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MECHANISMS OF FUNCTION OF NEURAL GRAFTS IN THE ADULT MAMMALIAN BRAIN

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SUMMARY

Evidence for the survival, growth and function of grafted neural tissues in the adult mammalian brain is reviewed. In addition to considering the viability of grafts in the different model systems that have been investigated, consideration is given to alternative mechanisms by which the grafts might exert a functional influence over the host brain and the host animal's behaviour: (a) acute influence over spontaneous recovery of function, (b) chronic but diffuse secretion of neurochemicals into the host neuropile, (c) tonic reinnervation of the host brain, (d) bridging grafts, and (e) reciprocal reinnervation and full incorporation of graft tissue into host circuitry. It is concluded that no one mechanism is primary, but that different levels of reorganization can take place in different graft paradigms and neural systems.

INTRODUCTION

> 'I think the main fact of this experiment – namely, that brain tissue has sufficient vitality to survive for seven weeks the operation of transplantation without wholly losing its identity as brain substance – suggests an interesting field for further research, and I have no doubt that other experimenters will be rewarded by investigating it.'
>
> (W. G. Thompson, 1890, p. 702)

> 'Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centres, the nerve paths are something fixed and immutable; everything may die, nothing may be regenerated.'
>
> (Santiago Ramon y Cajal, 1928, p. 750)

> 'The existence of human brain in lower animals also excites speculation from a purely philosophical standpoint. On the assumption that the human brain is the seat of the intellect, some alteration might be expected in the behavior of guinea pigs bearing such transplants. However, observation has shown no change suggestive

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> of higher faculties. In fact, the only variation differentiating a guinea pig bearing a human brain from a normal pig is a marked increase in libido.'
>
> (H. S. N. Greene & H. Arnold, 1945, p. 328)

These three quotations characterize several different perspectives of neural transplantation since the first investigations of the subject. The initial fascination raised by the possibility of grafting brain tissue between individuals, and the ultimate prospect of reconstructing brain damage, has been tempered by caution and scepticism from some observers, and with wild and fantastic speculation from some others. In the last decade it has become apparent from the work of several laboratories that grafted neural tissues can indeed have reliable functional effects that are beneficial to the host animal. In providing a brief review of this recent literature, we wish to suggest a framework within which the functional effects of different graft procedures can be assessed in terms of the mechanisms by which they exert their functional effects, in addition to describing a selection of the different model systems that have been investigated.

GRAFT SURVIVAL IN THE BRAIN

The study by Thompson (1890) cited above is the earliest attempt known to us of neural grafting in the brain, and is remarkable for the apparent demonstration of the viability of cortical tissue taken from a cat and implanted in the brain of a dog. Although these surviving grafts were probably made up of non-neuronal elements, Thompson foresaw the interest and applications that might arise from the successful grafting of neural tissues in the brain. Subsequent studies in the following 80 years (reviewed by Björklund & Stenevi, 1985, see Table 1) were more notable for only very infrequent success, and more generally the failure of the large majority of grafts. Nevertheless, in view of the periodic reports of successful results, it is surprising that the field was not more actively pursued. This is probably because the prevailing view throughout the first half of the present century was, as most cogently argued by Cajal (1928), that regeneration and growth simply do not take place in the adult mammalian brain. Consequently, reports of viable neural transplantation were received with scepticism or simply ignored.

It was only in the late 1960s that the dictum regarding the absence of regeneration of central nervous tissues was effectively challenged (see Finger & Stein, 1982, for a review). Thus, for example, Raisman (1969) provided the first electron microscopic demonstration of collateral sprouting of axon terminals in the partially deafferented septum. This encouraged a reconsideration of the regenerative capacity of nervous tissues, and led to several groups employing neural tissue grafts to manipulate experimentally source and target populations of neurones in the development (Das & Altman, 1971; Lund & Hauschka, 1976) and regeneration (Björklund & Stenevi 1971) of axonal connections in the brain and in the anterior chamber of the eye (Olson & Malmfors, 1970).

Of key importance in sustaining the renewed interest in neural transplantation was the identification and characterization of the conditions for reliable graft survival and growth. These were most explicitly formulated in a series of studies by Stenevi, Björklund & Svendgaard (1976). Catecholamine (CA) histofluorescence was used to visualize the survival and growth of different populations of CA-rich donor tissues in different sites in the adult brain. Three factors of critical importance for graft survival were identified or confirmed, as follows.

