of these restricted models, such as lesions of subcortical cholinergic or monoaminergic systems, or the process of ageing itself. Other models, such as scrapie-associated plaques or aluminium-induced neurofibrillary pathology, have yet to receive detailed therapeutic evaluation. Additionally, the transplantation technique itself is providing new approaches to providing more adequate models of the primary pathology of Alzheimer's disease, such as in recent studies of hippocampal grafts derived from the trisomy 16 mouse.

Therefore, the present review is organized in terms of the effects of neural grafts in different animal models that have been developed to reproduce the psychopathology and chemical neuropathology of human ageing, Alzheimer's disease and dementia. Section 2 compares the effects of neural grafts in young and aged animals. Section 3 considers the effects of neural grafts in young animals with experimental lesions of identified neurotransmitter systems that decline in human ageing and dementia. Section 4 considers the effects in animals of lesions and grafts of cortical and hippocampal systems, which undergo the greatest neuronal degeneration in human dementia. Section 5 considers the possibility of grafting of tissues to deliver growth factors in the context of the hypothesis that the degenerative changes in Alzheimer's disease may be attributable to a decline in trophic support of intrinsic neurons. Section 6 considers the use of neural grafts in situations where the primary interest is in the development of neurodegenerative changes within the grafted tissues themselves, rather than in graft−host interactions *per se*.

## 2. Grafts in ageing animals

### *2.1 Ageing in animals as a model of dementia in humans*

Neuropathological changes akin to the plaques and tangles of Alzheimer's disease (AD) are extremely uncommon in aged animals. Although plaque-like structures have been observed in aged animals such reports are rare, in particular in small laboratory animals (Dayan, 1971; Vaughan and Peters, 1981), although they may be more reliably observed in larger species such as old bears, dogs and primates (Kitt *et al.*, 1984, 1985; Struble *et al.*, 1985; Wisniewski *et al.*, 1970, 1973). Nevertheless, when plaque-like structures are observed they differ from the human senile plaques at the ultrastructural level (Vaughan and Peters, 1981; Wisniewski *et al.*, 1973), and intracellular tangles of paired helical filaments have not been observed in untreated 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 AD (for reviews see Algeri *et al.*, 1983; Dunnett and Barth, 1990; McGeer, 1981; Pradhan, 1980; Price *et al.*, 1988). The most extensive studies have been conducted in the classical monoaminergic systems. Aged rats and primates can manifest marked decline in the levels of dopamine, noradrenaline and their metabolites (Finch, 1973; Goldman-Rakic and Brown, 1981; McIntosh and Westfall, 1987; Osterberg *et al.*, 1981; Ponzio *et al.*, 1982), although parallel decline in serotonergic systems is generally less pronounced. Interest in the cholinergic system is more recent, and has been stimulated by the explicit formulation of the 'cholinergic hypothesis of geriatric memory dysfunction', in which it is proposed that decline in this neurotransmitter system may be particularly implicated in the cognitive deficits of ageing and dementia (Drachman and Sahakian, 1980; Bartus *et al.*, 1982; Coyle *et al.*, 1983). The decline in the cholinergic marker enzyme choline

acetyltransferase has generally been found to be relatively modest in the forebrain of aged rodents and primates (McGeer *et al.*, 1971; Strong *et al.*, 1980; Wenk *et al.*, 1989), but more marked changes have been reported in acetylcholine synthesis and release, high-affinity uptake mechanisms and in muscarinic receptor binding (Gibson *et al.*, 1981; Lippa *et al.*, 1980; Meyer *et al.*, 1984; Sherman *et al.*, 1981; Strong *et al.*, 1980). In parallel, morphometric analyses have confirmed significant shrinkage and/or loss of choline acetyltransferase-immunoreactive basal forebrain neurons in the septum diagonal band and nucleus basalis of aged rats (Fischer *et al.*, 1989; Hornberger *et al.*, 1985).

At the behavioural level, a wide variety of deficits are observed in aged animals in general sensory sensitivity, motivation and motor capacity as well as in cognitive tasks involving learning and memory functions (for reviews see Campbell *et al.*, 1980; Dean and Bartus, 1987; Elias and Elias, 1976; Gold and McGaugh, 1975; Ingram, 1985; Kubanis and Zornetzer, 1981; Price *et al.*, 1988). In addition, it must be noted that there can be a wide variation in the presence or degree of deficits in individual old animals, and the decline in performance from one animal to another is not necessarily correlated between different tasks (Gage *et al.*, 1984b, 1989; Markowska *et al.*, 1989). Of particular interest in this respect are studies which have demonstrated correlations between learning and other behavioural impairments on the one hand, and morphological or biochemical changes in identified forebrain systems on the other (e.g. Fischer *et al.*, 1989; Gage *et al.*, 1984c; Markowska *et al.*, 1989; Zornetzer, 1985).

The particular advantage of using aged animals as a model system for the evaluation of graft effects lies in its face validity. The particular disadvantage relates to the multidimensional nature of structural and functional changes. Although correlational approaches are often used, it can prove extemely difficult to relate specific patterns of behavioural symptoms to particular neuropathological or neurochemical deficits in the aged brain with any great degree of confidence about their causative nature (Gage *et al.*, 1983c). In this context, one interest in the neural transplantation strategy lies in the possibility that the pattern of behavioural recovery following transplantation of particular cell types can permit primary components of age-related neuropathology to be distinguished from secondary components (Gage *et al.*, 1983c).

### *2.2 The aged brain as a transplantation site*

The age of the donor tissue is one of the most critical parameters in achieving viable grafts of neural tissue (Olson and Seiger, 1972; Stenevi *et al.*, 1976; Das *et al.*, 1980). Good survival is generally dependent upon the use of embryonic or (in a few cases) neonatal donors, whereas brain tissues derived from more mature donors do not survive. In fact there appears to be a critical developmental period during which graft tissues should be taken. This time-window differs for each population of central nervous system (CNS) neurons, and may be only 2–3 days in duration (Das, 1983; Seiger, 1985). Thus, for example, the critical time window for embryonic dopamine neurons is E13–E15 in the rat, and only relatively poor survival is obtained once the embryos reach 17–20 days of gestational age (Brundin *et al.*, 1988; Finger and Dunnett, 1989). The critical period correlates to the stage when the particular populations of neural cells are undergoing or have just completed final mitosis and their fate is determined, but before they have established any extensive neurite outgrowth. The ability of embryonic cells to survive prolonged periods of anoxia, and the greater damage to the axonal and dendritic fibre plexus that is necessarily sustained by dissection of more mature neurons, may additionally contribute to the importance of taking donor tissue early in development (Das, 1983).

In early studies, the age of the host was also believed to be critically important. In particular, it was considered necessary for the grafts to be implanted in the neonatal brain in order to provide a sufficiently plastic host environment (Das, 1974; Das and Altman, 1971; Dunn, 1917; Lund and Hauschka, 1976). By contrast, very poor survival was seen when similar embryonic tissues were implanted in the adult brain (Das, 1974; Glees, 1955). In the intervening years, refinements in techniques have enabled transplantation to be achieved reliably in adult hosts, and host age does not appear to be a limiting factor if graft tissues of the optimal developmental age can be positioned in an appropriately nutritive environment (Stenevi *et al.*, 1976). Thus, it is generally the case that there are less restrictions with regard to donor age, site of implantation and transplantation technique when the hosts are of neonatal age (Björklund and Stenevi, 1984; Das and Hallas, 1978; Hallas *et al.*, 1980; McLoon and Lund, 1983; Sunde and Zimmer, 1983), although the grafts can survive as well in the adult brain when attention is given to optimization of these parameters. Once the host animals reach 10 days of age few further differences in graft viability are seen up to at least 6 months of age (Hallas *et al.*, 1980).

In contrast to many studies contrasting neonatal and adult host environments, the viability of neural grafts in the aged brain has only recently been considered explicitly. In the first such study, Azmitia *et al.* (1981) compared embryonic raphe grafts implanted into the intact hippocampus of adult (4–6-month-old) or aged (24-month-old)-mice. The grafts survived, contained healthy serotonin-immunoreactive neurons, and gave rise to a hyperinnervation of the hippocampus, in the hosts of either age group. Whereas the extent of hyperinnervation may have been less in the aged hosts, the laminar distribution of serotonergic fibres in the host hippocampus was similar in the two age groups and appropriate in comparison with the normal distribution. These observations suggested that even the aged brain can support the survival and growth of embryonic neural grafts.

A similar conclusion was reported by Gage *et al.* (1983a). They found that cholinergic-rich septal grafts survived as well in the aged hippocampus as had been observed in previous studies using young hosts. There was a suggestion that acetylcholinesterase (AChE)-positive fibre outgrowth in the aged brain was less extensive, and the laminar organization of the reinnervation in the host hippocampus was less precisely organized, than had been seen following grafting into the young brain. Nevertheless, the interpretation of these differences was ambiguous. In both young and aged rats the intrinsic cholinergic inputs to the hippocampus were lesioned (by transection of the fimbria-fornix) in order to reveal the fibres in the hippocampus that were explicitly derived from the grafts. However, the lesions were made before transplantation in the young animals but just before killing in the aged rats. In a subsequent study, it was found that similar grafts implanted in young animals grew to a larger volume, contained more AChE-positive neurons and gave rise to a more extensive cholinergic innervation of the hippocampus (as determined by choline acetyltransferase biochemistry) when additional fimbria-fornix lesions were made prior to transplantation (Gage and Björklund, 1986b). Thus, the difference between the young and old rats in the earlier report could be fully attributable to differences in the timing of the lesions rather than to the age difference of the hosts, and the contribution of this latter factor remains to be fully clarified.

Of particular interest in this series of studies was the demonstration that the grafted cholinergic neurons established extensive synaptic connections with target neurons in the dentate gyrus of the aged hosts (Clarke *et al.*, 1986b). The distribution of contacts on spines and the shafts of

dendrites of host granule cells was seen to be similar to the pattern observed in the intact hippocampus, but dissimilar to the pattern observed in young rats with fimbria-fornix lesions and grafts (Clarke *et al.*, 1986a). Thus, the remarkable conclusion of these observations was that implanted cholinergic neurons appear to achieve a more appropriate pattern of reorganization when implanted into the aged brain, where any dysfunction is attributable to slow degenerative processes, than when implanted into the brain of young animals in which extensive deafferentation has been induced by an acute experimental lesion.

Other studies have confirmed good survival and growth of cholinergic (Dunnett *et al.*, 1988b) and serotonergic (Azmitia, 1987) grafts in the aged hippocampus, with extensive fibre outgrowth of the appropriate populations of neurons as determined by histochemical and immunocytochemical staining, as well as survival and growth of dopaminergic, cholinergic and noradrenergic grafts into the lateral or third ventricles (Collier *et al.*, 1985, 1987, 1988; Matsumoto *et al.*, 1987), caudate-putamen (Date *et al.*, 1989; Gage *et al.*, 1983a,b; Pezzoli *et al.*, 1988), basal forebrain (Chen *et al.*, 1989), and neocortex (Dunnett *et al.*, 1988b). While reporting on the viability and functional capacity of the grafts, few of these studies have provided detailed morphological comparisons between the grafts in young and aged hosts. However, in one study, Kaplan *et al.* (1985) have employed Golgi staining to investigate the neuronal morphology of hypothalamic grafts in the third ventricles of young and aged hosts. In this study, there were no detectable differences in transplant size, or in the length or branching frequency of neuronal dendrites within the grafts.

The most detailed anatomical comparisons of the effects of host age on graft viability and growth have been conducted not using intracerebral transplantation but using the *in oculo* model made popular by Olson and colleagues (Olson *et al.*, 1984). In the first of this series of studies, Eriksdotter-Nilsson *et al.* (1986) found that embryonic cortical tissues grew to a larger size when grafted to the anterior eye chamber of 1.5-month-old host-rats than when grafted to the same site in 3- or 7.5-month-old hosts. The less viable grafts in the older two groups of hosts were distinguishable in that (a) they contained much higher densities of glial fibrillary acidic protein (GFAP) immunoreactive glia, and (b) they had abnormal swollen thick-walled capillaries, in comparison to the grafts in the youngest host group and to the normal parietal neocortex. In a subsequent study, this observation was extended to show an even greater reduction in growth when cortex grafts were implanted in 17-month-old hosts, and these grafts manifested even higher levels of gliosis and capillary abnormalities (Eriksdotter-Nilsson and Olson, 1989).

Comparable differences in growth, gliosis and vascularization between hosts of different ages have been seen in *in oculo* grafts derived from septal, cerebellar and hippocampal donor tissues as for cortical tissues, but were less marked for locus coeruleus tissues (Eriksdotter-Nilsson and Olson, 1989). By contrast to the age-dependence of vascular and glial markers, neurofilament staining in the grafts was comparable in all age groups. In a more detailed study of the internal organization of hippocampal grafts, Eriksdotter-Nilsson *et al.* (1989a) found a similar compact organization of pyramidal cells in intraocular grafts in young (2-month) and aged (20-month-old) hosts, and both the pattern and density of noradrenergic fibre ingrowth from the host iris, and the level of spontaneous electrophysiological activity were also comparable in the two age groups.

Thus, grafts of a variety of tissues which are allowed to survive 2–3 months *in oculo* show somewhat reduced survival and growth in aged than in young hosts, but appear to be comparable in their internal neuronal organization. Further analysis of neurodegenerative changes within the grafts surviving long term *in oculo* is considered further in section 6.1.

### 2.3 Dopaminergic grafts in the aged neostriatum

The first studies of the functional effects of grafts in aged animals considered motor impairments associated with ageing. A number of studies have indicated that aged rats can have profound impairments in a variety of motoric functions, such as motor co-ordination, balance and reflexive vigour (Campbell *et al.*, 1980; Ingram *et al.*, 1981; Wallace *et al.*, 1980). Although clearly some of these impairments are caused by peripheral skeletal and muscular degeneration (Roberts and Baskin, 1978), at least some are most likely to be due to CNS decline. For example, Marshall and Berrios (1979) showed that the movement disorders of aged rats in a test of swimming ability were akin to those seen in young rats with central dopamine depletion, and were reversed in the old rats by administration of low doses of the central dopamine agonist drug apomorphine.

Since many of the motor deficits in young rats treated with the dopaminergic toxin 6-hydroxydopamine can be reversed by grafts of fetal nigral dopamine neurons to the caudate-putamen (Dunnett *et al.*, 1985a; Freed, 1983), it was proposed that a similar transplantation strategy might also be effective against the motor impairments of aged rats. Gage *et al.* (1983b) tested this hypothesis and demonstrated a highly significant amelioration of motor co-ordination deficits 3 months after implantation of fetal nigral cells into the caudate putamen. The pattern of recovery was specific to the aged animals' co-ordination impairments, as assessed by their abilities to maintain balance on narrow beams, whereas no effect was seen in measures of global locomotor activity or of muscle strength.

Although these studies of nigral grafts have focused on motor rather than cognitive impairments, they illustrate the feasibility of a transplantation strategy to ameliorate age-related deficits in the absence of explicit experimental lesions.

### 2.4 Cholinergic grafts in the aged hippocampus and neocortex

The cholinergic hypothesis of geriatric memory dysfunction (Bartus *et al.*, 1982; Coyle *et al.*, 1983) stimulated an interest in the potential effects of cholinergic grafts on cognitive functions in aged animals, and the greatest attention has so far been directed to the loss and re-establishment of the cholinergic innervation of the hippocampal system. Among the variety of cognitive deficits manifested by aged rats, deficits in maze learning and other aspects of spatial navigation have been the most thoroughly characterized (Barnes, 1979; Barnes *et al.*, 1980; Gage *et al.*, 1984b, 1989). Moreover, deficits in aged rats' abilities to navigate spatial mazes have been found to correlate with the decline in metabolic and cholinergic activity in the hippocampus (Fischer *et al.*, 1989; Gage *et al.*, 1984c) and lesions in the septo-hippocampal circuitry of young animals produce a similar disruption of task performance (Morris *et al.*, 1982; O'Keefe and Nadel, 1978; Olton *et al.*, 1978, 1979; Sutherland *et al.*, 1982).

Gage *et al.* (1984a) screened large numbers of aged animals for impairments in the Morris water maze task before transplantation, because it has become apparent that aged rats constitute a heterogeneous population and not all animals manifest age-related impairments (Gage *et al.*, 1984b, 1989). One half of the aged impaired group then received cholinergic-rich septal grafts into the hippocampus. The grafted subgroup showed a substantial improvement in maze navigation when retested 3 months later, in contrast to the non-grafted subgroup that maintained their initial level of impairment. The recovery in the grafted aged rats was proportional to graft survival and cholinergic fibre reinnervation of the hippocampus, and performance approached the level of unimpaired control animals in the best cases. In a subsequent more comprehensive

study of various parameters of maze learning performance, Gage and Björklund (1986a) found a similar pattern of recovery by aged rats with septal grafts. Moreover, low doses of atropine were found to impair performance in recovered aged rats with grafts, indicating that the recovery was by an atropine-sensitive (i.e. presumed cholinergic) mechanism.

This laboratory has used an alternative test paradigm, involving an operant delayed response task (delayed nonmatching to position) to obtain a more specific evaluation of memory functions in aged rats. In parallel to the observations in the water maze, aged rats manifest a specific delay-dependent deficit in short-term memory (Dunnett *et al.*, 1988a) that is partially ameliorated by septal implants into either the hippocampus or the neocortex (Dunnett *et al.*, 1988b). It appears that both hippocampal and medial prefrontal circuits are implicated in the short-term memory functions measured in such delayed response tasks, and it remains to be seen whether a combined graft placement into both sites would provide an additive benefit, as has been observed in alcohol intoxicated rats (Arendt *et al.*, 1988b; see section 3.5).

The recovery observed after septal implants into the hippocampus of aged animals exemplifies the power of the transplantation strategy for assessing hypotheses of geriatric cognitive dysfunction. Associations between cognitive deficits and postmortem indices of neurotransmitter function or neuropathology are correlational in nature and cannot determine causative relationships (Gage *et al.*, 1983c). Similarly, lesions in the septo-hippocampal circuitry of young animals inevitably induce widespread nonspecific damage rather than selective cholinergic disturbance. The induction of impairments by peripheral or central injections of anticholinergic drugs in young animals certainly induces deficits akin to those observed in aged subjects (Brito *et al.*, 1983; Drachman and Sahakian, 1980; Eckerman *et al.*, 1980), but this cannot demonstrate whether the same transmitter systems are primary to the deficits in ageing. By contrast, the reversal of age-related impairments by cholinergic drugs or by target specific implantation of septal neurons into the hippocampus does provide strong support for the hypothesis that dysfunction of the intrinsic cholinergic projections to the hippocampus and neocortex underlies some of the cognitive impairments seen in aged animals and humans (Bartus *et al.*, 1982; Gage *et al.*, 1983c). Although the pharmacological strategy has so far yielded only limited improvements (Bartus *et al.*, 1982; Christie *et al.*, 1981; Sahakian, 1988; Sahakian *et al.*, 1989), the transplantation strategy has already provided convincing evidence in support of the causative nature of the relationship, even though such studies are still in their infancy.