First, whereas peripheral nervous tissues will survive transplantation from adult donors, central tissue is only viable from immature (and usually embryonic) donors. In fact there appears to be a limited developmental time window during which graft tissue should be taken. This window may only be of 1–2 days duration and differs for each population of neurones to be grafted (Seiger, 1985). For each population of cells, the critical time window appears to correspond to the end of mitosis, when the phenotype is determined and the rate of neurite outgrowth is maximal. The ability of embryonic cells to withstand prolonged periods of anoxia, and the greater damage to the axonal and dendritic fibre plexus necessarily sustained by dissection of mature neurones, may additionally contribute to the importance of taking donor tissue early in development.

Second, it is necessary to select a transplantation site in the host brain that is richly vascularized and so can provide support and rapid incorporation of the newly grafted tissue into the host blood and cerebrospinal fluid circulation. The pia in the choroidal fissure, the choroid plexus in the brain ventricles, or the iris in the anterior eye

Table 1. *Early history of neural grafting in the mammalian central nervous system*

1890	W. G. Thompson	New York, USA	First attempt to graft adult CNS tissue to the brain
1898	J. Forssman	Lund, Sweden	First report of neurotrophic effects of grafted tissue
1907	G. Del Conte	Naples, Italy	First attempt to graft embryonic tissues to the brain
1909	W. Ranson	Chicago, USA	First successful grafting of spinal ganglia to the brain
1911	F. Tello	Madrid, Spain	First successful grafting of peripheral nerve to the brain
1917	E. Dunn	Chicago, USA	First successful grafting of neonatal CNS to the brain
1921	Y. Shirai	Tokyo, Japan	First demonstration of brain as an immunologically privileged site
1924	G. Faldino	Pisa, Italy	First successful grafting of foetal CNS to the anterior eye chamber
1940	W. E. LeGros Clark	Oxford, UK	First successful grafting of foetal CNS to the neonatal brain
1957	B. Flerko & J. Szentagothai	Pecs, Hungary	First successful intraventricular grafting of endocrine tissue
1970 and 1971	Olson & Seiger, Das & Altman and Björklund & Stenevi		First reports of conditions for reliable transplantation to the brain and anterior eye chamber

Taken from Björklund & Stenevi (1985).

chamber all provide natural sites that fulfil this condition. Alternatively, artificial vascular sites can be surgically created. In the early studies, Stenevi *et al.* (1976) made a 'vascular bridge' of an iris graft, which itself becomes vascularized when placed at one end adjacent to the choroidal pia, and can then serve as a bed for a subsequent neural graft in other adjacent sites in the host brain. A graft which is placed directly into a cortical cavity does not survive, because of the lack of an adequate blood supply. However, as an alternative to the vascular bridge, Stenevi, Björklund & Dunnett (1980) found that if the cavity is filled with gel foam and left for 3–6 weeks, a new pial lining reforms over the floor and walls of the cavity and does provide a suitable bed for transplantation. Most recently, it has become apparent that pieces of tissue, when inserted either as small minced pieces or as a dissociated cell suspension, can survive transplantation directly into the brain parenchyma (Björklund, Schmidt & Stenevi, 1980*b*). The advantage of such suspension grafts is that they can be implanted into any site within the host brain with stereotaxic accuracy, in multiple placements if required, and with less trauma to the host than is generally obtained with grafts of whole pieces of tissue.

Third, immunological factors have turned out to be less important in the brain than might be expected from experience of transplantation in other organs of the body. The brain has long been considered to be 'immunologically privileged', and rejection of graft tissue has not been a problem in studies using outbred strains of rats or mice. Indeed, several studies have reported at least limited graft survival even when transplanting between different species (Björklund, Stenevi, Dunnett & Gage, 1982; Low, Lewis & Bunch, 1983), although good survival of xenografts is only achieved when made in combination with immunosuppressive treatment (Brundin, Nilsson, Gage & Björklund, 1985). Stenevi *et al.* (1976) noted, when working with donor and host animals of the same strain, that graft failure was more likely to be attributable to infections and other damage sustained during surgery than to immunological reaction. They therefore recommended that grafting should be conducted under aseptic conditions, which is generally not necessary for other types of brain surgery in rodents. Nevertheless, the immunological privilege is only partial, and recent studies are beginning to disentangle the relative contributions of the afferent and efferent limbs of the immune response in the protection of tissue in the brain from rejection (Mason *et al.* 1986).