### 2.5 Noradrenergic grafts in the aged brain

Other hippocampal neurotransmitter systems also decline in ageing, and the noradrenergic and serotonergic systems have recently received limited attention (Arnsten and Goldman-Rakic, 1985a; Pradhan, 1980; Zornetzer, 1985). Thus, for example, the age-related decline in the numbers of noradrenergic neurons in the locus coeruleus and the loss of hippocampal noradrenergic activity has been seen to correlate with impairments in avoidance learning by aged rats and mice (Leslie *et al.*, 1985; Zornetzer, 1985), and delayed response deficits in aged monkeys can be reduced by injections of the $\alpha_2$ receptor agonists clonidine and guanfacine (Arnsten and Goldman-Rakic, 1985b; Arnsten *et al.*, 1988). Collier *et al.* (1985; 1988) have implanted embryonic locus coeruleus grafts into the ventricles of aged rats and demonstrated an amelioration of passive avoidance learning. The noradrenergic specificity of these graft effects was confirmed by demonstrating (a) that no similar benefit was provided by control grafts of cerebellar tissues, (b) the recovery could be mimicked by chronic intraventricular infusion of noradrenaline, and (c) the recovery in grafted rats was reversed by treatment with the $\beta$-blocker propanolol. It is well established that locus coeruleus grafts can provide an extensive fibre reinnervation of the hippocampus, the laminar pattern of which is normal, when the grafts are implanted into cavities adjacent to the deafferented hippocampus of young rats (Björklund *et al.*, 1976). However, although the grafts in the present study provided a limited fibre ingrowth into the host hypothalamus, the ventricular placement of the grafts and the parallel recovery following intraventricular infusion of noradrenaline suggest that the recovery in the aged rats was attributable to a more diffuse mechanism of systemic noradrenaline release, perhaps influencing mechanisms of arousal (Collier *et al.*, 1988).

## 3. Neurotransmitter-specific lesions as models of dementia

### 3.1 Subcortical lesions as models of dementia

The most extensively studied models of dementia including those considering the effects of neural grafts, have been models of the consequences of subcortical lesions which disrupt neurotransmitter pathways that decline spontaneously in ageing and that undergo particular decline in Alzheimer's disease. In the context of the cholinergic hypothesis, lesions of the basal forebrain projections to the neocortex and hippocampus have received particular attention. This model has been the focus of numerous reviews (Bartus *et al.*, 1983, 1986; Dunnett, 1989; Dunnett and Barth, 1990; Fisher and Hanin, 1986; Olton and Wenk, 1987; Price, 1986; Smith, 1988; Wenk and Olton, 1987), and consequently a detailed account is unnecessary. In summary, electrolytic or neurotoxic lesions of the basal forebrain disrupt performance of rats and monkeys on a wide variety of tasks of learning and memory functions, which have been considered to be akin to the cognitive deficits of human dementia.

Although such effects are reliable and well replicated, their interpretation has been more controversial. In particular, there has been dispute over the specificity of the lesions. Although the lesions reliably destroy cholinergic neurons in the basal forebrain, damage is also sustained by other noncholinergic neurons in the vicinity, and it has proved difficult to demonstrate the cholinergic specificity of the lesion-induced deficits. This issue has been brought into particular relief by the recent demonstration that the two toxins quisqualic acid and ibotenic acid are equally toxic against cholinergic neurons of the nucleus basalis, but can have quite different behavioural sequelae (see section 3.4). These observations strongly suggest that destruction of noncholinergic populations of basal forebrain neurons underlie some (or even all) of the functional deficits induced by lesions of this area. Similarly, it has proved equally difficult to achieve selective lesions of the cholinergic innervation of the hippocampus, and studies of this system have employed electrolytic or neurotoxic lesions of the medial septum or, more commonly, gross transection of the fimbria-fornix to disconnect all subcortical afferents and efferents of the hippocampus. Again, the attribution of functional deficits in such studies specifically to damage of the cholinergic afferents is troublesome.

One reason, therefore, for interest in neural transplantation has been the possibility that such studies might provide a resolution of the issue of lesion specificity. Although attention has to be paid to the involvement of noncholinergic neurons within cholinergic-rich grafts, it can nevertheless be suggested that the demonstration of functional recovery

following cortical or hippocampal implantation and target reinnervation would support the hypothesis that the basal forebrain cholinergic innervation of these targets is critically involved in the behaviours under investigation.

### 3.2 Cholinergic grafts in the hippocampus

Involvement of the hippocampus with memory processes has been suspected since the observations of profound amnesia resulting from temporal lobectomy in humans. It was initially thought that hippocampal lesions do not produce similar memory impairments in animals (Douglas, 1967; Kimble, 1968), but it has become apparent that this discrepancy is in large part attributable to the use of test procedures that were not comparable (Gaffan, 1972). Indeed, once attention is given to subdivisions within memory systems and the selection of appropriate tests, lesions in the hippocampal system of humans, monkeys and rats do induce clear deficits in aspects of short-term memory that have variously been designated as 'working', 'declarative', 'episodic' or 'recognition' memory (Gaffan, 1976; Olton, 1983; Olton *et al.*, 1979), in addition to the clear-cut deficits in spatial mapping tasks (Morris *et al.*, 1982; O'Keefe and Nadel, 1978).

The first functional studies of cholinergic grafts in the hippocampus employed two maze tasks dependent upon spatial memory—paired trial alternation learning in a T maze and the Olton radial maze. Performance of both tasks is disrupted by lesions within the septo-hippocampal circuitry (Olton, 1983; Olton *et al.*, 1978; Rawlins and Olton, 1982) as well as by anticholinergic drugs, suggesting a cholinergic involvement in some aspect of task performance. Dunnett *et al.* (1982a) compared the effects of septal and locus coeruleus grafts implanted into the hippocampus of rats with fimbria-fornix lesions (which transect cholinergic, noradrenergic and other subcortical connections of the hippocampus). The septal grafts alone restored the animals' ability to learn the T-maze alternation task, whereas the rats with locus coeruleus grafts remained as impaired as rats with lesions alone. The degree of recovery correlated significantly with the extent of acetylcholinesterase-positive fibre ingrowth provided by the septal grafts. However, one animal with surviving septal grafts and good ingrowth still failed to learn the task, and it appeared that cholinergic reinnervation of the hippocampus was a necessary, but not a sufficient condition for recovery of learning ability. Recovery in this T-maze task in rats with septal grafts has been replicated using xenografts from mouse donors (Daniloff *et al.*, 1985), and using the aziridinium ion AF64A as an alternative to fimbria-fornix lesions to cholinergically denervate the hippocampus (Ikegami *et al.*, 1989).

In the eight-arm radial maze, Low *et al.* (1982) have investigated the capacity of similar grafts to reverse lesion-induced deficits in learning. In this case, no spontaneous recovery was seen in the rats with septal grafts unless the animals were additionally treated with the cholinesterase inhibitor physostigmine (which had no effect on the rats with lesions alone). By contrast, septal grafts have been found to be effective in the absence of pharmacological treatment in this task when the toxin AF64A has been used to make a (possibly more selective) cholinergic denervation of the hippocampus (Ikegami *et al.*, 1989).

Other learned behaviours, such as spatial navigation in the Morris water maze task, have revealed a complex pattern of changes following septal cell transplantation. In the first such study we saw impairments as well as improvements that did not appear to relate in any coherent manner to particular patterns of cholinergic reinnervation (Dunnett *et al.*, 1982b). However, more detailed analysis of water maze performance by Nilsson *et al.* (1987) has revealed subtle benefits from septal grafts in the navigation skills of the transplanted animals. As in the previous T-maze alternation tasks, the grafted rats manifested a moderate recovery in their ability to learn the water maze task, and the spatial precision of their search patterns on probe trials in which the escape platform was removed from the pool. Similar to the effects of similar grafts in aged rats, the improvement in the grafted rats was confirmed to be by an atropine-dependent mechanism (Nilsson *et al.*, 1987).

It remains the case that the recovery observed following implantation of septal grafts in rats with fimbria-fornix lesions remains moderate, when contrasted to the occasionally almost complete reversal of deficits that has been achieved with similar grafts in aged animals. This highlights the fact that the fimbria-fornix lesion (or indeed any other experimental lesion) is not a true model of the neurodegeneration associated with ageing, but produces one aspect of the natural syndrome *in extremis*. Moreover, although the septal graft studies were formulated in the context of the cholinergic hypothesis of dementia, the fimbria-fornix lesion does not produce a specific cholinergic lesion. Thus, fimbria-fornix lesions disrupt noradrenergic, GABAergic and serotonergic afferents and other subcortical efferents of the hippocampus, in addition to disruption of the cholinergic afferents from the septum.

One approach to this problem has been the attempt to make more circumscribed lesions within the medial septum or fimbria than is provided by gross transection of the fimbria-fornix. Thus, for example, Segal *et al.* (1987) have compared the effects of septal grafts in rats which had sustained septo-hippocampal damage either by fimbria-fornix transection or by electrolytic lesion of the medial septal nucleus. Both lesions severely disrupted acquisition of the Morris water maze task. Whereas the grafts provided no significant change in learning deficits in rats with fimbria-fornix damage, they provided significant amelioration of the deficit in rats with more circumscribed medial septal damage. These authors speculated that sparing of the hippocampal efferents in the case of the septal lesion, in combination with the graft-derived replacement of cholinergic afferents, is necessary for functional benefit.

Along similar lines, Pallage *et al.* (1986) demonstrated that septal grafts implanted in the hippocampus ameliorated the deficits of rats with septal lesions when tested in a radial maze task 5 and 9 months (but not 1 month) after transplantation surgery. Whereas additional administration of nerve growth factor (NGF) had previously been found to enhance choline acetlytransferase activity in septal grafts in the hippocampus (Toniolo *et al.*, 1985), in this study NGF treatment added to, rather than improved, the functional impairment in rats with septal lesions, whether or not they had additional grafts. In a subsequent study, this same group investigated the effects of septal transplants on serial alternation and radial maze performance of rats with selective lesions of the medial fimbria, dorsal fornix, or both combined (Dalrymple-Alford *et al.*, 1988). In this case, the lesions induced deficits on the radial maze, but not the serial alternation task. In contrast to previous studies, the transplants induced deficits on both tasks over and above those induced by the lesions of either type. This appeared to be attributable to the very extensive growth of the grafts which induced gross distortion of the target hippocampus of the host animals. Thus, attention needs to be paid to the possible adverse consequences as well as benefits of transplantation of neural tissues.

Factors influencing the functional viability of septal grafts have recently been further investigated by Dunnett *et al.* (1990). This study tested animals' ability to time spaced responding in an operant differential reinforcement of low rates (DRL) task, in contrast to the variety of maze learning tests that have otherwise been used for functional assessment of this model. Fimbria-fornix lesions disrupted DRL performance,

which could be reversed by septal grafts taken from embryos of 13–14 days of gestational age, but not by grafts derived from older donors, even though somewhat older embryos still provided a good acetylcholinesterase-positive reinnervation of the host hippocampus. Indeed, grafts derived from the oldest embryos actually disrupted performance beyond the level of deficit observed in rats with lesions alone. Thus, although cholinergic reinnervation of the host hippocampus by the graft was a necessary factor in recovery, this was not a sufficient explanation for the differences between graft groups, but rather suggested that the presence or absence of other (unidentified) connections may be critical to the development of functional changes, whether beneficial or detrimental in nature.

The involvement of noncholinergic damage in aspects of the lesion syndrome is also suggested by the observation that some simple behaviours related to the animals' level of arousal, such as locomotor hyperactivity, are not affected by septal grafts of optimal age, but may be ameliorated by noradrenaline-rich locus coeruleus grafts or by septal grafts from older donors when the cholinergic neurons are no longer viable (Dunnett *et al.*, 1982b; 1990). Consequently, a few recent studies have begun to consider the functional capacity of noncholinergic grafts in the hippocampus, either alone or in combination with cholinergic-rich septal implants. So far such studies have been limited to considering the additional role of serotonergic afferents.

### 3.3 Serotonergic interactions in the hippocampus

The serotonergic neurons of the midbrain raphe nucleus innervate the hippocampus via the fimbria-fornix, and this system has also been found to undergo decline in ageing. Serotonergic grafts have been found to survive and give rise to extensive fibre outgrowth in a variety of subcortical sites in the rat brain (Azmitia, 1987; Dunnett *et al.*, 1988c; Foster *et al.*, 1988a,b; McRae-Degueurce *et al.*, 1981, 1983, 1984; Segal and Azmitia, 1986; Tsubokawa *et al.*, 1988). However, whereas serotonergic grafts have been investigated histologically in the hippocampus of aged animals (Azmitia *et al.*, 1981; Azmitia, 1987), functional studies (including models of dementia) have only been conducted in young animals with lesions.

As indicated above, the classical fimbria-fornix lesion disrupts serotonergic and noradrenergic as well as cholinergic afferents to the hippocampus. Vanderwolf (1987) first demonstrated that combined cholinergic and serotonergic blockade (with scopolamine and *p*-chlorophenylalanine, respectively) disrupted rats' acquisition of shock avoidance and swimming escape tests, concluding that the disruption was in some ambiguous process of stimulus control rather than necessarily a deficit in learning and/or memory *per se*. Richter-Levin and Segal (1988) replicated these observations of performance deficits following a similar combined pharmacological blockage using the standard Morris swim maze. Neither drug had any substantial effect when administered on its own. This observation suggested a degree of redundancy such that either serotonergic or cholinergic grafts might be able to reverse deficits associated with combined cholinergic and serotonergic dysfunction. In a first test of this hypothesis (Richter-Levin and Segal, 1989), the forebrain serotonergic system was depleted with intraventricular injection of the serotonergic toxin 5,7-dihydroxytryptamine (5,7-DHT), half of the lesioned rats received additional raphe grafts in the hippocampus, and then all rats were trained in the water maze. The single lesions alone produced no deficits, and the three groups (control, 5,7-DHT lesion, 5,7-DHT lesion+raphe graft) did not differ in acquisition. However, the animals were then given atropine injections prior to the daily trials, which disrupted performance in the lesion group, but against which additional raphe grafts provided protection.

Along similar lines Nilsson *et al.* (1988b) have employed a more systematic analysis of components of the classic fimbria-fornix transection by employing more selective lesions of distinct sets of afferents. Septohippocampal cholinergic neurons were lesioned by electrolytic lesions of the septum and the forebrain serotonergic system was depleted with 5,7-DHT. The two lesions had opposite effects on locomotor activity: the septal rats manifested the classical symptoms of hyperactivity whereas the 5,7-DHT rats were hypoactive. Of more interest to the present discussion is the fact that rats with the two lesions had far more profound deficits in the Morris water maze task than did rats with either lesion alone. Although in the absence of any pharmacological treatment the 5,7-DHT lesions deplete noradrenaline as well as serotonin, this did not appear to contribute to the animals deficits because an identical pattern of performance was seen in rats which had been pretreated with the uptake blocker desmethylimipramine to protect the noradrenergic system from 5,7-DHT toxicity (Nilsson *et al.*, 1988b). In an attempt to confirm the relevance of combined cholinergic and serotonergic denervation to the water maze deficits, Nilsson *et al.* (1990) have gone on to compare the efficacy of cholinergic (septal), serotonergic (raphe) or combined grafts in rats with combined septal/5,7-DHT lesions. Although few effects were seen 4 months after transplantation, by 10 months the rats with combined grafts showed substantial improvement in the water maze task, and were not distinguishable from unlesioned controls on several measures. By contrast, no improvement over lesion baseline was seen in the rats with either septal or raphe grafts alone.

These three sets of studies agree in the observation that combined serotonergic and cholinergic lesions or receptor blockade are necessary to produce profound deficits on spatial navigation tasks. However, they are not entirely consistent: the Nilsson *et al.* (1990) study suggests that combined septal and raphe grafts are necessary to reverse the deficits of the combined lesion, whereas the data of Richter-Levin and Segal (1989) suggest that the serotonergic reinnervation alone is sufficient. However, these studies differ in a number of important procedural respects. In particular, the Richter-Levin study employed pharmacological means to block cholinergic receptors acutely. Consequently, the animals were tested for performance of a task that had previously been learned in the presence of an intact cholinergic system. By contrast, in the Nilsson *et al.* (1990) study, the animals had a permanent cholinergic as well as serotonergic denervation, and the grafted animals were tested in the more demanding context of task acquisition.

### 3.4 Cholinergic grafts in the neocortex

In addition to the long-standing interest in the role of septo-hippocampal systems in memory processes, the cholinergic hypothesis stimulated interest in the possibility that parallel cholinergic projections from basal forebrain to neocortex may be implicated to an equal extent in the mnemonic deficits associated with ageing and dementia. This hypothesis was based on the observations that (a) there is a decline in neurochemical cholinergic markers in patients with dementia (Bowen *et al.*, 1976; Davies and Maloney, 1976; Perry *et al.*, 1977), (b) that these cortical neurochemical deficits are associated with loss or atrophy of cholinergic neurons in the nucleus basalis of Meynert in the basal forebrain in Alzheimer's disease (Whitehouse *et al.*, 1982), (c) that the cholinergic decline correlates with the degree of dementia as assessed in clinical cognitive tests (Perry *et al.*, 1978), and (d) that many of the cognitive features of dementia can be mimicked by muscarinic antagonists (e.g.

scopolamine) in young human subjects (Drachman and Leavitt, 1974; Drachman and Sahakian, 1980).

The explicit formulation of the cholinergic hypothesis (Bartus *et al.*, 1982; Coyle *et al.*, 1983) stimulated numerous studies directed at development of an animal model of dementia based on making experimental lesions in the basal forebrain of young animals using a variety of procedures (electrolytic or radiofrequency lesions, amino acid neurotoxins, the aziridinium ion AF64A, or hemicholinium) with varying degrees of specificity. It is now clearly established that such lesions can induce deficits on a range of avoidance, maze learning and operant tasks (for reviews see: Dunnett and Barth, 1990; Fisher and Hanin, 1986; Price, 1986; Olton and Wenk, 1987; Smith, 1988). Less clear are the issues of (a) whether the deficits are mnemonic, as opposed to disruption of other cognitive (e.g. attention) or noncognitive (e.g. sensory or motor reactivity) functions (Dunnett *et al.*, 1989; Everitt *et al.*, 1987), and (b) whether the deficits are indeed due to disruption of cholinergic neurons of the nucleus basalis magnocellularis in the basal forebrain, as opposed to nonspecific damage of other noncholinergic neurons in the vicinity (Dunnett *et al.*, 1987b; Etherington *et al.*, 1987; Everitt *et al.*, 1987; Robbins *et al.*, 1989a,b; Wenk *et al.*, 1989). The first issue requires the development of more sensitive and selective tests for specific aspects of learning and memory than have generally been used. A variety of strategies have been used to address the latter issue, including testing whether cholinergic replacement, by pharmacological or neural graft procedures, can reverse deficits associated with basal forebrain lesions. Recovery of a particular set of deficits following transplantation of cholinergic (but not noncholinergic control) grafts into the neocortex (but not into other subcortical sites), would strongly support the conclusion that those deficits were attributable to disruption of nucleus basalis projections to the cortex, as opposed to damage of other noncholinergic circuitries in the basal forebrain. Thus, the majority of studies of neural grafts of cholinergic-rich tissues in rats with basal forebrain lesions have been concerned as much with assessing the validity of the lesion model as with the issue of the viability of grafts as a therapeutic strategy for dementia.

The first studies of transplantation in animals with kainic acid or ibotenic acid lesions of the basal forebrain demonstrated that basal forebrain grafts implanted in multiple cortical sites could yield substantial amelioration of deficits on simple active and passive avoidance learning tests (Arendash and Mouton, 1987; Arendash *et al.*, 1985; Dunnett *et al.*, 1985b; Fine *et al.*, 1985a; Sinden *et al.*, 1990). However, these lesions induce a range of regulatory, neurological and sensorimotor deficits in addition to the deficits in passive avoidance and water maze learning (Whishaw *et al.*, 1985). Several of these noncognitive deficits, such as contralateral sensory neglect, were also reversed by cortical septal grafts, whereas the grafted animals remained as impaired as the rats with lesions alone on some of the learning deficits, such as in acquisition of the Morris water maze (Dunnett *et al.*, 1985b). Similarly, Sinden *et al.* (1990) have recently demonstrated that neither cholinergic-rich septal grafts nor cholinergic-poor hippocampal grafts implanted in the neocortex of rats with ibotenic acid lesions of the nucleus basalis have any detectable benefit on the animals' deficits in operant win-stay/lose-shift and win-shift/lose-stay tasks, even though the grafts reverse the passive avoidance deficits in the same animals. These authors were unable to distinguish between the alternative interpretations either that graft-derived recovery is task-specific or that the animals' deficits on the operant tasks are attributable to additional noncholinergic damage induced by the lesions, although other results (see below) lead us to favour the latter conclusion.

In the light of these complications, subsequent studies have attempted to refine the specificity of (a) the grafts, (b) the lesions, and (c) the behavioural assessment paradigms. The development of more selective behavioural paradigms, such as the use of operant delayed response tasks for the assessment of specifically mnemonic aspects of performance, has been reviewed elsewhere (Dunnett, 1987, 1989). Such tasks have been employed to assess the effects of grafts on the memory capacity of aged rats (Dunnett *et al.*, 1988b; see section 2.4), but have as yet received only limited application in the context of grafts in rats with basal forebrain lesions (but see Sinden *et al.*, 1990, above). Consequently, the present review considers only the first two areas of refinement.

*Improving graft specificity*

In the hippocampus, it has been found that cholinergic neurons of the septum give rise to a more extensive and precise laminar reinnervation of AChE positive fibres than do grafts containing other (striatal, brain stem, spinal) populations of cholinergic neurons (Gibbs *et al.*, 1986; Lewis and Cotman, 1983; Nilsson *et al.*, 1988a). The initial studies of cortical grafts employed a standard dissection of embryonic ventral forebrain which contains precursors predominantly of the septum and diagonal band subpopulations of cholinergic neurons (as well as the associated populations of noncholinergic neurons), rather than of the nucleus basalis *per se*. We therefore employed a differential ventral forebrain dissection in order to compare the viability of septal and nucleus basalis grafts into the neocortex and hippocampus (Dunnett *et al.*, 1986). Whereas independent source and target factors influenced the survival and growth of the alternative tissues (i.e. nucleus basalis tissues tended to grow larger than septal tissues in either target site, and grafts of either type tended to grow larger in the hippocampus than in the neocortex), the extent of acetylcholinesterase-positive fibre outgrowth depended on the appropriateness of the graft to the target. Thus, cholinergic neurons derived from the nucleus basalis gave rise to a more extensive reinnervation of the neocortex than of the hippocampus, whereas cholinergic neurons of the septum gave rise to a more extensive reinnervation of the hippocampus than of the neocortex.

Thus, there exists a considerable degree of tissue specificity in regulating the pattern and extent of connections of neuronal grafts, even when considering cells employing the same neurotransmitter (acetylcholine in this case) and derived from the same general extended basal forebrain nuclei. Additionally, whereas the interest is usually in particular transmitter-specific populations of cells, virtually all graft studies employ relatively crude embryonic dissections, containing multiple cell populations. Consequently, although the demonstration that acetylcholine-rich grafts ameliorate deficits on a particular task, it is extremely difficult to conclude that this particular population of neurons subserves the observed functional effects. For example, Fine *et al.* (1985b) demonstrated immunocytochemically that ventral forebrain grafts contain a variety of peptidergic (neuropeptide Y, enkephalin, somatostatin) as well as cholinergic neurons. Of these, neuropeptide Y immunoreactive cells also appeared to establish fibre connections into the host neocortex. Although a variety of cell sorting techniques are being developed in order to provide the means to select identified populations of neurons for transplantation (Lindsay *et al.*, 1987; Lopez-Lozano *et al.*, 1987; Notter *et al.*, 1988), these have not yet reached the stage of widespread application to resolve the issue of neuronal specificity within basal forebrain (or indeed any other) graft tissues.

*Improving lesion specificity*

The most widely used toxins to study the effects of basal forebrain lesions have been the excitotoxins, kainic acid and ibotenic acid. Whereas these

are effective in destroying cholinergic neurons of the nucleus basalis it has become apparent that they induce extensive damage of other non-cholinergic neurons in the vicinity of the injections, and that many of the animals deficits may be attributable to this noncholinergic damage (Abrogast and Kozlowski, 1988; Dunnett *et al.*, 1987b). Nonspecific interpretations of the lesion deficits have been brought into sharp focus by the demonstration that the excitotoxin quisqualic acid is as efficient in inducing extensive lesions of cortical cholinergic projections whereas the lesioned animals may have much reduced impairments on a variety of maze learning tasks as well as in general neurological tests (Dunnett *et al.*, 1987b; Etherington *et al.*, 1987; Robbins *et al.*, 1989a,b; Wenk *et al.*, 1989). This suggests that the profound deficits observed following ibotenic acid lesions cannot be attributable to the cholinergic disruption *per se*.

Nevertheless, rats with quisqualate lesions do manifest a range of cognitive impairments, particularly in aspects of discrimination learning or attention rather than in specifically mnemonic aspects of task performance (Everitt *et al.*, 1987; Evenden *et al.*, 1989; Dunnett *et al.*, 1989; Robbins *et al.*, 1989a,b), and several of these deficits are ameliorated by cholinergic grafts in the neocortex. For example, Welner *et al.* (1988) have found that quisqualic acid lesions of the nucleus basalis will disrupt performance on a paired-trial delayed alternation task in a T-maze, and this deficit is ameliorated by septal grafts in the neocortex. Greater functional specificity is provided in a second study by Muir *et al.* (1989) employing a five-choice attentional task. Whereas ibotenic acid lesions induce a greater disruption of choice accuracy in this task, the quisqualic acid lesions have a particularly disruptive effect on latency measures of correct responding (Robbins *et al.*, 1989b). Correspondingly, choline-rich septal grafts implanted in the neocortex were found to ameliorate deficits in correct response latencies, but not in choice accuracy measures of performance of rats with quisqualic acid lesions of the nucleus basalis (Muir *et al.*, 1989). Thus, whereas the techniques are not available for making lesions that are selective for cortical cholinergic projections, the judicious combination of alternative toxins and basal forebrain grafts indicate a role for this projection not only in specific attentional aspects of discrimination learning (Everitt *et al.*, 1987; Muir *et al.*, 1989), but also in aspects of sensorimotor performance which may be attentional in nature (Dunnett *et al.*, 1985b, 1987b). In this light, consistent deficits in tasks such as passive avoidance learning after basal forebrain lesions, and recovery after transplantation, do not reflect specific mnemonic impairments. Rather, basal forebrain cholinergic systems project to the whole neocortical mantle in a relatively diffuse manner, and lesions of this projection are likely to disrupt the integrity of many different aspects of cortical function in the sensory and motor as well as associational realms (Richardson and DeLong, 1988). Indeed, quisqualate as well as ibotenate lesions are found to induce marked regulatory and sensorimotor deficits on more detailed neurological evaluation (Dunnett *et al.*, 1987b; Whishaw *et al.*, 1985).

### 3.5 Cholinergic grafts in cortex and hippocampus combined

A number of studies indicate that combined lesions of the cholinergic neurons in the medial septum and the nucleus basalis could provide greater deficits in spatial maze learning studies than lesions of either area alone. In some tasks, the results have indicated a dissociation of functions associated with such lesions (Hagan *et al.*, 1988; Kesner, 1988; Kesner *et al.*, 1986; Knowlton *et al.*, 1985; Meck *et al.*, 1987; Miyamoto *et al.*, 1987), whereas in other studies the two lesions have been seen to produce similar deficits and an additive effect when combined (Arendt *et al.*, 1989; Hepler *et al.*, 1985a,b).

In the study by Arendt *et al.* (1989), the animals were tested on both spatial ('place') and non-spatial ('cue') variants of a radial maze task that additionally enabled separation of working and reference memory components of performance. As mentioned above, they found that either medial septum/diagonal band or nucleus basalis lesions had approximately comparable disruptive effects on each component of performance, and that the deficit induced by combined lesions was more profound than either individual lesion alone. In a particularly elegant study, Hodges *et al.* (1990) employed this same task to evaluate the effects of cholinergic-rich grafts on the deficits manifested by rats with the combined lesion. As in their previous study, the combined lesion disrupted both reference and working memory in both the place and cue variants of the task, and the deficit was lasting and stable over at least 12 months. Two groups of rats received control implants of (cholinergic-poor) hippocampal grafts into the cortex and hippocampus or of (cholinergic-rich) septal transplants into the basal forebrain. In neither case did these animals differ in any measure from the rats with lesions alone. By contrast, cholinergic-rich septal grafts implanted in denervated target sites provided a significant amelioration of all deficits. Thus, the rats with septal grafts showed a progressive reduction of working memory errors so that by 8 weeks after transplantation they did not differ significantly from sham-operated controls. A similar pattern of recovery was observed when the septal grafts were implanted into the hippocampus, into the neocortex, or into both sites combined. The same grafts also provided a significant reduction in reference memory errors. However, on this measure, the improvement was less dramatic, and in no case did the septal graft rats achieve the level of performance observed in the controls. Nevertheless, the partial recovery in reference memory performance was similar in both extent and time course between the two groups with hippocampal or cortical graft placements, and the combined grafts provided somewhat greater benefit than either placement alone.

Arendt and colleagues (1988b, 1989) have further examined the effects of septal grafts on this radial maze task, using alcohol intoxication as an alternative procedure to deplete forebrain cholinergic systems. Prolonged administration (28 weeks) of alcohol via the drinking water has been found to induce a profound depletion of levels of acetylcholine, choline uptake, acetylcholinesterase and choline acetyltransferase activity, although noradrenaline and serotonin were also depleted (Arendt *et al.*, 1988a, 1989). Such animals manifest pronounced working and reference memory deficits in both the cue and place variants of the radial maze task, similar to the deficits observed after combined septal/diagonal band and nucleus basalis lesions (Arendt *et al.*, 1989). Implants of cholinergic-rich septal grafts into either the neocortex or the hippocampus produced moderate recovery of the alcohol-induced impairment (Arendt *et al.*, 1988b, 1989). As in the Hodges *et al.* (1990) study, the two alternative graft placements each produced a similar generalized improvement on all task measures, and the effects were additive when the two placements were combined. Although the alcohol treatment reduced forebrain levels of noradrenaline and serotonin as well as acetylcholine, the observation of similar behavioural deficits after ibotenic acid lesions of the septum and nucleus basalis (which had no effect on levels of noradrenaline, serotonin or dopamine) and the reversal of deficits by cholinergic-rich grafts together supported the view that the functional deficits induced by alcohol had a cholinergic substrate.

The similar effects of differential or combined lesions in the septum and/or nucleus basalis, and of differential or combined graft placements in the cortex and hippocampus have led Arendt, Hodges and colleagues to the natural conclusion that the basal forebrain cholinergic system functions as a whole in the regulation of different types of memory (Arendt *et al.*, 1989; Hodges *et al.*, 1990). However, the similar effects of both

lesions and grafts on both the working memory and reference memory components of both the spatial and non-spatial variants of the task also suggested that the forebrain cholinergic system subserves a more generalized function that is common to all behavioural measures (such as some attentional process) than the regulation of specific aspects of memory *per se*.

## 4. Cortical and hippocampal replacement by grafts

Notwithstanding the functional successes that have been achieved with grafting discrete populations of neurons, selected on the basis of neurotransmitter characteristics, to neo- and allo-cortical sites of host animals with sub-cortical 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 or of multiple small focal lesions in multi-infarct dementia are associated with neuronal cell loss in the neocortex, and associated enlargement of the ventricular spaces and cortical sulci (Terry *et al.*, 1981; Tomlinson *et al.*, 1968, 1970). Although they have not generally been concerned with models of dementia, a separate line of transplantation research has been concerned with the issue of whether cortical cell loss can be functionally replaced by neuronal transplants.

### *4.1 Cortical grafts*

Cortical grafts have been found to be able to reform extensive, and occasionally remarkably specific, connections with the host brain. This is particularly the case for cortical tissues implanted into the cortices of neonatal hosts. Thus, afferent and efferent connections with the basal forebrain, thalamus and even with the spinal cord have been observed following implants into the neocortex of neonatal rats (Castro *et al.*, 1987, 1988; Chang *et al.*, 1984, 1986; Stanfield and O'Leary, 1985). Such studies have been particularly valuable in demonstrating the topographic determinants of the formation of inputs and outputs of the major sensorimotor areas of neocortex in development (McConnell, 1989; O'Leary, 1989; Stanfield and O'Leary, 1985). In the adult host brain, the potential for afferent connections to become established in embryonic neocortical grafts from the contralateral host neocortex and from subcortical thalamic, basal forebrain and brainstem nuclei has been well established (Dunnett *et al.*, 1987a; Gibbs and Cotman, 1987; Gibbs *et al.*, 1985; Höhmann and Ebner, 1988; Labbe *et al.*, 1983; Sofroniew *et al.*, 1986; Stein and Mufson, 1987). Formation of long-distance efferent connections from cortical grafts have been less clearly demonstrated, but sparse projections to the hippocampus, amygdala and thalamus have been reported (Dunnett *et al.*, 1987a; Escobar *et al.*, 1989; Gibbs *et al.*, 1985; Gonzalez *et al.*, 1988).

Electrophysiological techniques have provided the clearest demonstration of functional incorporation of cortical tissue grafts in the adult host brain. Thus, Bragin (Bragin, 1986; Bragin *et al.*, 1987, 1990) have recorded from isotopic cortical grafts implanted in the barrel-field zone of somatosensory cortex of adult rats, and found that cells in the grafts responded to peripheral nerve or vibrissae stimulation. Although the receptive fields of grafted cells were somewhat larger than observed in intact barrel-field neurons, the bursting pattern of cellular responses was essentially typical of normal somatosensory neocortex. The functional re-establishment of barrel-field inputs in cortical grafts has been confirmed using 2-deoxyglucose autoradiography to map changes in metabolic activity in response to peripheral stimulation (Levin *et al.*, 1987). The specificity of the responses in each set of studies was demonstrated by a failure to observe any similar changes in electrophysiological or metabolic activity in noncortical grafts implanted within the barrel-field, or in cortical grafts implanted outside the somatosensory neocortex.

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 first showed that rats' abilities to learn a delayed alternation task in a T-maze, which are disrupted by aspirative lesions of the prefrontal cortex, could be substantially restored 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 (Dunnett *et al.*, 1987a; Kesslak *et al.*, 1986a), and similar effects have since been reported on the recovery of a variety of other tasks following transplantation of embryonic cortical tissues. These include recovery of spatial navigation learning in the Morris water maze following prefrontal lesions (Kolb *et al.*, 1988; but see Dunnett *et al.*, 1987a), of visual brightness and pattern discrimination following occipital cortex lesions (Haun *et al.*, 1985; Stein *et al.*, 1985), of taste aversion learning following gustatory neocortex lesions (Bermudez-Rattoni *et al.*, 1987; Escobar *et al.*, 1989), and of spatial maze learning following allo-cortical (hippocampal) lesions (Kimble *et al.*, 1986).

### *4.2 Trophic mechanisms of recovery*

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 influence recovery by means of a functional reconstruction of damaged cortical neural circuitries. However, this conclusion is premature. As mentioned in section 1, a variety of mechanisms have been proposed by which grafted tissues can influence the behavioural capacities of the host animal (Björklund *et al.*, 1987). These include: nonspecific or negative consequences of the implantation surgery, trophic actions on the host brain, diffuse release of hormones on transmitters and reformation of afferent and or efferent connections between the graft and the host brain.

*Non-specific or negative consequences of the implantation surgery*
These may include graft growth inducing space occupying lesions, influencing the development of cyst and scar formation or changes in the blood-brain barrier, or induction of further degenerative changes in the host brain.

*Trophic actions on the host brain*
The acute secretion of trophic factors and migration of glial cells into the host brain may reduce lesion-induced cell death or promote functional reorganization and recovery within the host brain, independently of any sustained effect of the grafted neurons.

*Diffuse release of hormones or transmitters*
The grafted cells may provide a chronic secretion of deficient neuroactive chemicals such as hormones or neurotransmitters to the host brain.