GRAFT GROWTH IN THE BRAIN

In the lesioned brain

The majority of studies of neural transplantation in the adult brain have been conducted in animals with lesions in various intrinsic neuroanatomical systems, whether the focus has been on factors guiding regeneration or on the possibility of reconstructing damaged circuits following injury. The system which has received most extensive investigation in this regard is the graft-derived reinnervation of the hippocampus following disruption of its various afferents. The laminar structure of the dentate gyrus and hippocampus proper provide an internal organization against

which the regularity of new axonal ingrowth from grafts can be clearly assessed at the light microscopic level.

Monoaminergic and cholinergic fibres arising from subcortical cell groups innervate the dorsal hippocampus *via* projections passing through the fimbria–fornix and the supracallosal stria. These inputs can be quantified by biochemical assays of noradrenaline (NA), serotonin (5-HT) or the cholinergic synthetic enzyme choline acetyl transferase (ChAT), and visualized by histochemical staining by the formaldehyde histofluorescence reaction for monoamines, by one of the classical acetylcholinesterase (AChE) procedures which is relatively selective for the distribution of cholinergic terminals in the hippocampus, or by more recent immunocytochemical procedures using antibodies raised against 5-HT, ChAT or the noradrenergic synthetic enzyme dopamine-B-hydroxylase. Aspirative or knife-cut transections of the fimbria–fornix, which also disrupt the supracallosal projections, then deafferent the hippocampus of these inputs. This results in a dramatic loss of histochemical staining of the different populations of subcortical innervation and a decline in measurements of the respective biochemical markers.

In their first studies, Björklund and co-workers studied the growth of monoaminergic and cholinergic fibres derived from grafted neurones back into the deafferented hippocampus (Björklund & Stenevi, 1977; Björklund, Stenevi & Svendgaard, 1976). Cholinergic cells for grafting were taken from the developing septal–diagonal band complex in the forebrain of 16- to 17-day-old rat embryos, noradrenergic cells were taken from the developing locus coeruleus region of the dorsal pons, and the developing midline pontine and mesencephalic regions provided raphe serotonin cells. In these early studies the tissue was grafted as solid pieces to aspirative cavities adjacent to the hippocampus and exposing the choroidal fissure – either the same cavity as provided by the aspirative transection of the fimbria–fornix, or a specially prepared retrosplenial cavity caudomedial to the host hippocampus and overlying the superior colliculus. The graft tissue survived well in both of these sites, and in each case gave rise to an extensive innervation of large parts of the host hippocampus. Of particular interest, however, was the observation that the pattern of reinnervation differed markedly between different populations of grafted neurones, irrespective of which site they were transplanted to. Thus the noradrenergic fibres from locus coeruleus grafts grew extensively into those areas that normally receive a rich noradrenergic innervation in the intact brain, such as the hilar zone of the dentate gyrus (Björklund *et al.* 1976). By contrast, septal grafts provide a dense AChE-positive fibre innervation of the hilus and supragranular zones in the dentate gyrus and of the supra- and infrapyramidal zones and the stratum lacunosum moleculare in the CA1 and CA3 fields of the hippocampus, which are the regions most densely innervated by the normal cholinergic afferents in the intact hippocampus (Björklund & Stenevi, 1977). Thus, even though the host hippocampus has been deafferented of several different inputs, axons from each population of grafted cells grow back to reinnervate the zone that is appropriate for the particular population. Moreover, although axons growing into the denervated hippocampus from a graft placement in the fimbria–fornix have the possibility of following a normal route, the

similar pattern of reinnervation from fibres entering in the opposite direction from a retrosplenial site suggests that specific diffusible rather than mechanical factors guide the direction of axonal growth.

It is becoming clear that a variety of different mechanisms regulate the extent and direction of axonal ingrowth from grafts following lesions. For example, Björklund & Stenevi (1981) found that some consequence of the fimbria–fornix lesion, possibly the cholinergic deafferentation, has an important influence on the growth potential of ingrowing noradrenergic fibres. Noradrenergic grafts, whether of central (locus) or peripheral (sympathetic) origin, show only limited ingrowth to the hippocampus if placed in a retrosplenial cavity when the fimbria–fornix is intact. This is not simply because the intrinsic noradrenergic innervation is intact, since only limited ingrowth is seen following selective noradrenergic deafferentation with the neurotoxin 6-hydroxydopamine (6-OHDA). Only when the cholinergic afferents are also lesioned does extensive noradrenergic innervation result. This suggests that different factors are responsible for the general promotion of growth and the guidance of ingrowing noradrenergic fibres.