*Reformation of afferent and/or efferent connections between the graft and the host brain*
Only in this case do the formation and activity of neuronal connections between the graft and host brain subserve functional changes observable in the behaviour of the host animal. This category of mechanism can

be further subdivided between situations where the grafts provide a relatively unregulated tonic reinnervation of the host brain, and situations where reformation of reciprocal graft-host connections result in the graft tissue coming under dynamic regulation of host neural activity. In the best cases, this latter situation might ultimately result in full incorporation of the graft into (and thence reconstruction of) the host neural circuitry.

Evidence for each of these mechanisms of action has been observed in different model systems for neural transplantation (Björklund *et al.*, 1987; Dunnett and Björklund, 1987), and consequently must be considered in the case of the effects on more complex behaviours of animals with grafts in the neocortex.

One suggestive feature in these various studies of the functional effects of cortical grafts is that the timing of transplantation and behavioural testing have turned out to be critical. Firstly, recovery is only observed when the graft surgery is conducted within 7−14 days of the lesions, and not with either shorter or longer intervals (Dunnett *et al.*, 1987a; Kesslak *et al.*, 1986a; Stein *et al.*, 1988). Secondly, the grafts are only effective in studies where behavioural testing commences within a few days of transplantation surgery, before sufficient time has elapsed for the growth of any graft-host connections, and not when behavioural testing is delayed by 4 weeks or more (Dunnett *et al.*, 1987a; Kolb *et al.*, 1988; Stein *et al.*, 1985). Indeed, Dunnett *et al.* (1987a) demonstrated one group of animals, transplanted 7 days following frontal cortex lesion, which were significantly impaired in T-maze alternation learning with respect to rats with lesions alone when tested after a 6 month interval, even though these same animals had shown an initial improvement when tested 1 week after surgery. Similarly, Kolb *et al.* (1988) trained rats in the Morris water maze commencing either immediately (early-test groups) or 4 weeks after transplantation surgery (late-test groups). Whereas in the early-test the transplanted rats showed a significant improvement over their lesions control group, in the late-test the transplanted rats were significantly impaired with respect to the recovery that had taken place in the parallel lesion group. Thus, the benefit provided by the transplants is only apparent when assessed immediately after surgery, and at later times the grafts may actually add to the host animals' impairments. It has not been resolved whether the long-term impairments are due to inhibition of long-term recovery in the host brain, to the grafts developing space-occupying lesions, or to graft-derived inputs adding noise to processing in the remaining intact host cortex.

These observations suggest that although the cortical graft tissue may come to form connections with the host brain this process does not underlie the functional recovery that is often observed. Rather, in view of the rapid sequence of the behavioural changes, it has been sugested that cortical grafts stimulate or secrete neurotrophic substances that promote functional recovery in the host brain (Kesslak *et al.*, 1986b; Dunnett *et al.*, 1987a; Stein, 1987; Stein *et al.*, 1985, 1988). Thus, Kesslak *et al.* (1986a,b) demonstrated that implants of purified cultured astrocytes or of adult tissue grafts predominantly comprised of glia were as effective as transplants of embryonic cortex in reducing deficits in delayed alternation learning. Moreover, it has been argued that if some trophic mechanism is promoting host recovery, then subsequent removal of the grafts should have no deleterious effect once recovery has taken place (LeVere and LeVere, 1985). This has been tested in a study by Stein (1987), in which he demonstrated that graft removal just prior to training in the Morris water maze task did not abolish the recovery from the deficits induced by prefrontal lesions in rats with cortical grafts.

A similar conclusion has been reached in studies of allo-cortical grafts. Thus, aspirative lesions of the hippocampus induce deficits in spatial mazes (Kimble *et al.*, 1986) and in the temporal control of responding on operant differential reinforcement of low rate schedules (Woodruff *et al.*, 1987), and can be reversed by hippocampal tissue grafts implanted into the hippocampus. In these studies, the extensive reformation of graft-host connections was never convincingly established, and Woodruff and colleagues have recently demonstrated that the improved performance of grafted rats remained even when the grafts were removed (Woodruff *et al.*, 1990).

In conclusion, the limited number of studies that have so far investigated the functional capacity of cortical grafts on the performance of cognitive tasks indicate that the grafts can ameliorate some deficits induced by aspirative cortical lesions. However, it is likely that the acute benefit provided by the grafts is not due to any specific replacement of damaged neuronal circuitry, but rather to some trophic interactions with the dynamic development of the primary lesion. Therefore, at least based on our present level of understanding, these studies do not offer any substantial prospect for transplantation strategies in the general repair of nonspecific damage in cortical circuitries, whether sustained by trauma or neurodegenerative disease.

## 5. Grafts to deliver growth factors

Although not encouraging for the prospect of general surgical repair of the damaged brain, the identification of acute trophic mechanisms of action of cortical grafts does suggest a more restricted manner in which neural transplantation might inhibit the progress of degenerative changes in neurodegenerative disease, including dementia. Neurons are dependent on their targets for trophic support. Consequently it may be feasible to employ transplantation strategies to promote trophic support, either by providing new targets to support central axons, or by the direct supply of identified trophic factors themselves.

### *5.1 Trophic inhibition of retrograde degeneration*

The potential for grafts to provide trophic support for intrinsic neurons which have lost their normal targets was first studied developmentally in the thalamus. Neonatal lesions of frontal or occipital cortex result in developmental atrophy of the corresponding afferent nuclei of the thalamus. Haun and Cunningham (1984, 1987) found that transplantation of embryonic neocortex (but not control grafts of cerebellar tisue) into the cavity formed by a neonatal occipital lesion, attenuated lesion-induced atrophy in the corresponding dorsal lateral geniculate nucleus of the host. In these studies, using cell suspension grafts of the cortical cells, the protection was only temporary. However, Sharp and Gonzalez (1986) have achieved permanent prevention of retrograde thalamic atrophy using cortical implants into neonatal frontal cortical lesions. These observations suggested that the trophic interactions which are necessary for survival of developing neurons, and which are lost by removal of appropriate targets, can be re-established by transplant-derived replacement of those targets. In particular, it may be necessary for developing host thalamic neurons to innervate the grafts to achieve such protection, although it cannot at present be excluded that the influence is entirely attributable to diffusable neurotrophic factors. Nor is it known if degenerative changes would be re-initiated if the graft were removed.

However, these observations relate primarily to a developmental context rather than protection against retrograde degeneration following axotomy or target removal in adulthood. This issue has been investigated in the magnocellular cholinergic cells of the nucleus basalis which become atrophied in response to extensive loss of cortical targets, whether made

by mechanical devascularization or excitotoxic lesion (Sofroniew *et al.*, 1983; Sofroniew and Pearson, 1985). Cortical cell suspensions implanted in the damaged cortex have the capacity to prevent retrograde atrophy of the cholinergic neurons of the host nucleus basalis system, which sprouted to extensively reinnervate the cortical tissue grafts (Sofroniew *et al.*, 1986). These observations support the notion that target-derived trophic factors are necessary for the maintenance of neural connections in the mature central nervous system as well as for their normal development, and can be substituted by neural tissue grafts.

### *5.2 Nerve growth factor and central cholinergic systems*

A variety of lines of evidence have indicated that nerve growth factor (NGF) exerts a trophic role on central cholinergic neurons (Hefti and Will, 1987). In particular, NGF promotes the survival and growth of septal and basal forebrain cholinergic neurons *in vitro* (Gähwiler *et al.*, 1987; Hartikka and Hefti, 1988; Hatanaka *et al.*, 1988) and following transplantation (Eriksdotter-Nilsson *et al.*, 1989c; Springer *et al.*, 1988; Toniolo *et al.*, 1985), and intraventricular injections of NGF promote the survival of septal cholinergic neurons following axotomy (Gage *et al.*, 1988; Hefti, 1986; Kromer, 1987; Montero and Hefti, 1988; Williams *et al.*, 1986). In parallel, treatment with NGF has been seen to reduce behavioural deficits associated with basal forebrain or fimbria-fornix lesions (Haroutunian *et al.*, 1986; Will and Hefti, 1985).

Because these same populations of neurons decline in Alzheimer's disease, Hefti (Hefti, 1983; Hefti and Weiner, 1986) suggested that the loss of cholinergic neurons in the disease may reflect an insufficient availability of NGF to these cells. Although there have been difficulties in demonstrating reduced levels of NGF expression in the post-mortem Alzheimer brain (Goedert *et al.*, 1986), Fischer *et al.* (1987) have found that chronic NGF administration can ameliorate both the atrophy of septal cholinergic neurons and the impairments in retention of spatial navigation learning between blocks of test sessions in aged rats. This suggests that NGF replacement might provide a potential therapeutic strategy for Alzheimer's disease. Nevertheless, there are considerable practical problems in such an approach, because NGF must be administered intracerebrally and chronically to be effective (Montero and Hefti, 1988). This raises the issue of whether cell transplants might provide a more effective system for NGF delivery than is provided by chronic intracerebral infusions.

The viability of grafts to deliver NGF has already been investigated in a different context. The observation that NGF promotes survival of adrenal chromaffin cells (Strömberg *et al.*, 1985) has led to the successful co-transplantation of seural nerve as a source of NGF (Hansen *et al.*, 1990; Watts *et al.*, 1990). In fact, adrenal medulla itself has been proposed to have substantial trophic influence on dopaminergic fibre systems of the host brain (Bohn *et al.*, 1987). An even richer source of NGF is the mouse submaxillary gland, although a preliminary study of co-transplantation of this tissue with adrenal medulla provided little evidence for any promotion of differentiation of chromaffin cells (Freed *et al.*, 1985a). Nevertheless, a subsequent study has indicated that intraventricular implantation of the mouse submaxillary gland can substantially increase survival of axotomized cholinergic neurons 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 (Gage *et al.*, 1987). Considerable preliminary success has been achieved in the transfection of fibroblasts with the NGF gene. These engineered cells have been demonstrated to be capable of secreting NGF (Ernfors *et al.*, 1989; Gage *et al.*, 1990), and to have biological activity in the rescue of axotomized septal cholinergic neurons (Rosenberg *et al.*, 1988; Gage *et al.*, 1990) and the promotion of chromaffin cell differentiation *in oculo* (Ernfors *et al.*, 1989; Olson *et al.*, 1990).

Nevertheless, a substantial qualification applies to the relevance of these studies to the neurodegenerative pathology of dementia; it remains likely that the primary pathology in the human disease is cortical rather than in the neurotransmitter-specific subcortical systems for which trophic factor delivery has been found to be effective.

## 6. Alzheimer-type pathology in neural grafts

There are at present no established models of the pathogenesis of Alzheimer's disease. As a consequence, there remain substantial limitations on the development not only of neural transplantation strategies, but of novel therapies of all kinds. Several recent developments in neural transplantation, however, suggest that grafts themselves might provide new, and potentially more valid, models of the disease process itself.

### *6.1 Pathological features in ageing grafts*

One approach has been to employ neural transplantation strategies to investigate cellular ageing processes independently of the age of the global host environment. For example, in the *in oculo* studies described above (section 2.2), Olson, Eriksdotter-Nilsson and colleagues have not only compared embryonic cerebellar, cortical and hippocampal tissues in the anterior eye chambers of young and aged hosts after 3 months survival, but also followed up some of their grafts over 21 months survival *in oculo*. In one series of studies, factors involved in cellular ageing of noradrenaline projections to the cerebellum have been investigated. Cerebellar neurons in the aged brain are hyposensitive to locally applied noradrenaline, and the modulatory role of noradrenaline on their responses to olivary stimulation is much reduced. Bickford-Wimer *et al.* (1988) examined the extent to which similar changes were observed in cerebellar grafts *in oculo*. Young and aged grafts each established an extensive noradrenergic innervation from the host iris. However, whereas young cerebellar grafts showed consistent responsiveness to applied noradrenaline (whether implanted in young or old hosts), responsiveness declines dramatically in old grafts in old hosts of a similar age. These observations suggest that the age-related decline in cerebellar noradrenergic systems is intrinsic to the postsynaptic neurons of the cerebellum rather than to a decline in the functional integrity of afferent noradrenergic axons *per se*.

In other studies, hippocampal or cerebellar grafts have been followed for 22–23 months *in oculo*, and marked differences observed in neuronal organization, noradrenergic innervation, and sensitivity to applied noradrenaline (Eriksdotter-Nilsson *et al.*, 1989a,b; Granholm *et al.*, 1987). In addition to an increased gliosis, the old grafts manifested a marked accumulation of autofluorescent lipofuscin granules (Eriksdotter-Nilsson *et al.*, 1989a,b), which is a characteristic feature of the normal ageing process in the brain (Brizzee and Ordy, 1979; Brizzee *et al.*, 1974).

Other studies have focused on morphological changes in the neurons or glia of ageing grafts. One intriguing observation has been the demonstration of Hirano bodies and immunoreactivity with antibody RT97 in CNS grafts isolated for long periods (over 6 months) in a peripheral transplantation site (Doering and Aguayo, 1987). The RT97

antibody recognizes the 200 kD subunit of neurofilaments which are characteristic of tangle bearing cortical and hippocampal neurons in Alzheimer's disease (Anderton *et al.*, 1982; Cork *et al.*, 1986). Similarly, an increased incidence of Hirano bodies have been observed in the Alzheimer cortex (Gibson and Tomlinson, 1977; Terry and Katzman, 1983; Tomonaga, 1974). However, other markers of senile plaques or neurofibrillary tangles, such as staining with Congo red, thioflavin-S or antibodies against paired helical filaments were not observed in these grafts (Doering and Aguayo, 1987). Nevertheless, these observations provided a clear demonstration of the accumulation of particular features of the human neuropathology in isolated grafts, and offered a model system in which their development could be studied experimentally.

### *6.2 Transplantation of pathogenic tissues*

An alternative strategy has been to consider implantation of pathological tissues in order to monitor pathogenic processes in the grafts or host brain. In one such study, van den Bosch de Aguilar *et al.* (1984) transplanted fragments of temporal cortex from a postmortem Alzheimer brain to the cortex of 7-week-old rats. Although neuronal elements did not survive, the grafts were seen to contain abundant neurofibrillary tangles and induced an extensive fibrous gliosis in the host brain. Filament bundles in host brain astrocytes were seen to contain twisted filaments which were considered to be structurally similar to Alzheimer's paired helical filaments, and were interpreted as suggesting either the incorporation of abnormal structural subunits into host cytoskeleton or the presence of some transmissable pathogenic agent within the diseased brain. However, neurons did not survive within the grafts. Therefore although this study is based on a transplantation strategy, it is conceptually similar to other studies of inoculation with pathogens or pathogenic tissues, such as have been used for the identification of neurodegenerative processes associated with toxins or slow virus transmission (Bruce and Dickinson, 1982; Bruce and Fraser, 1975; De Boni *et al.*, 1976; Gajdusek, 1977; Goudsmit, 1980; Klatzo *et al.*, 1965).

### *6.3 Amyloidosis in trisomy 16 grafts*

At the time of writing this review, a novel approach to the induction of Alzheimer-like pathology in grafts is just being described, based on the established association between Down syndrome and Alzheimer's disease. Down syndrome (trisomy 21) patients manifest the classical amyloid plaques and neurofibrillary tangles characteristic of Alzheimer's disease, but expressed at 30–40 years of age, rather than in old age (Oliver and Holland, 1986; Williams and Matthysse, 1986). This observation suggests that overexpression of genes on chromosome 21 can lead to the neuropathology of Alzheimer's disease, and conversely that Alzheimer's disease may be due to abnormal expression of chromosome 21 genes. In support of this hypothesis, linkage of the chromosome 21 marker D21S13 has been reported in pedigrees with familial Alzheimer's disease (van Broeckhoven *et al.*, 1987). Moreover, the amyloid precursor protein (APP) has recently been mapped to chromosome 21 (Goldgaber *et al.*, 1987; Kang *et al.*, 1987), although the demonstration of cross-overs in linkage studies between the familial disease locus and the APP indicated that the $\beta$A4 protein is not itself the primary lesion (van Broeckhoven *et al.*, 1987).

A variety of markers on human chromosome 21 map to chromosome 16 in mice (Coyle *et al.*, 1986, 1988; Reeves *et al.*, 1987). It is therefore of interest to consider whether trisomy 16 mice might develop any of the neuropathological features of Alzheimer's disease. Previously it has not been possible to directly address this issue, because trisomy 16 fetuses do not survive beyond term. However, neural transplantation of embryonic trisomy 16 tissue into normal host mice has recently been employed to enable the long-term study of developmental processes (Höhmann *et al.*, 1990a,b) and pathogenetic events (Richards *et al.*, 1990,a,b,c) in trisomic tissues.

The studies by Richards *et al.* (1990a,b,c) were directed explicitly towards the issue of whether trisomic tissues would develop particular neuropathological features of Alzheimer's disease. Trisomic hippocampal tissue grafts were found after 4 months' survival to contain neuronal cells that were immunostained by antibodies raised against the amyloid $\beta$A4 protein, the amyloid precursor protein, purified paired helical filaments (PHFs), monoclonal Tau 6.423, and $\alpha_1$-antichymotrypsin (Richards *et al.*, 1990a,b,c). The $\beta$A4 and Tau 6.423 immunoreactivity was exclusively intraneuronal, co-localized in the same cells, and manifested a similar pattern of granular staining to that observed in neurons in Alzheimer brain (Benowitz *et al.*, 1989; C.M.Wischik, personal communication). The APP, PHF and $\alpha_1$-antichymotrypsin immunoreactivity was also seen to be co-localized within neurons, but these antibodies also manifested diffuse extracellular staining in the region of positive neurons.

This pattern of staining within trisomic grafts indicates a high degree of specificity. Of various neurodegenerative dementias associated with senile plaques and neurofibrillary tangle formation, staining with the $\alpha_1$-antichymotrypsin and Tau 6.423 antibodies have been found to be specific to Alzheimer's disease (Abraham *et al.*, 1988; Wischik *et al.*, 1988). No similar immunoreactivity was seen either in control grafts taken from litter-mates or in the trisomic embryos.

In conclusion, grafts of trisomy 16 mouse hippocampus develop neuropathological features that are remarkably similar, at least at the immunohistochemical level, to cardinal neuropathological features of Alzheimer's disease. This graft paradigm therefore provides perhaps the first viable animal model not only for monitoring the development of the cellular pathology involved in the human disease, but also for the development and assessment of therapeutic strategies aimed at inhibiting or reversing the pathogenic process.

## 7. Conclusion: the utility of neural transplantation strategies

The present review has considered the utility of neural transplantation as an experimental strategy directed towards understanding the neuropathological and functional consequences of ageing and dementia. Although it is still a relatively novel technique in the neurosciences, it provides a powerful means of addressing a variety of different issues. Thus, a first theme in neural transplantation studies has been to provide systems for the study of the ageing of neuronal tissues independently from the rest of the body, and the development of new animal models that more closely mimic specific neuropathological features of human Alzheimer's disease. In particular, grafts of embryonic trisomy 16 mouse tissues suggest the first valid model of Alzheimer neuropathology in animals.

A second theme has involved the use of neural transplantation in the study of neuronal plasticity and intrinsic regenerative properties of the nervous system. Whereas, this interest began with using transplants to experimentally manipulate source and target tissues, the identification of alternative mechanisms of graft function have led to the use of transplants to provide more general manipulations of the brain environment, such as the chronic and stable delivery of trophic factors.

Functional analyses have been used to provide noninvasive screening

of the viability of transplants, to evaluate the success of alternative strategies for brain repair, and to provide greater specificity of experimental manipulations. In this latter case, manipulations, such as explicit lesions or the ageing process itself disturb multiple systems in the brain in addition to the system of interest. As a consequence, it has proved difficult to dissociate effects that are due to the target manipulation from consequences of other nonspecific disturbance. The demonstration of recovery after implantation of selected tissues goes a substantial way to support the primary involvement of the systems reconstructed by the transplanted cells. Nevertheless, present techniques using crude embryonic dissections can result in the presence of relatively diverse populations of cells within the grafts. It can be expected that the experimental power of transplantation strategies will continue to develop, in particular as more refined techniques are developed for selecting and manipulating identified populations of cells for transplantation.

A final focus of recent interest has been to consider whether neural transplantation might provide a viable strategy for the clinical treatment of senile dementia, and in particular senile dementia of the Alzheimer's type. The studies reviewed here provide clear evidence of the viability of structural and functional repair of neural degeneration in identified neurotransmitter systems of the brain, such as the cholinergic decline associated both with ageing and with explicit lesions. However, present evidence suggests that these specific neurotransmitter changes in most forms of dementia are secondary to more widespread degenerative events in the forebrain of affected individuals. The conditions have yet to be achieved whereby neural transplants can reconstruct complex neural circuits in the cortex and hippocampus, and the functional effects that are occasionally observed in grafted animals appear to be due to relatively diffuse rather than reconstructive mechanisms of action. Consequently, the prospect of using neural transplantation for the reconstruction of neurodegenerative damage in dementia appears limited in our present state of knowledge. Nevertheless, neural transplantation is providing new, more powerful models of the primary pathogenic processes in dementia, and it is plausible that such studies will lead to new understandings of the degenerative process and novel strategies for the amelioration of dementia.

## Acknowledgements

I thank Anders Björklund and Sarah-Jane Richards for helpful discussion during the preparation of this manuscript. I gratefully acknowledge research funding from the Medical Research Council and the Mental Health Foundation.

## Abbreviations

AChE acetylcholinesterase
AD Alzheimer's disease
APP amyloid precursor protein
CRF corticotrophin releasing factor
CNS central nervous system
DRL differential reinforcement of low rates
GABA gamma-aminobutyric acid
GFAP glial fibrillary acid protein
NGF nerve growth factor
PHF paired helical filament

## References

Abraham, C. R., Selkoe, D. J. and Potter, H. (1988) Immunochemical identification of the serine protease inhibitor $\alpha_1$-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. Cell 52: 487–501.

Abrogast, R. E. and Kozlowski, M. R. (1988) Quantitative morphometric analysis of the neurotoxic effects of the excitotoxin, ibotenic acid, on the basal forebrain. Neurotoxicology 9: 39–46.

Algeri, S., Calderini, G., Toffano, G. and Ponzio, F. (1983) Neurotransmitter alterations in aging rats. In: Samuel, D., Algeri, S., Gershon, S., Grimm, V. E. and Toffano, G. Aging of the Brain pp. 227–243. Raven Press, New York.

Anderton, B. H., Breinburg, D., Downes, M. J., Green, P. J., Tomlinson, B. E., Ulrich, J., Wood, J. N. and Kahn, J. (1982) Monoclonal antibodies show that neurofibrillary tangles and neurofilaments share antigenic determinants. Nature 298: 84–86.

Arendash, G. W. and Mouton, P. R. (1987) Transplantation of nucleus basalis magnocellularis cholinergic neurons into the cholinergic-depleted cerebral cortex: morphological and behavioral effects. Ann. N.Y. Acad. Sci. 495: 431–443.

Arendash, G. W., Strong, P. N. and Mouton, P. R. (1985) Intracerebral transplantation of cholinergic neurons in a new animal model for Alzheimer's disease. In: Hutton, J. T. and Kenny, A. D. Senile Dementia of the Alzheimer Type pp. 351–376. A. R. Liss, New York.

Arendash, G. W., Millard, W. J., Dunn, A. J. and Meyer, E. M. (1987) Long-term neuropathological and neurochemical effects of nucleus basalis lesions in the rat. Science 238, 952–956.

Arendt, T., Henning, D., Gray, J. A. and Marchbanks, R. M. (1988a) Loss of neurons in the rat basal forebrain cholinergic projection system after prolonged intake of ethanol. Brain Res. Bull. 21: 563–570.

Arendt, T., Allen, Y., Sinden, J., Schugens, M. M., Marchbanks, R. M., Lantos, P. L. and Gray, J. A. (1988b) Cholinergic-rich brain transplants reverse alcohol-induced memory deficits. Nature 332: 448–450.

Arendt, T., Allen, Y., Marchbanks, R. M., Schugens, M. M., Sinden, J., Lantos, P. L. and Gray, J. A. (1989) Cholinergic system and memory in the rat: effects of chronic ethanol, embryonic basal forebrain transplants and excitotoxic lesions of cholinergic basal forebrain projection systems. Neuroscience 33: 435–462.

Arnsten, A. F. T. and Goldman-Rakic, P. S. (1985a) Catecholamines and cognitive decline in aged nonhuman primates. Ann. N.Y. Acad. Sci. 444: 218–234.

Arnsten, A. F. T. and Goldman-Rakic, P. S. (1985b) Alpha$_2$-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science 230: 1273–1276.

Arnsten, A. F. T., Cai, J. X. and Goldman-Rakic, P. S. (1988) The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes. J. Neurosci. 8: 4287–4298.

Azmitia, E. C. (1987) A serotonin-hippocampal model indicates adult neurons survive transplantation and aged target may be deficient in a soluble serotonergic growth factor. Ann. N.Y. Acad. Sci. 405: 362–376.

Azmitia, E. C. and Björklund, A. (1987) Cell and Tissue Transplantation into the Adult Brain, Annals of the New York Academy of Science, Vol. 495, New York Academy of Science, New York.

Azmitia, E. C., Perlow, M. J., Brennan, M. J. and Lauder, J. M. (1981) Fetal raphe and hippocampal transplants in adult and aged C57BL/6N mice: an immunohistochemical study. Brain Res. Bull. 7: 703–710.

Barnes, C. A. (1979) Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J. comp. physiol. Psychol. 93: 74–104.

Barnes, C. A., Nadel, L. and Honig, W. K. (1980) Spatial memory deficit in senescent rats. Can. J. Psychol. 34: 29–39.

Bartus, R. T., Dean, R. L., Beer, B. and Lippa, A. S. (1982) The cholinergic hypothesis of geriatric memory dysfunction. Science 217: 408–417.

Bartus, R. T., Flicker, C. and Dean, R. L. (1983) Logical porinciples for the development of animal models of age-related memory impairments. In: Crook, T., Ferris, S. and Bartus, R. T. Assessment in Geriatric Psychopharmacology pp. 263–299. Mark Powley, New Canaan, Conn.

Bartus, R. T., Flicker, C., Dean, R. L., Fisher, S., Pontecorvo, M. and Figueirdo, J. (1986) Behavioral and biochemical effects of nucleus basalis magnocellularis lesions: implications and possible relevance to understanding or treating Alzheimer's disease. Prog. Brain Res. 70: 345–361.

Benowitz, L. I., Rodriguez, W., Paskevich, P., Mufson, E. J., Schenk, D. and Neve, R. L. (1989) The amyloid precursor protein is concentrated in neuronal lysosomes in normal and Alzheimer disease subjects. Exp. Neurol. 106: 237–250.

Bermudez-Ratoni, F., Fernandez, J., Sanchez, M. A., Aguilar-Roblero, R. and Drucker-Colin, R. (1987) Fetal brain transplants induce recuperation of taste aversion learning. Brain Res. 416: 147–152.

Bickford-Wimer, P. C., Granholm, A.-C. and Gerhardt, G. A. (1988) Cerebellar

noradrenergic systems in aging: studies *in situ* and in *in oculo* grafts. Neurobiol. Aging 9: 591–599.

Björklund, A. and Stenevi, U. (1979) Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. Brain Res. 177: 555–560.

Björklund, A. and Stenevi, U. (1984) Intracerebral neural implants: neuronal replacement and reconstruction of damaged circuitries. Ann. Rev. Neurosci. 7: 279–308.

Björklund, A. and Stenevi, U. (1985) Neural Grafting in the Mammalian CNS, Elsevier, Amsterdam.

Björklund, A., Stenevi, U. and Svendgaard, N.-Aa. (1976) Growth of transplanted monoaminergic neurones into the adult hippocampus along the perforant path. Nature 262: 787–790.

Björklund, A., Stenevi, U., Schmidt, R. H., Dunnett, S. B. and Gage, F. H. (1983) Intracerebral grafting of neuronal cell suspensions. I. Introduction and general methods of preparation. Acta Physiol. Scand. suppl. 522: 1–7.

Björklund, A., Lindvall, O., Isacson, O., Brundin, P., Wictorin, K., Strecker, R. E., Clarke, D. J. and Dunnett, S. B. (1987) Mechanisms of action of intracerebral neural implants: studies on nigral and striatal grafts to the lesioned striatum. Trends Neurosci. 10: 509–516.

Bohn, M. C., Cupit, L., Marciano, F. and Gash, D. M. (1987) Adrenal medulla grafts enhance recovery of striatal dopaminergic fibers. Science 237: 913–916.

Bondareff, W., Mountjoy, C. Q. and Roth, M. (1982) Loss of neurons of origin of the adrenergic projection to the cerebral cortex (nucleus locus ceruleus) in senile dementia. Neurology 32: 164–168.

Bowen, D. M., Smith, C. B., White, P. and Davison, A. N. (1976) Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain 99: 459–496.

Bragin, A. (1986) Neuronal response of embryonic rat somatosensory cortex grafted into adult rat barrelfield (in Russian). Neurophysiologia 18: 833–836.

Bragin, A. G., Bohne, A. and Pavlik, V. D. (1987) Electrophysiologiocal indexes of the degree of grafted neural tissue integration with the host brain (in Russian). Neurophysiologia 19: 498–504.

Bragin, A. G., Bohne, A., Kitchigina, V. F. and Vinogradova, O. (1990) Functional integration of neurones in homotopic and heterotopic intracortical grafts with the host brain. Prog. Brain Res. 82: 287–300.

Brito, G. N. O., Davis, B. J., Stopp, L. C. and Stanton, M. E. (1983) Memory and the septo-hippocampal cholinergic system in the rat. Psychopharmacology 81: 315–320.

Brizzee, K. R. and Ordy, J. M. (1979) Age pigments, cell loss and hippocampal function. Mech. Aging Dev. 9: 143–162.

Brizzee, K. R., Ordy, J. M. and Kaack, B. (1974) Early appearance and regional differences in intraneuronal and extraneuronal lipofuscin accumulation with age in a nonhuman primate (*Macaca mulatta*). J. Gerontol. 29: 366–381.

Brown, R. G. and Marsden, C. D. (1988) 'Subcortical dementia': the neurophysiological evidence. Neuroscience 25: 363–387.

Bruce, M. E. and Dickinson, A. G. (1982) Dementias and unconventional slow virus infections. In: Wheatley, D. Psychopharmacology of Old Age pp. 15–23. Oxford University Press, Oxford.

Bruce, M. E. and Fraser, H. (1975) Amyloid plaques in the brains of mice infected with scrapie: morphological variation and staining properties. Neuropathol. Appl. Neurobiol. 1: 189–202.

Brundin, P. and Björklund, A. (1987) Survival, growth and function of dopaminergic neurons grafted to the brain. Prog. Brain Res. 71: 293–308.

Brundin, P., Barbin, G., Strecker, R. E., Isacson, O., Prochiantz, A. and Björklund, A. (1988) Survival and function of dissociated rat dopamine neurones grafted at different developmental stages or after being cultured in vitro. Dev. Brain Res. 39: 233–243.

Campbell, B. A., Krauter, E. E. and Wallace, J. E. (1980) Animal models of aging: sensorimotor and cognitive function in the aged rat. In: Stein, D. The Psychobiology of Aging pp. 201–226. Elsevier North Holland, Amsterdam.

Castro, A. J., Tønder, N., Sunde, N. A. and Zimmer, J. (1987) Fetal cortical transplants in the cerebral hemisphere of newborn rats: a retrograde fluorescent analysis of connections. Exp. Brain Res. 66: 533–542.

Castro, A. J., Tønder, N., Sunde, N. A. and Zimmer, J. (1988) Fetal neocortical transplants grafted to the cerebral cortex of newborn rats receive afferents from the basal forebrain, locus coeruleus and midline raphe. Exp. Brain Res. 69: 613–622.

Chang, F. L., Steedman, J. G. and Lund, R. D. (1984) Embryonic cerebral cortex placed in the occipital region of newborn rats make connections with the host brain. Dev. Brain Res. 13: 164–166.

Chang, F. L., Steedman, J. G. and Lund, R. D. (1986) The lamination and connectivity of embryonic cerebral cortex transplanted into newborn rat cortex. J. comp. Neurol. 244: 401–411.

Chen, K. S., Buzsaki, G., Benoualid, M. and Gage, F. H. (1989) Fetal cholinergic grafts to the basal forebrain in the aged rat. Soc. Neurosci. Abstr. 15: 1095.

Christie, J. E., Shering, A., Ferguson, J. and Glen, A. I. M. (1981) Physostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. Brit. J. Psychiat. 138: 46–50.

Clarke, D. J., Gage, F. H. and Björklund, A. (1986a) Formation of cholinergic synapses by intrahippocampal septal grafts as revealed by choline acetyltransferase immunocytochemistry. Brain Res. 369: 151–162.

Clarke, D. J., Gage, F. H., Nilsson, O. and Björklund, A. (1986b) Grafted septal neurons form cholinergic synaptic connections in the dentate gyrus of behaviorally impaired aged rats. J. comp. Neurol. 252: 483–492.

Coffey, P. J., Lund, R. D. and Rawlins, N. (1990) Open-field behaviour and conditioned suppression learning following retinal implant illumination. Prog. Brain Res. 82: 269–275.

Collier, T. J., Gash, D. M., Bruemmer, V. and Sladek, J. R. (1985) Impaired regulation of arousal in old age and the consequences for learning and memory: replacement of brain norepinephrine via neuron transplants improves memory performance in aged F344 rats. In: Davis, B. B. and Wood, W. G. Homeostatic Function and Aging pp. 99–110. Raven Press, New York.

Collier, T. J., Gash, D. M. and Sladek, J. R. (1987) Norepinephrine deficiency and behavioral senescence in aged rats: transplanted locus coeruleus neurons as an experimental replacement therapy. Ann. N.Y. Acad. Sci. 495: 396–403.

Collier, T. J., Gash, D. M. and Sladek, J. R. (1988) Transplantation of norepinephrine neurons into aged rats improves performance of a learned task. Brain Res. 448: 77–87.

Cork, L. C., Sternberger, N. H., Sternberger, L. A., Casanova, M. F., Struble, R. G. and Price, D. L. (1986) Phosphorylated neurofilament antigens in neurofibrillary tangles in Alzheimer's disease. J. Neuropathol. Exp. Neurol. 45: 56–64.

Corsellis, J. A. N. (1976) Ageing and the dementias. In: Blackwood, W. and Corsellis, J. A. N. Greenfield's Neuropathology, 3rd edn. pp. 796–848. Matthew Arnold, London.

Coyle, J. T., Price, D. L. and DeLong, M. R. (1983) Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 219: 1184–1190.

Coyle, J. T., Oster-Granite, M. L. and Gearhart, J. D. (1986) The neurobiologic consequences of Down syndrome. Brain Res. Bull. 16: 773–787.

Coyle, J. T., Oster-Granite, M. L., Reeves, R. H. and Gearhart, J. D. (1988) Down syndrome, Alzheimer's disease and the trisomy 16 mouse. Trends Neurosci. 11: 290–393.

Craner, S. J., Radel, J. R., Jen, L. S. and Lund, R. D. (1989) Light-evoked cortical activity produced by illumination of intracranial retinal transplants: experimental studies in rats. Exp. Neurol. 104: 93–100.

Cummings, J. L. (1986) Subcortical dementia: neuropsychology, neuropsychiatry and pathophysiology. Brit. J. Psychiat. 149: 682–697.

Dalrymple-Alford, J. C., Kelch, C., Cassel, J. C., Toniolo, G., Pallage, V. and Will, B. E. (1988) Behavioral deficits after intrahippocampal fetal septal grafts in rats with selective fimbria-fornix lesions. Exp. Brain Res. 69: 545–558.

Daniloff, J. K., Bodony, R. P., Low, W. C. and Wells, J. (1985) Cross-species embryonic septal transplants: restoration of conditioned learning behavior. Brain Res. 346: 176–180.

Das, G. D. (1974) Transplantation of embryonic neural tissue in mammalian brain. I. Growth and differentiation of neuroblasts from various regions of the embryonic brain in the cerebellum of neonate rats. T.I.T. J. Life Sci. 4: 93–124.

Das, G. D. (1983) Neural transplantation in mammalian brain: some conceptual and technical considerations. In: Wallace, R. B. and Das, G. D. Neural Tissue Transplantation Research pp. 1–64. Springer-Verlag, New York, Berlin, Heidelberg, Tokyo.

Das, G. D. and Altman, J. (1971) The fate of transplanted precursors of nerve cells in the cerebellum of young rats. Science 173: 637–638.

Das, G. D. and Hallas, B. H. (1978) Transplantation of brain tissue in the brain of adult rats. Experientia 34: 1304–1306.

Das, G. D., Hallas, B. H. and Das, K. G. (1980) Transplantation of brain tissue in the brain of rat. I. Growth characteristics of neocortical transplants from embryos of different ages. Am. J. Anat. 158: 135–145.

Date, I., Feltin, S. Y. and Feltin, D. L. (1989) The effect of adrenal medullary grafts in MPTP treated aging mouse brain. Soc. Neurosci. Abstr. 15: 1356.