The identity and functional role of growth and trophic factors in maintaining the survival, stimulating and guiding the growth of both intrinsic and grafted neurones is currently an area of active research. Thus, nerve growth factor (NGF) itself, although it appears to have little influence on promoting the survival and growth of grafted catecholaminergic neurones (Olson & Seiger, 1976), may play a role in stimulating the growth of central noradrenergic neurones into grafts of other tissues (Bjerre, Björklund & Stenevi, 1973). NGF may also be important in promoting the survival of damaged central cholinergic neurones (Hefti, 1986; Williams *et al.* 1987) and appears to influence the metabolic activity, even if not the extent of growth, in cholinergic grafts (Toniolo, Dunnett, Hefti & Will, 1985). Recently, Cotman and co-workers have found that extracts derived from wounds in the brain can promote the survival and growth of grafted striatal cholinergic neurones in the hippocampus (Nieto-Sampedro *et al.* 1984), although the identity of the active component in these extracts has not yet been determined.

Although the hippocampus has provided the model system for the most extensive analysis of factors regulating the extent and patterning of growth from neural grafts, several other neural systems have been studied, often with a different focus, but from which other general principles have been discerned. One such system, that has been considered more extensively from a functional perspective, is the dopaminergic innervation of the striatum which is involved in the regulation of motor control. In these studies, dopamine neurones from the embryonic ventral mesencephalon have been grafted to the dopamine-denervated striatum to provide a dopaminergic reinnervation of the host brain. Solid mesencephalic grafts placed in a cavity in the dorsal parietal cortex showed very little ingrowth into adjacent cortical areas, in contrast to the extensive fibre growth into the striatum (Björklund *et al.* 1980*a*). Similarly, suspension grafts that fell on the borders of the striatum and the neocortex or globus pallidus provided an extensive ingrowth into the denervated striatum but only very limited growth into the other non-target structures (Björklund *et al.* 1983).

Moreover, whereas dopamine fibres might grow up to 3–4 mm into the host striatum, a graft that falls more than 200–500 μm outside the striatum shows very little fibre growth beyond the graft border and no directed growth towards a distant target. This suggests that the factors that generally promote growth and guidance of grafted neurones are relatively local in their influence and do not diffuse great distances, although wound-derived survival factors may exert an influence over greater distances (Manthorpe *et al.* 1983).

It might nevertheless be possible artificially to supply growth factors or alternative substrates for axonal growth to enable graft connections to be made over longer distances. Thus, Aguayo, Björklund, Stenevi & Carlstedt (1984) have used peripheral nerve bridges to link dopaminergic grafts placed in the mesencephalon with the denervated striatum. This provides a growth-promoting substrate along which dopamine fibres elongate from the grafts to grow the full length of the sciatic nerve bridge and to sprout from the far end into the striatal target.

The importance of graft–target proximity is not yet clear, however, and there exist a number of examples where the reinnervation of distant targets does appear to be possible. Thus, whereas dopamine grafts placed into the region of the substantia nigra do not appear to have the spontaneous capacity to regenerate new connections to distant striatal targets, grafts of striatal neurones implanted into the striatum that has been denervated of intrinsic neurones by injections of a neurotoxic amino acid (such as kainic acid or ibotenic acid) develop a 'striosomal' internal organization (Isacson *et al.* 1987), and develop efferent projections not only to adjacent pallidal targets but also in some animals to reach the pars reticulata of the substantia nigra (Pritzel *et al.* 1986).

Although there have been several ultrastructural studies of internal graft organization (Alvarado-Mallart & Sotelo, 1982; Jaeger, 1985; Strömberg *et al.* 1985), and of the graft–host interface (Krüger *et al.* 1986), only recently have the efferent connections of grafts in adult recipients been investigated electron microscopically. For example, the axonal outgrowth from dopamine-rich grafts into the denervated neostriatum makes synaptic connections at appropriate sites on the shafts and necks of spines of medium spiny striatal neurones (Freund *et al.* 1985; Mahalik, Finger, Strömberg & Olson, 1985). However, in addition to these normal sites of connectivity, Freund *et al.* (1985) found that the grafts also made a set of quite aberrant connections onto giant aspiny (presumed cholinergic) interneurones of the host striatum. Similarly, cholinergic fibre outgrowth from septal grafts makes morphologically normal synaptic connections onto the dendrites of cortical and hippocampal pyramidal neurones, (Anderson, Gibbs, Salvaterra & Cotman, 1986; Clarke & Dunnett, 1986; Clarke, Gage & Björklund, 1986), whereas both studies by Clarke and colleagues indicate that there is an abnormally high density of axosomatic as opposed to axodendritic contacts. The similarity of the patterns of normal and abnormal connections in these quite different systems is striking, and although the aberrant connections have interesting functional implications (for discussion see Clarke & Dunnett, 1986; Freund *et al.* 1985), the mechanisms determining patterns of abnormal connectivity are completely unknown.