Davies, P. and Maloney, A. J. F. (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet ii: 1403.

Dayan, A. D. (1971) Comparative neuropathology of ageing. Studies on the brains of 47 species of vertebrates. Brain 94: 31–42.

Dean, R. L. and Bartus, R. T. (1987) Behavioral models of aging in nonhuman primates. In: Iversen, L. L., Iversen, S. D. and Snyder, S. H. Handbook of

Psychopharmacology, Volume 20 pp. 325–392 Plenum, London, New York.
De Boni, U., Otvos, A., Scott, J. W. and Crapper, D. R. (1976) Neurofibrillary degeneration induced by systemic aluminum. Acta Neuropathol. 35: 285–294.
Doering, L. C. and Aguayo, A. J. (1987) Hirano bodies and other cytoskeletal abnormalities in fetal rat CNS grafts isolated for long periods in peripheral nerve. Brain Res. 401: 178–184.
Douglas, R. J. (1967) The hippocampus and behavior. Psychol. Bull. 67: 416–442.
Drachman, D. A. and Leavitt, J. (1974) Human memory and the cholinergic system. Arch. Neurol. 30: 113–121.
Drachman, D. A. and Sahakian, B. J. (1980) Memory, aging and pharmacosystems. In: Stein, D. The Psychobiology of Aging: Problems and Perspectives pp. 347–368. Elsevier North Holland, Amsterdam.
Dunn, E. H. (1917) Primary and secondary findings in a series of attempts to transplant cerebral cortex in the albino rat. J. comp. Neurol. 27: 565–582.
Dunnett, S. B. (1987) Anatomical and behavioral consequences of cholinergic-rich grafts to the neocortex of rats with lesions of the nucleus basalis magnocellularis. Ann. N.Y. Acad. Sci. 495: 415–429.
Dunnett, S. B. (1989) Short-term memory in rodent models of ageing: effects of cortical cholinergic grafts. In: Gage, F. H., Privat, A. and Christen, Y. Neuronal Grafting and Alzheimer's Disease pp. 85–102. Springer-Verlag, Berlin, Heidelberg, New York.
Dunnett, S. B. and Barth, T. W. (1990) Animal models of dementia (with an emphasis on cortical cholinergic systems). In: Willner, P. Animal Models in Psychopharmacology (in press). Cambridge University Press, Cambridge.
Dunnett, S. B. and Björklund, A. (1987) Mechanisms of function of neural grafts in the adult mammalian brain. J. exp. Biol. 132: 265–289.
Dunnett, S. B. and Richards, S.-J. (1990) Neural Transplantation: From Molecular Basis to Clinical Application, Progress in Brain Research, Volume 82. Elsevier, Amsterdam.
Dunnett, S. B., Low, W. C., Iversen, S. D., Stenevi, U. and Björklund, A. (1982a) Septal transplants restore maze learning in rats with fimbria-fornix lesions. Brain Res. 251: 335–348.
Dunnett, S. B., Gage, F. H., Björklund, A., Stenevi, U., Low, W. C. and Iversen, S. D. (1982b) Hippocampal deafferentation: transplant-derived reinnervation and functional recovery. Scand. J. Psychol. suppl. 1: 104–111.
Dunnett, S. B., Björklund, A., Schmidt, R. H., Stenevi, U. and Iversen, S. D. (1983) Intracerebral grafting of neuronal cell suspensions. IV. Behavioural recovery in rats with unilateral implants of dopamine cell suspensions in different forebrain sites. Acta Physiol. Scand. suppl. 522: 29–37.
Dunnett, S. B., Björklund, A., Gage, F. H. and Stenevi, U. (1985a) Transplantation of mesencephalic dopamine neurons to the striatum of adult rats. In Björklund, A. and Stenevi, U. Neural Grafting in the Mammalian CNS pp. 451–469. Elsevier, Amsterdam.
Dunnett, S. B., Toniolo, G., Fine, A., Ryan, C. N., Björklund, A. and Iversen, S. D. (1985b) Transplantation of embryonic ventral forebrain neurons to the neocortex of rats with lesions of nucleus basalis magnocellularis. II. Sensorimotor and learning impairments. Neuroscience 16: 787–797.
Dunnett, S. B., Whishaw, I. Q., Bunch, S. T. and Fine, A. (1986) Acetylcholine-rich neuronal grafts in the forebrain of rats: effects of environmental enrichment, neonatal noradrenaline depletion, host transplantation site, and regional source of embryonic donor cells on graft size and acetylcholinesterase-positive fibre outgrowth. Brain Res. 378: 357–373.
Dunnett, S. B., Ryan, C. N., Levin, P. D., Reynolds, M. and Bunch, S. T. (1987a) Functional consequences of embryonic neocortex transplanted to rats with prefrontal cortex lesions. Behav. Neurosci. 101: 489–503.
Dunnett, S. B., Whishaw, I. Q., Jones, G. H. and Bunch, S. T. (1987b) Behavioural, biochemical and histochemical effects of different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats. Neuroscience 20: 653–669.
Dunnett, S. B., Evenden, J. L. and Iversen, S. D. (1988a) Delay-dependent short-term memory impairments in aged rats. Psychopharmacology 96: 174–180.
Dunnett, S. B., Badman, F., Rogers, D. C., Evenden, J. L. and Iversen, S. D. (1988b) Cholinergic grafts in the neocortex or hippocampus of aged rats: reduction of delay-dependent deficits in the delayed non-matching to position task. Exp. Neurol. 102: 57–64.
Dunnett, S. B., Hernandez, T. D., Summerfield, A., Jones, G. H. and Arbuthnott, G. (1988c) Graft derived recovery from 6-OHDA lesions: specificity of ventral mesencephalic graft tissues. Exp. Brain Res. 71: 411–424.
Dunnett, S. B., Isacson, O., Siriniathsinghji, D. J. S., Clarke, D. J. and Björklund, A. (1988d) Striatal grafts in rats with unilateral neostriatal lesions. III. Recovery from dopamine-dependent motor asymmetry and deficits in skilled paw reaching. Neuroscience 24: 811–819.
Dunnett, S. B., Rogers, D. C. and Jones, G. H. (1989) Effects of nucleus basalis magnocellularis lesions on delayed matching and non-matching to position tasks: disruption of conditional discrimination learning but not of short-term memory. Eur. J. Neurosci. 1: 395–406.
Dunnett, S. B., Martel, F. L., Rogers, D. C. and Finger, S. (1990) Factors affecting septal graft amelioration of differential reinforcement of low rates (DRL) and activity deficits after fimbria-fornix lesions. Rest. Neurol. Neurosci. 1: 83–92.
Eckerman, D. A., Gordon, W. A., Edwards, J. D., MacPhail, R. C. and Gage, M. I. (1980) Effects of scopolamine, pentobarbital, and amphetamine on radial arm maze performance in the rat. Pharmacol. Biochem. Behav. 12: 595–602.
Elias, P. K. and Elias, M. F. (1976) Effects of age on learning ability: contributions from the animal literature. Exp. Aging Res. 2: 165–186.
Eriksdotter-Nilsson, M. and Olson, L. (1989) Growth of brain tissue grafts is dependent upon host age. Mech. Ageing Dev. 49: 1–22.
Eriksdotter-Nilsson, M., Björklund, H., Dahl, D. and Olson, L. (1986) Growth and development of intraocular fetal cortex cerebri grafts in rats of different ages. Dev. Brain Res. 28: 75–84.
Eriksdotter-Nilsson, M., Gerhardt, G., Seiger, Å., Hoffer, B. and Granholm, A.-C. (1989a) Multiple changes in noradrenergic mechanisms in the coeruleo-hippocampal pathway during aging. Structural and functional correlates in intraocular double grafts. Neurobiol. Aging 10: 117–124.
Eriksdotter-Nilsson, M., Gerhardt, G., Seiger, Å., Olson, L., Hoffer, B. and Granholm, A.-C. (1989b) Age-related alterations in noradrenergic input to the hippocampal formation: structural and functional studies in intraocular transplants. Brain Res. 478: 269–280.
Eriksdotter-Nilsson, M., Skirboll, S., Ebendal, T. and Olson, L. (1989c) Nerve growth factor can influence growth of cortex cerebri and hippocampus: evidence from intraocular grafts. Neuroscience 30: 755–766.
Ernfors, P., Ebendal, T., Olson, L., Mouton, P., Strömberg, I. and Persson, H. (1989) A cell line producing recombinant nerve growth factor evokes growth responses in intrinsic and grafted central cholinergic neurons. Proc. Natl. Acad. Sci. USA 86: 4756–4760.
Escobar, M., Fernandez, J., Guevara-Aguilar, R. and Bermudez-Rattoni, F. (1989) Fetal brain grafts induce recovery of learning deficits and connectivity in rats with gustatory neocortex lesions. Brain Res. 478: 368–374.
Etherington, R. E., Mittleman, G. and Robbins, T. W. (1987) Comparative effects of nucleus basalis and fimbria-fornix lesions on delayed matching and alternation tests of memory. Neurosci. Res. Comm. 1: 135–143.
Evenden, J. L., Marston, H. M., Jones, G. H., Giardini, V. and Lenard, L. (1989) Effects of excitotoxic lesions of the substantia innominata, ventral and dorsal globus pallidus on visual discrimination acquisition, performance and reversal in the rat. Behav. Brain Res. 32: 129–149.
Everitt, B. J., Robbins, T. W., Evenden, J. L., Marston, H. M., Jones, G. H. and Sirkiä, T. E. (1987) The effects of excitotoxic lesions of the substantia innominata, ventral and dorsal globus pallidus on the acquisition and retention of a conditional visual discrimination: implications for cholinergic hypotheses of learning and memory. Neuroscience 22: 441–469.
Finch, C. B. (1973) Catecholamine metabolism in the brains of ageing male mice. Brain Res. 52: 261–276.
Fine, A., Dunnett, S. B., Björklund, A. and Iversen, S. D. (1985a) Cholinergic ventral forebrain grafts into the neocortex improve passive avoidance memory in a rat model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 82: 5227–5230.
Fine, A., Dunnett, S. B., Björklund, A., Clarke, D. J. and Iversen, S. D. (1985b) Transplantation of embryonic ventral forebrain neurons to the neocortex of rats with lesions of nucleus basalis magnocellularis—I. Anatomical observations. Neuroscience 16: 769–786.
Finger, S. and Dunnett, S. B. (1989) Nimodipine enhances growth and vascularization of neural grafts. Exp. Neurol. 104: 1–9.
Fischer, W., Wictorin, K., Björklund, A., Williams, L. R., Varon, S. and Gage, F. H. (1987) Amerlioration of cholinergic neuron atrophy and spatial memory impairment in aged rats by nerve growth factor. Nature 329: 65–68.
Fischer, W., Gage, F. H. and Björklund, A. (1989) Degenerative changes in forebrain cholinergic nuclei correlate with cognitive impairments in aged rats. Eur. J. Neurosci. 1: 34–45.
Fisher, A. and Hanin, I. (1986) Potential animal models for senile dementia of Alzheimer's type, with emphasis on AF64A-induced cholinotoxicity. Ann. Rev. Pharmacol. Toxicol. 26: 161–181.
Foster, G. A., Schultzberg, M., Gage, F. H., Björklund, A., Hökfelt, T., Cuello, A. C., Verhofstad, A. A. J., Visser, T. J. and Emson, P. C. (1988a) Transmitter expression and morphological development of embryonic medullary and mesencephalic raphe neurones after transplantation to the adult rat central

nervous system. II. Grafts to the hippocampus. Exp. Brain Res. 70: 225–241.
Foster, G. A., Schultzberg, M., Gage, F. H., Björklund, A., Hökfelt, T., Cuello, A. C., Verhofstad, A. A. J., Visser, T. J. and Emson, P. C. (1988b) Transmitter expression and morphological development of embryonic medullary and mesencephalic raphe neurones after transplantation to the adult rat central nervous sytem. III. Grafts to the striatum. Exp. Brain Res. 70: 242–255.
Freed, W. J. (1983) Functional brain tissue transplantation: reversal of lesion-induced rotation by intraventricular substantia nigra and adrenal medulla grafts, with a note on intracranial retinal grafts. Biol. Psychiat. 18: 1205–1267.
Freed, W. J., Perlow, M. J., Karoum, F., Seiger, Å., Olson, L., Hoffer, B. J. and Wyatt, R. J. (1980) Restoration of dopaminergic function by grafting fetal rat substantia nigra to the caudate nucleus: long-term behavioral, biochemical and histochemical studies. Ann. Neurol. 8: 510–519.
Freed, W. J., Morihisa, J. M., Spoor, E., Hoffer, B. J., Olson, L., Seiger, Å., and Wyatt, R. J. (1981) Transplanted adrenal chromaffin cells in rat brain reduce lesion-induced rotational behaviour. Nature 292: 351–352.
Freed, W. J., Cannon-Spoor, H. E. and Krauthamer, E. (1985a) Factors influencing the efficacy of adrenal medulla and embryonic substantia nigra grafts. In: Björklund, A. and Stenevi, U. Neural Grafting in the Mammalian CNS pp. 491–504. Elsevier, Amsterdam.
Freed, W. J., de Medinaceli, L. and Wyatt, R. J. (1985b) Promoting functional plasticity in the damaged nervous system. Science 227: 1544–1552.
Gaffan, D. (1972) Loss of recognition memory in rats with lesions of the fornix. Neuropsychologia 10: 327–341.
Gaffan, D. (1976). Recognition memory in animals. In: Brown, R. Recognition and Recall pp. 229–242. Wiley, London.
Gage, F. H. and Björklund, A. (1986a) Cholinergic septal grafts into the hippocampal formation improve spatial learning and memory in aged rats by an atropine-sensitive mechanism. J. Neurosci. 6: 2837–2847.
Gage, F. H. and Björklund, A. (1986b) Enhanced graft survival in the hippocampus following selective denervation. Neuroscience 17: 89–98.
Gage, F. H. and Buzsaki, U. (1989) CNS grafting: potential mechanisms of action. In: Seil, F. J. Neural Regeneration and Transplantation pp. 211–226. Alan R. Liss, New York.
Gage, F. H., Björklund, A., Stenevi, U. and Dunnett, S. B. (1983a) Intracerebral grafting of neuronal cell suspensions. VIII. Survival and growth of implants of nigral and septal cell suspensions in intact brains of aged rats. Acta Physiol. Scand. suppl. 522: 67–75.
Gage, F. H., Dunnett, S. B., Stenevi, U. and Björklund, A. (1983b) Aged rats: recovery of motor impairments by intrastriatal nigral grafts. Science 221: 966–969.
Gage, F. H., Björklund, A., Stenevi, U. and Dunnett, S. B. (1983c) Intracerebral grafting in the aged brain. In: Gispen, W. H. and Traber, B. V. Aging of the Brain pp. 125–137. Elsevier, Amsterdam.
Gage, F. H., Björklund, A., Stenevi, U., Dunnett, S. B. and Kelley, P. A. T. (1984a) Intrahippocampal septal grafts ameliorate learning deficits in aged rats. Science 225: 533–536.
Gage, F. H., Dunnett, S. B. and Björklund, A. (1984b) Spatial learning and motor deficits in aged rats. Neurobiol. Aging 5: 43–48.
Gage, F. H., Kelly, P. A. T. and Björklund, A. (1984c) Regional changes in brain glucose metabolism reflect cognitive impairments in aged rats. J. Neurosci. 4: 2856–2865.
Gage, F. H., Wolff, J. A., Rosenberg, M. B., Xu, L., Yee, J.-K., Shults, C. and Friedmann, T. (1987) Grafting genetically modified cells to the brain: possibilities for the future. Neuroscience 23: 795–807.
Gage, F. H., Armstrong, D. M., Williams, L. R. and Varon, S. (1988) Morphological response of axotomized septal neurons to nerve growth factor. J. comp. Neurol. 269: 147–155.
Gage, F. H., Dunnett, S. B. and Björklund, A. (1989) Age-related impairments in spatial memory are independent of those in sensorimotor skills. Neurobiol. Aging 10: 347–352.
Gage, F. H., Fisher, L. J., Jinnah, J. H. A., Rosenberg, M. B., Tuszynski, M. and Friedmann, T. (1990) Grafting genetically modified cells to the brain: conceptual and technical issues. Prog. Brain Res. 82: 1–10.
Gähwiler, B. H., Enz, A. and Hefti, F. (1987) Nerve growth factor promotes development of the rat septo-hippocampal cholinergic projection in vitro. Neurosci. Lett. 75: 6–10.
Gajdusek, D. C. (1977) Unconventional viruses and the origin and disappearance of kuru. Science 197: 943–960.
Gash, D. M. (1987) Neural transplantation: potential therapy for Alzheimer's disease. J. neur. Trans. suppl. 24: 301–308.
Gash, D. M. and Sladek, J. R. (1988) Transplantation into the Mammalian CNS, Progress in Brain Research, Vol. 78. Elsevier, Amsterdam.
Gibbs, R. B. and Cotman, C. W. (1987) Factors affecting survival and outgrowth from transplants of entorhinal cortex. Neuroscience 21: 699–706.
Gibbs, R. B., Harris, E. W. and Cotman, C. W. (1985) Replacement of damaged cortical projections by homotypic transplants of entorhinal cortex. J. comp. Neurol. 237: 47–65.
Gibbs, R. B., Anderson, K. and Cotman, C. W. (1986) Factors affecting innervation in the CNS: comparison of three cholinergic cell types transplanted to the hippocampus of adult rats. Brain Res. 383: 362–366.
Gibson, G. E., Peterson, C. and Jenden, D. J. (1981) Brain acetylcholine synthesis declines with senescence. Science 213: 674–676.
Gibson, M. J., Krieger, D. T., Charlton, H. M., Zimmer, E. A., Silverman, A. J. and Perlow, M. J. (1984) Mating and pregnancy can occur in genetically hypogonadal mice with preoptic area grafts. Science 225: 949–951.
Gibson, P. H. and Tomlinson, A. N. (1977) Numbers of Hirano bodies in hippocampus of normal and demented people with Alzheimer's disease. J. neurol. Sci. 33: 199–206.
Glees, P. (1955) Studies on cortical regeneration with special reference to central implants. In: Windle, W. F. Regeneration in the Central Nervous System pp. 94–111. Thomas, Springfield, Illinois.
Goedert, M., Fine, A., Hunt, S. P. and Ullrich, A. (1986) Nerve growth factor mRNA in peripheral and central rat tissues and in the human central nervous system. Lesion effects in the rat brain and levels in Alzheimer's disease. Molec. Brain Res. 1: 85–92.
Gold, P. E. and McGaugh, J. L. (1975) Changes in learning and memory during aging. In: Ordy, J. M. and Brizzee, K. R. Neurobiology of Aging pp. 145–158. Plenum Press, New York.
Goldgaber, D., Lerman, M. I., McBride, O. W., Saffiotti, U. and Gajdusek, D. C. (1987) Characterization and chromosomal localisation of a cDNA encoding brain amyloid of Alzheimer's disease. Science 235: 877–880.
Goldman-Rakic, P. S. and Brown, R. M. (1981) Regional changes of monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys. Neuroscience 7: 177–187.
Gonzalez, M. F., Sharp, F. R. and Loken, J. E. (1988) Fetal frontal cortex transplanted to injured motor/sensory cortex of adult rats. I. NADPH-diaphorase neurons. J. Neurosci. 7: 2991–3001.
Goudsmitt, J., Morrow, C. H., Asher, D. M., Yanagihara, R. T., Masters, C. L., Gibbs, C. J. and Gajdusek, D. C. (1980) Evidence for and against the transmissibility of Alzheimer disease. Neurology 30: 945–950.
Granholm, A.-C., Gerhardt, G., Eriksdotter-Nilsson, M., Bickford-Wimer, P. C., Palmer, M. R., Seiger, Å., Olson, L. and Hoffer, B. (1987) Age-related changes in cerebellar noradrenergic pre- and post-synaptic mechanisms: determinants evaluated with brain grafts *in oculo*. Brain Res. 423: 71–78.
Hagan, J. J., Salamone, J. D., Simpson, J., Iversen, S. D. and Morris, R. G. M. (1988) Place navigation in rats is impaired by lesions of medial septum and diagonal band but not nucleus basalis magnocellularis. Behav. Brain Res. 27: 9–20.
Hallas, B. H., Das, G. D. and Das, K. G. (1980) Transplantation of brain tissue in the brain of rat. II. Growth characteristics of neocortical transplants in hosts of different ages. Am. J. Anat. 158: 147–159.
Hansen, J. T., Fiandaca, M. S., Kordower, J. H., Notter, M. F. D. and Gash, D. M. (1990) Striatal adrenal medulla/sural nerve cografts in hemiparkinsonian monkeys. Prog. Brain Res. 82: 573–580.
Haroutunian, V., Kanof, P. D. and Davis, K. L. (1986) Partial reversal of lesion-induced deficits in cortical cholinergic markers by nerve growth factor. Brain Res. 386: 397–399.
Hartikka, J. and Hefti, F. (1988) Development of septal cholinergic neurons in culture: plating density and glial cells modulate effects of NGF on survival, fiber growth, and expression of transmitter-specific enzymes. J. Neurosci. 8: 2967–2985.
Hatanaka, H., Tsukui, H. and Nihonmatsu, I. (1988) Developmental changes in the nerve growth factor action from induction of choline acetyltransferase to promotion of cell survival in cultured basal forebrain cholinergic neurons from postnatal rats. Dev. Brain Res. 39: 85–95.
Haun, F. and Cunningham, T. J. (1984) Cortical transplants reveal CNS trophic interactions in situ. Dev. Brain Res. 15: 290–294.
Haun, F. and Cunningham, T. J. (1987) Specific neurotrophic interactions between cortical and subcortical visual structures in developing rat: in vivo studies. J. comp. Neurol. 256: 561–569.
Haun, F., Rothblat, L. A. and Cunningham, T. J. (1985) Visual cortex transplants in rats restore normal learning of a difficult visual pattern discrimination. Invest. Ophthalmol. Vis. Sci. 26, suppl. 3: 288.
Hefti, F. (1983) Is Alzheimer's disease caused by a lack of nerve growth factor? Ann. Neurol. 13: 109–110.

Hefti, F. (1986) Nerve growth factor promotes survival of septal cholinergic neurons after fimbria transections. J. Neurosci. 6: 2155–2162.

Hefti, F. and Weiner, W. J. (1986) Nerve growth factor and Alzheimer's disease. Ann. Neurol. 20: 275–281.

Hefti, F. and Will, B. (1987) Nerve growth factor is a neurotrophic factor for forebrain cholinergic neurons: implications for Alzheimer's disease. In: Wurtman, R. J., Corkin, S. H. and Growdon, J. H. Alzheimer's Disease: Advances in Basic Research and Therapies pp. 265–274. Center for Brain Sciences and Metabolism, Cambridge, MA.

Hepler, D. J., Wenk, G. L., Cribbs, B. L., Olton, D. S. and Coyle, J. T. (1985a) Memory impairments following basal forebrain lesions. Brain Res. 346: 8–14.

Hepler, D. J., Olton, D. S., Wenk, G. L. and Coyle, J. T. (1985b) Lesions in nucleus basalis magnocellularis and medial septal area produce quantitatively similar memory impairments. J. Neurosci. 5: 866–873.

Hodges, H., Allen, Y., Sinden, J., Lantos, P. L. and Gray, J. A. (1990) Cholinergic-rich transplants alleviate cognitive deficits in lesioned rats, but exacerbate response to cholinergic drugs. Prog. Brain Res. 82: 347–358.

Höhmann, C. F. and Ebner, F. F. (1988) Basal forebrain lesions facilitate adult host fiber ingrowth into neocortical transplants. Brain Res. 448: 53–66.

Höhmann, C. F., Capone, G., Oster-Granite, M.-L. and Coyle, J. T. (1990a) Transplantation of fetal cortex from murine trisomy 16 and normal litter mate controls into newborn mouse cortex. Rest. Neurol. Neurosci. 1: 140.

Höhmann, C. F., Capone, G., Oster-Granite, M.-L. and Coyle, J. T. (1990b) Transplantation of brain tissue from murine trisomy 16 into euploid hosts: effects of gene imbalance on brain development. Prog. Brain Res. 82: 203–214.

Hornberger, J. C., Buelli, S. J., Flood, D. G., McNeill, T. H. and Colman, P. D. (1985) Stability of numbers but not size of mouse forebrain cholinergic neurons to 53 months. Neurobiol. Aging 6: 269–275.

Huang, H. H., Kissane, J. Q. and Hawrylewicz, E. J. (1987) Restoration of sexual function and fertility by fetal hypothalamic transplant in impotent aged male rats. Neurobiol. Aging 8: 465–472.

Huber, S. J. and Paulson, G. W. (1985) The concept of subcortical dementia. Am. J. Psychiat. 142: 1312–1317.

Ikegami, S., Nihonmatsu, I., Hatanaka, H., Takei, N. and Kawamura, H. (1989) Transplantation of septal cholinergic neurons to the hippocampus improves memory impairments of spatial learning in rats treated with AF64A. Brain Res. 496: 321–326.

Ingram, D. K. (1985) Analysis of age-related impairments in learning and memory in rodent models. Ann. N.Y. Acad. Sci. 444: 312–331.

Ingram, D. K., London, E. D., Reynolds, M. A., Waller, S. B. and Goodrick, C. L. (1981) Differential effects of age on motor performance in two mouse strains. Neurobiol. Aging 2: 221–227.

Isacson, O., Dunnett, S. B. and Björklund, A. (1986) Graft-induced behavioral recovery in an animal model of Huntington disease. Proc. Natl. Acad. Sci. USA 83: 2728–2732.

Kaplan, A. S., Gash, D. M., Flood, D. G. and Coleman, P. D. (1985) A Golgi study of hypothalamic transplants in young and old host rats. Neurobiol. Aging 6: 205–211.

Kang, J., Lemaire, H. G., Unterbeck, A., Salbaum, M., Masters, C. L., Grzeschik, K. H., Multhaup, G., Beyreuther, K. and Muller-Hill, B. (1987) The precursor of Alzheimer's disease amyloid protein resembles a cell-surface receptor. Nature 325: 733–736.

Kesner, R. P. (1988) Reevaluation of the contribution of the basal forebrain cholinergic system to memory. Neurobiol. Aging 9: 609–616.

Kesner, R. P., Crutcher, K. A. and Measom, M. O. (1986) Medial septal and nucleus basalis magnocellularis lesions produce order memory deficits in rats which mimic symptomatology of Alzheimer's disease. Neurobiol. Aging 7: 287–295.

Kesslak, J. P., Brown, L., Steichen, C. and Cotman, C. W. (1986a) Adult and embryonic frontal cortex transplants after frontal cortex ablation enhance recovery on a reinforced alternation task. Exp. Neurol. 94: 615–626.

Kesslak, J. P., Nieto-Sampedro, M., Globus, J. and Cotman, C. W. (1986b) Transplants of purified astrocytes promote behavioral recovery after frontal cortex ablation. Exp. Neurol. 92: 377–390.

Khachaturian, Z. S. (1985) Diagnosis of Alzheimer's disease. Arch. Neurol. 42: 1097–1105.

Kimble, D. P. (1968) Hippocampus and internal inhibition. Psychol. Bull. 70: 285–295.

Kimble, D. P., Bremiller, R. and Stickrod, G. (1986) Fetal brain implants improve maze performance in hippocampal lesioned rats. Brain Res. 363: 356–363.

Kitt, C. A., Price, D. L., Struble, R. G., Cork, L. C., Wainer, B. H., Becher, M. W. and Mobley, W. C. (1984) Evidence for cholinergic neurites in senile plaques. Science 226: 1443–1445.

Kitt, C. A., Struble, R. G., Cork, L. C., Mobley, W. C., Walker, L. C., Joh, T. H. and Price, D. L. (1985) Catecholaminergic neurites in senile plaques in prefrontal cortex of aged nonhuman primates. Neuroscience 16: 691–699.

Klatzo, I., Wisniewski, H. and Streicher, E. (1965) Experimental production of neurofibrillary degeneration. I. Light microscopic observations. J. Neuropathol. exp. Neurol. 24: 187–199.

Knowlton, B. J., Wenk, G. L., Olton, D. S. and Coyle, J. T. (1985) Basal forebrain lesions produce a dissociation of trial-dependent and trial-independent memory performance. Brain Res. 345: 315–321.

Kolb, B., Reynolds, B. and Fantie, B. (1988) Frontal cortex grafts have opposite effects at different postoperative recovery times. Behav. neur. Biol. 50: 193–206.

Kromer, L. F. (1987) Nerve growth factor treatment after brain injury prevents neuronal death. Science 235: 214–216.

Kubanis, P. and Zornetzer, S. F. (1981) Age-related behavioral and neurobiological changes: a review with an emphasis on memory. Behav. Neur. Biol. 31: 115–172.

Labbe, R., Firl, A., Mufson, E. J. and Stein, D. G. (1983) Fetal brain transplants: reduction of cognitive deficits in rats with frontal cortex lesions. Science 221: 470–472.

Leslie, F. M., Loughlin, S. E., Sternberg, D. B., McGaugh, J. L., Young, L. E. and Zornetzer, S. F. (1985) Noradrenergic changes and memory loss in aged mice. Brain Res. 359: 292–299.

LeVere, T. E. and LeVere, N. D. (1985) Transplants to the central nervous system as a therapy for brain pathology. Neurobiol. Aging 6: 151–152.

Levin, B. E., Dunn-Meynell, A. and Sced, A. F. (1987) Functional integration of fetal cortical grafts into the afferent pathway of the rat somatosensory cortex (SmI). Brain Res. Bull. 19: 723–734.

Lewis, E. R. and Cotman, C. W. (1983). Neurotransmitter characteristics of brain grafts: Striatal and septal tissues form the same laminated input to the hippocampus. Neuroscience 8: 57–66.

Lindsay, R. M., Emmett, C., Raisman, G. and Seeley, P. J. (1987) Application of tissue culture and cell-marking techniques to the study of neural transplants. Ann. N.Y. Acad. Sci. 495: 35–52.

Lippa, A. S., Pelham, R. W., Beer, B., Critchett, D. J., Dean, R. L. and Bartus, R. T. (1980) Brain cholinergic dysfunction and memory in aged rats. Neurobiol. Aging 1: 13–19.

Lopez-Lozano, J. J., Gash, D. M., Leary, J. F. and Notter, M. F. D. (1987) Survival and integration of transplanted hypothalamic cells in the rat CNS after sorting by flow cytometry. Ann. N.Y. Acad. Sci. 495: 736–739.

Low, W. C., Lewis, P. R., Bunch, S. T., Dunnett, S. B., Thomas, S. R., Iversen, S. D., Björklund, A. and Stenevi, U. (1982) Functional recovery following neural transplantation of embryonic septal nuclei in adult rats with septo-hippocampal lesions. Nature 300: 260–262.

Lund, R. D. and Hauschka, S. D. (1976) Transplanted neural tissue develops connections with host rat brain. Science 193: 582–584.

Mann, D. M. A. and Yates, P. O. (1983) Serotonergic nerve cells in Alzheimer's disease. J. Neurol. Neurosurg. Psychiat. 46: 96.

Markowska, A. J., Stone, W. S., Ingram, D. K., Reynolds, J., Gold, P. E., Conti, L. H., Pontecorvo, M. J., Wenk, G. L. and Olton, D. S. (1989) Individual differences in aging: behavioral and neurobiological correlates. Neurobiol. Aging 10: 31–43.

Marshall, J. F. and Berrios, N. (1979) Movement disorders of aged rats: reversal by dopamine receptor stimulation. Science 206: 477–479.

Matsumoto, A., Murakami, S., Arai, Y. and Nagatsu, I. (1987) Ultrastructural and immunohistochemical analysis of fetal mediobasal hypothalamic tissue transplanted into the aged brain. Ann. N.Y. Acad. Sci. 495: 404–413.

McConnell, S. K. (1989) The determination of neuronal fate in the cerebral cortex. Trends Neurosci. 12: 342–349.

McGeer, E. G. (1981) Neurotransmitter systems in aging and senile dementia. Prog. Neurobiol. 8: 111–119.

McGeer, E. G., Fibiger, H. C., McGeer, P. L. and Wickson, V. (1971) Aging and brain enzymes. Exp. Gerontol. 6: 391–396.

McIntosh, H. H. and Westfall, T. C. (1987) Influence of aging on catecholamine levels, accumulation, and release in F-344 rats. Neurobiol. Aging 8: 233–239.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984) Clinical diagnosis of Alzheimer's disease: report on the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. Neurology 34: 939–944.

McLoon, S. C. and Lund, R. D. (1983) Development of fetal retina, tectum and cortex transplanted to the superior colliculus of adult rats. J. comp. Neurol. 217: 376–389.

McRae-Degueurce, A., Didier, M. and Pujol, J. F. (1981) The viability of

transplants of mesencephalic raphe nuclei in the IVth ventricle of the adult rat. Neurosci. Lett. 24: 251–254.

McRae-Degueurce, A., Lauder, J. M. and Privat, A. (1983) Adult age destruction versus neonatal age destruction of the serotonin system: two models to investigate the survival of serotonin neurons transplanted in adult rats. Neurosci. Lett. 40: 27–32.

McRae-Degueurce, A., Serano, A., Sandillon, F., Privat, A. and Scatton, B. (1984) In vivo voltametric measurement of extracellular 5-hydroxyindoleacetic acid in the denervated striatum after transplantation of mesencephalic raphe neurons. Neurosci. Lett. 48: 97–102.

Meck, W. H., Church, R. M., Wenk, G. L. and Olton, D. S. (1987) Nucleus basalis magnocellularis and medial septal area lesions differentially impair temporal memory. J. Neurosci. 7: 3505–3511.

Meyer, E. M., St. Onge, E. and Crews, F. T. (1984) Effects of aging on rat cortical presynaptic cholinergic processes. Neurobiol. Aging 5: 315–317.

Miyamoto, M., Kato, J., Narumi, S. and Nagaoka, A. (1987) Characteristics of memory impairment following lesioning of the basal forebrain and medial septal nucleus in rats. Brain Res. 419: 19–31.

Montero, C. N. and Hefti, F. (1988) Rescue of lesioned septal cholinergic neurons by nerve growth factor: specificity and requirement for chronic treatment. J. Neurosci. 8: 2986–2999.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P. and O'Keefe, J. (1982) Place navigation impaired in rats with hippocampal lesions. Nature 297: 681–683.

Muir, J. L., Dunnett, S. B., Everitt, B. J. and Robbins, T. W. (1989) Effects of nucleus basalis lesions and cortical cholinergic grafts on attentional performance in the rat. Soc. Neurosci. Abstr. 15: 1104.

Nilsson, O. G., Shapiro, M. L., Olton, D. S., Gage, F. H. and Björklund, A. (1987) Spatial learning and memory following fimbria-fornix transection and grafting of fetal septal neurons to the hippocampus. Exp. Brain Res. 67: 195–215.

Nilsson, O. G., Clarke, D. J., Brundin, P. and Björklund, A. (1988a) Comparison of growth and reinnervation properties of cholinergic neurons from different brain regions grafted to the hippocampus. J. Comp. Neurol. 268: 204–222.

Nilsson, O. G., Strecker, R. E., Daszuta, A. and Björklund, A. (1988b) Combined cholinergic and serotonergic denervation of the forebrain produces severe deficits in a spatial learning task. Brain Res. 453: 235–246.

Nilsson, O. G., Brundin, P. and Björklund, A. (1990) Amerlioration of spatial memory impairment by intrahippocampal grafts of mixed septal and raphe tissue in rats with combined cholinergic and serotonergic denervation of the forebrain. Brain Res. (in press).

Notter, M. F. D., Gash, D. M. and Leary, J. F. (1988) Flow cytometric analysis and sorting of neural cells for transplantation. Prog. Brain Res. 78: 605–611.

O'Keefe, J. and Nadel, L. (1978) The Hippocampus as a Cognitive Map. Clarendon Press, Oxford.

O'Leary, D. D. M. (1989) Do cortical areas emerge from a protocortex? Trends Neurosci. 12: 400–406.

Oliver, C. and Holland, A. J. (1986) Down's syndrome and Alzheimer's disease: a review. Psychol. Med. 16: 307–322.

Olson, L. and Seiger, Å. (1972) Brain tissue transplanted to the anterior chamber of the eye. I. Fluorescence histochemistry of immature catecholamine and 5-hydroxytryptamine neurons reinnervating the rat iris. Z. Zellforsch. 195: 175–194.

Olson, L., Björklund, H. and Hoffer, B. J. (1984) Camera bulbi anterior: new vistas on a classical locus for neural tissue transplantation. In: Sladek, J. R. and Gash, D. M. Neural Transplants: Development and Function pp. 125–165. Plenum Press, New York, London.

Olson, L., Ayer-LeLievre, C., Ebendal, T., Eriksdotter-Nilsson, M., Ernfors, P., Henschen, A., Hoffer, B., Giacobini, M. B., Mouton, P., Palmer, M., Persson, H., Sara, V., Strömberg, I. and Wetmore, C. (1990) Grafts, growth factors, and grafts that make growth factors. Prog. Brain Res. 82: 55–66.

Olton, D. S. (1983) Memory functions and the hippocampus. In: Seifert, W. Neurobiology of the Hippocampus pp. 335–373. Academic Press, London, New York.

Olton, D. S. and Wenk, G. L. (1987) Dementia: animal models of the cognitive impairments produced by degeneration of the basal forebrain cholinergic system. In: Meltzer, H. Y. Psychopharmacology: the Third Generation of Progress pp. 941–953. Raven Press, New York.

Olton, D. S., Walker, J. A. and Gage, F. H. (1978) Hippocampal connections and spatial discrimination. Brain Res. 139: 295–308.

Olton, D. S., Becker, J. T. and Handelman, G. E. (1979) Hippocampus, space, and memory. Behav. Brain Sci. 2: 313–322.

Osterburg, H. H., Donahue, H. G., Severson, J. A. and Finch, C. E. (1981) Catecholamine levels and turnover during aging in brain regions of male C57BL/6J mice. Brain Res. 224: 337–352.

Pallage, V., Toniolo, G., Will, B. E. and Hefti, F. (1986) Long-term effects of nerve growth factor and neural transplants on behavior of rats with medial septal lesions. Brain Res. 386: 197–208.

Perlow, M. J., Freed, W. J., Hoffer, B. J., Seiger, Å., Olson, L. and Wyatt, R. J. (1979) Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 204: 643–647.

Perry, E. K., Perry, R. H., Blessed, G. and Tomlinson, B. E. (1977) Necropsy evidence of central cholinergic deficits in senile dementia. Lancet i: 189.

Perry, E. K., Tomlinson, B. E., Blessed, G., Bergmann, K., Gibson, P. H. and Perry, R. H. (1978) Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Brit. Med. J. ii: 1457–1459.

Pezzoli, G., Fahn, S., Dwork, A., Truong, D. D., de Yebenes, J. G., Jackson-Lewis, V., Herbert, J. and Cadet, J. L. (1988) Non-chromaffin tissue plus nerve growth factor reduces experimental parkinsonism in aged rats. Brain Res. 459: 398–403.

Ponzio, F., Calderini, G., Lomuscio, G., Vantani, G. and Toffano, G. (1982) Changes in monoamines and their metabolite levels in brain regions of aged rats. Neurobiol. Aging 3: 23–29.

Pradhan, S. N. (1980) Central neurotransmitters and aging. Life Sci. 26: 1643–1656.

Price, D. L. (1986) New perspectives on Alzheimer's disease. Ann. Rev. Neurosci. 9: 489–512.

Price, D. L., Koo, E. H., Muma, N. A., Applegate, M. D., Wagster, M. V., Walker, L. C., Struble, R. G., Troncoso, J. C. and Cork, L. C. (1988) Alzheimer's disease and animal models: correlations of behavioral and brain abnormalities. In: Henderson, A. S. and Henderson, J. H. Etiology of Dementia of Alzheimer's Type pp. 65–81. Wiley, New York.

Rawlins, J. N. P. and Olton, D. S. (1982) The septo-hippocampal system and cognitive mapping. Behav. Brain Res. 5: 331–358.

Reeves, R. H., Robakis, N. K., Oster-Granite, M. L., Wisniewski, H. M., Coyle, J. T. and Gearhart, J. D. (1987) Gene linkage in the mouse of genes involved in Down syndrome and Alzheimer's disease in man. Molec. Brain Res. 2: 215–221.

Richards, S.-J., Rogers, D. C., Martel, F. L., Waters, J. J. and Dunnett, S. B. (1990a) Cortical and hippocampal grafts derived from embryonic Ts16 mice provide an animal model of Alzheimer's disease with amyloid A4 pathology. Rest. Neurol. Neurosci. 1: 108.

Richards, S.-J., Waters, J. J., Rogers, D. C., Martel, F. L., Sparkman, D. R., White, C. L., Bayreuther, K., Masters, C. L. and Dunnett, S. B. (1990b) Hippocampal grafts derived from embryonic trisomy 16 mice exhibit amyloid (A4) and neurofibrillary pathology. Prog. Brain Res. 82: 215–223.

Richards, S.-J., Waters, J. J., Abraham, C. R., Sparkman, D. R., White, C. L., Beyreuther, K., Masters, C. L. and Dunnett, S. B. (1990c) Transplants of mouse trisomy 16 hippocampus provide an in vivo model of the neuropathology of Alzheimer's disease. Science submitted.

Richardson, R. T. and DeLong, M. R. (1988) A reappraisal of the functions of the nucleus basalis of Meynert. Trends Neurosci. 11: 264–267.

Richter-Levin, G. and Segal, M. (1988) Spatial performance is severely impaired in rats with combined reduction of serotonergic and cholinergic transmission. Brain Res. 477: 404–407.

Richter-Levin, G. and Segal, M. (1989) Raphe cells grafted into the hippocampus can ameliorate spatial memory deficits in rats with combined serotonergic/cholinergic deficiencies. Brain Res. 478: 184–186.

Robbins, T. W., Everitt, B. J., Ryan, C. N., Marston, H. M., Jones, G. H. and Page, K. J. (1989a) comparative effects of quisqualic and ibotenic acid-induced lesions of the substantia innominata and globus pallidus on the acquisition of a conditional visual discrimination: differential effects on cholinergic mechanisms. Neuroscience 28: 337–352.

Robbins, T. W., Everitt, B. J., Marston, H. M., Wilkinson, J., Jones, G. H. and Page, K. J. (1989b) Comparative effects of ibotenic acid- and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. Behav. Brain Res. 35: 221–241.

Roberts, J. and Baskin, S. I. (1978) Age changes in the neuromuscular system of rats. In: Gibson, D. C., Adelman, R. C. and Finch, C. Development of the Rodent as a Model System of Aging pp. 165–173. U.S. Dept. of Health, Education and Welfare, Washington.

Rosenberg, M. B., Friedmann, T., Robertson, R. C., Tuszynski, M., Wolff, J. A., Breakefield, X. O. and Gage, F. H. (1988) Grafting of genetically modified cells to the damaged brain: restorative effects of NGF expression.

Science 242: 1575–1578.
Rossor, M. N. and Iversen, L. L. (1986) Non-cholinergic neurotransmitter abnormalities in Alzheimer's disease. Brit. Med. Bull. 42: 70–74.
Sahakian, B. J. (1988) Cholinergic drugs and human cognitive performance. In: Iversen, L. L., Iversen, S. D. and Snyder, S. H. Handbook of Psychopharmacology Volume 20, Psychopharmacology of the Aging Nervous System pp. 393–424. Plenum Press, New York, London.
Sahakian, B., Jones, G., Levy, R., Gray, J. and Warburton, D. (1989) The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Brit. J. Psychiat. 154: 797–800.
Sarter, M. (1987) Animal models of brain ageing and dementia. Comp. Gerontol. A 1: 4–15.
Segal, M. and Azmitia, E. C. (1986) Fetal raphe neurons grafted into the hippocampus develop normal adult psychological properties. Brain Res. 364: 162–166.
Segal, M., Greenberger, V. and Milgram, N. W. (1987) A functional analysis of connections between grafted septal neurons and host hippocampus. Prog. Brain Res. 71: 349–357.
Seiger, Å. (1985) Preparation of immature central nervous system regions for transplantation. In: Björklund, A. and Stenevi, U. Neural Grafting in the Mammalian CNS pp. 71–77. Elsevier, Amsterdam.
Sharp, F. R. and Gonzalez, M. F. (1986) Fetal cortical transplants ameliorate thalamic atrophy ipsilateral to neonatal frontal cortex lesions. Neurosci. Lett. 71: 247–251.
Sherman, K. A., Kuster, J. E., Dean, R. L., Bartus, R. T. and Friedman, E. (1981) Presynaptic cholinergic mechanisms in brain of aged rats with memory impairments. Neurobiol. Aging 2: 99–104.
Sinden, J. D., Allen, Y. S., Rawlins, J. N. P. and Gray, J. A. (1990) The effects of ibotenic acid lesions of the nucleus basalis and cholinergic-rich neural transplants on win-stay/lose-shift and win-shift/lose-stay performance in the rat. Behav. Brain Res. 36: 229–249.
Smith, G. (1988) Animal models of Alzheimer's disease: experimental cholinergic denervation. Brain Res. Rev. 13: 103–118.
Sofroniew, M. V. and Pearson, R. C. A. (1985) Degeneration of cholinergic neurons in the basal nucleus following kainic acid or N-methyl-D-aspartic acid application to the cerebral cortex in the rat. Brain Res. 339: 186–190.
Sofroniew, M. V., Pearson, R. C. A., Eckenstein, F., Cuello, A. C. and Powell, T. P. S. (1983) Retrograde changes in cholinergic neurons in the basal nucleus of the forebrain of the rat following cortical damage. Brain Res. 289: 370–374.
Sofroniew, M. V., Isacson, O. and Björklund, A. (1986) Cortical grafts prevent atrophy of cholinergic basal nucleus neurons induced by excitotoxic cortical damage. Brain Res. 378: 409–415.
Springer, J. E., Collier, T. J., Sladek, J. R. and Loy, R. (1988) Transplantation of male mouse submaxillary gland increases survival of axotomised basal forebrain neurons. J. Neurosci. Res. 19: 291–296.
Stanfield, B. B. and O'Leary, D. D. M. (1985) Fetal occipital cortical neurones transplanted to the rostral cortex can extend and maintain a pyramidal tract axon. Nature 313: 135–137.
Stein, D. G. (1987) Transplant-induced functional recovery without specific neuronal connections. Progress in Research, American Paralysis Association, 18: 4–5.
Stein, D. G. and Mufson, E. J. (1987) Morphological and behavioral characteristics of embryonic brain tissue transplants in adult, brain-damaged subjects. Ann. N.Y. Acad. Sci. 495: 444–463.
Stein, D. G., Labbe, R., Attella, M. J. and Rakowsky, H. A. (1985) Fetal brain tissue transplants reduce visual deficits in adult rats with bilateral lesions of the occipital cortex. Behav. Neur. Biol. 44: 266–277.
Stein, D. G., Palatucci, C., Kahn, D. and Labbe, R. (1988) Temporal factors influence recovery of function after embryonic brain tissue transplants in adult rats with frontal cortex lesions. Behav. Neurosci. 102: 260–267.
Stenevi, U., Björklund, A. and Svendgaard, N.-Aa. (1976) Transplantation of central and peripheral monoamine neurons to the adult rat brain: techniques and conditions for survival. Brain Res. 114: 1–20.
Strömberg, I., Herrera-Marschitz, M., Ungerstedt, U., Ebendal, T. and Olson, L. (1985) Chronic implants of chromaffin tissue into the dopamine-denervated striatum. Effects of NGF on graft survival, fiber growth and rotational behavior. Exp. Brain Res. 60: 335–349.
Strong, R., Hicks, P., Hsu, L., Bartus, R. T. and Enna, S. J. (1980) Age-related alterations in the rodent brain cholinergic system and behavior. Neurobiol. Aging 1: 59–63.
Struble, R. G., Price, D. L. Jr, Cork, L. C. and Price, D. L. (1985) Senile plaques in cortex of aged normal monkeys. Brain Res. 361: 267–275.
Sunde, N. A. and Zimmer, J. (1983) Cellular, histochemical and connective organisation of the hippocampus and fascia dentata transplanted to different regions of immature and adult rat brains. Dev. Brain Res. 8: 165–191.
Sutherland, R. J., Kolb, B. and Whishaw, I. Q. (1982) Spatial mapping: definitive disruption by hippocampal or medial frontal cortical damage in the rat. Neurosci. Lett. 31: 271–276.
Terry, R. D. and Katzman, R. (1983) Senile dementia of the Alzheimer type: defining a disease. In: Katzman, R. and Terry, R. D. The Neurology of Aging pp. 51–84. F. A. Davis, Philadelphia.
Terry, R. D., Peck, A., DeTeresa, T., Schechter, R. and Haroupian, D. S. (1981) Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann. Neurol. 10: 184–192.
Thompson, W. G. (1890) Successful brain grafting. N.Y. Med. J. 51: 701–702.
Tomlinson, B. E., Blessed, G. and Roth, M. (1968) Observations on the brains of non-demented old people. J. neurol. Sci. 7: 331–356.
Tomlinson, B. E., Blessed, G. and Roth, M. (1970) Observations on the brains of demented old people. J. neurol. Sci. 11: 205–242.
Tomlinson, B. E., Irving, D. and Blessed, G. (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. J. neurol. Sci. 49: 419–428.
Tomonaga, M. (1974) Ultrastructure of Hirano bodies. Acta Neuropathol. 30: 365–366.
Toniolo, G., Dunnett, S. B., Hefti, F. and Will, G. (1985) Acetylcholine-rich transplants in the hippocampus: influence of intrinsic growth factors and application of nerve growth factor on choline acetyltransferase activity. Brain Res. 345: 141–146.
Tsubokawa, T., Katayama, Y., Miyazaki, S., Ogawa, H., Iwasaki, M., Shibanoki, S. and Ishikawa, K. (1988) Supranormal levels of serotonin and its metabolite after raphe cell transplantation in serotonin-denervated rat hippocampus. Brain Res. Bull. 20: 303–306.
Van Broeckhoven, C., Genthe, A. M., Vandenberghe, A., Horsthemke, B., Backhovens, H., Raeymaekers, P., Van Hul, W., Wehnert, A., Gheuens, J., Cras, P., Bruyland, M., Martin, J. J., Salbaum, M., Multhaup, G., Masters, C. L., Beyreuther, K., Gurling, H. M., Mullan, M., Holland, A., Barton, A., Irving, N., Williamson, R., Richards, S.-J. and Hardy, J. A. (1987) Failure of familial Alzheimer's disease to segregate with the A4 amyloid gene in several European families. Nature 329: 153–155.
van den Bosch de Aguilar, P., Langhendries-Weverberg, C., Goemaere-Vanneste, J., Flament-Durand, J., Brion, J. P. and Couck, A. M. (1984) Transplantation of human cortex with Alzheimer's disease into rat occipital cortex: a model for the study of Alzheimer's disease. Experientia, 40, 402–403.
Vanderwolf, C. H. (1987) Near-total loss of 'learning' and 'memory' as a result of combined cholinergic and serotonergic blockade in the rat. Behav. Brain Res. 23: 43–57.
Vaughan, D. W. and Peters, A. (1981) The structure of neuritic plaques in the cerebral cortex of aged rats. J. Neuropathol. exp. Neurol. 40: 472–487.
Wallace, J. E., Krauter, E. E. and Campbell, B. A. (1980) Motor and reflexive behavior in the aging rat. J. Gerontol. 35: 364–370.
Welner, S. A., Dunnett, S. B., Salamone, J. D., MacLean, B. and Iversen, S. D. (1988) Transplantation of embryonic ventral forebrain grafts to the neocortex of rats with bilateral lesions of nucleus basalis magnocellularis ameliorates a lesion-induced deficit in spatial memory. Brain Res. 463: 192–197.
Watts, R. L., Bakay, R. A. E., Herring, C. J., Sweeney, K. M., Colbassani, H. J., Mandir, A., Byrd, L. D. and Iuvone, P. M. (1990) Preliminary report on adrenal medullary grafting and co-grafting with sural nerve in the treatment of hemiparkinson monkeys. Prog. Brain Res. 82: 581–591.
Wenk, G. L. and Olton, D. S. (1987) Basal forebrain cholinergic neurons and Alzheimer's disease. In: Coyle, J. T. Animal Models of Dementia pp. 81–101. Alan R. Liss, New York.
Wenk, G. L., Markowska, A. L. and Olton, D. S. (1989) Basal forebrain lesions and memory: alterations in neurotensin, not acetylcholine, may cause amnesia. Behav. Neurosci. 103: 765–769.
Whishaw, I. Q., O'Connor, W. T. and Dunnett, S. B. (1985) Disruption of central cholinergic systems in the rat by basal forebrain lesions or atropine: effects on feeding, sensorimotor behaviour, locomotor activity and spatial navigation. Behav. Brain Res. 17: 103–115.
Whitehouse, P. J., Price, D. L., Struble, R. G., Clark, A. W., Coyle, J. T. and DeLong, M. R. (1982) Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science 215: 1237–1239.
Will, B. and Hefti, F. (1985) Behavioral and neurochemical effects of chronic intraventricular injections of nerve growth factor in adult rats with fimbria lesions. Behav. Brain Res. 17: 17–24.
Williams, L. R., Varon, S., Peterson, G. M., Wictorin, K., Fischer, W., Björklund, A. and Gage, F. H. (1986) Continuous infusion of nerve growth factor prevents basal forebrain neuronal death after fimbria fornix transection.

Proc. Natl. Acad. Sci. USA 83: 9231–9235.

Williams, R. S. and Matthysse, S. (1986) Age-related changes in Down syndrome brain and the cellular pathology of Alzheimer disease. Prog. Brain Res. 70: 49–66.

Wischik, C. M., Novak, M., Thorensen, H. C., Edwards, P. C., Runswick, M. J., Jakes, R., Walker, J. E., Milstein, C., Roth, M. and Klug, A. (1988) Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 85: 4506–4510.

Wisniewski, H. M., Terry, R. D. and Hirano, A. (1970) Neurofibrillary pathology. J. Neuropathol. exp. Neurol. 29: 163–176.

Wisniewski, H. M., Ghetti, B. and Terry, R. D. (1973) Neuritic (senile) plaques and filamentous changes in aged rhesus monkeys. J. Neuropathol. exp. Neurol. 32: 566–584.

Woodruff, M. L., Baisden, R. H., Whittington, D. L. and Benson, A. E. (1987) Embryonic hippocampal grafts ameliorate the deficit in DRL acquisition produced by hippocampectomy. Brain Res. 408: 97–117.

Woodruff, M. L., Baisden, R. H. and Nonneman, A. J. (1990) Transplantation of fetal hippocampus may prevent or produce behavioral recovery from hippocampal ablation and recovery persists after removal of the transplant. Prog. Brain Res. 82: 367–376.

Yamamoto, T. and Hirano, A. (1985) Nucleus raphe dorsalis in Alzheimer's disease: neurofibrillary tangles and loss of large neurons. Ann. Neurol. 17: 573–577.

Zornetzer, S. F. (1985) Catecholaminergic involvement in age-related memory dysfunction. Ann. N.Y. Acad. Sci. 444: 242–254.