In the intact brain

The effects of grafts implanted into otherwise intact animals have been extensively studied in the developing nervous system (see for example Lund, 1980; Lund, Harvey, Jaeger & McLoon, 1982), and in the anterior eye chamber as a model transplantation site (see Olson, Björklund & Hoffer, 1984). However, in contrast to the studies of grafting in the lesioned brain, the literature on grafting in the intact adult central nervous system (CNS) is relatively sparse. This is in part because most experiments based on transplantation of solid pieces of embryonic graft tissue have used lesion cavities as an essential component of the procedure. Thus, for example, the retrosplenial cavity used by Björklund *et al.* (1976) itself damaged the perforant path afferents to the hippocampus. Even grafted cells that do not normally innervate the hippocampus, such as the nigral dopamine neurones, nevertheless gave rise to limited non-specific ingrowth into the outer molecular layer of the dentate gyrus which is the normal terminal zone for perforant path afferents. Additionally, of course, the rationale for many studies on grafting in the adult CNS has been with a focus on the possibilities for neural reconstruction following brain damage.

However, to consider the effects of the insertion of graft tissue into the otherwise intact brain, implantation into one of the brain ventricles and, more recently, injection of cell suspensions, can be conducted with minimal additional disruption of brain circuitry. For example, Rosenstein & Brightman (1984) have used the fourth ventricle as a transplantation site explicitly to study the interactions between grafts and an otherwise intact brain. In grafts of superior cervical ganglion to the ventricle, only very few of the ganglionic neurones survive when the host brain is otherwise intact. However, bilateral sympathectomy resulted in a seven-fold promotion of neuronal survival. This was attributed to the provision of denervated targets in the pial and choroidal vessels for the ganglionic neurones to make new contacts with, and necessary for their survival. By contrast, in other studies of embryonic hypothalamic tissue placed into the lateral ventricle of normal rats, Coates & Strahlendorf (1983) report not only good survival of the grafts attached to the ependymal lining of the ventricles, but also the penetration of fibres across the border connecting the grafts with the host brain. Thus it appears that explicit lesions are not necessary for survival of central neurones grafted into the ventricles, and this is further illustrated in the studies of grafts in the brains of mutant or aged rodents (see below).

A similar situation has been found with suspension grafts of brain tissue directly into host parenchyma. Thus, in an early report of this technique, Schmidt, Björklund & Stenevi (1981) implanted dopamine neurones into the intact striatum, only lesioning the intrinsic dopamine system just prior to the host animal's death in order to reveal the graft-derived fibre outgrowth. Although the extent of fibre outgrowth was not as great as that seen in subsequent studies when the implant was placed into the denervated striatum (Björklund *et al.* 1983), the survival of the grafts was comparable.

An explicit comparison of the survival and growth of cholinergic septal neurones in suspension grafts placed into the intact or deafferented hippocampus has recently

been conducted by Gage & Björklund (1986*b*). Grafts in the hippocampus deafferented by a fimbria–fornix lesion grew to about twice the size and contained more surviving cholinergic neurones than when placed into the intact hippocampus. Moreover, ChAT activity in the hippocampus was approximately three times higher in the animals with a previous denervating lesion. This may also suggest a more extensive ingrowth into the host brain, although the assay data do not separate ChAT activity in the graft itself from that attributable to axonal ingrowth into the host brain.

In the mutant brain

In recent years several research groups have utilized the advantages of mutant strains of rats or mice to provide a more complete and consistent degeneration of identified neuronal populations or neurotransmitter type than can be produced by explicit lesions.

The first mutant strain to be studied as a model for neural transplantation was the Brattleboro rat, in which a single base deletion in the gene encoding vasopressin neurophysin results in a failure of the antidiuretic control of vasopressin neurones in the hypothalamus over urine concentration and excretion. Gash & Sladek (1980) and Sladek & Gash (1984) grafted the anterior hypothalamic area taken from normal embryos into the third ventricle of Brattleboro rats. The grafts survived well, and frequently became attached to the walls of the ventricle, in particular at the ventral surface with the median eminence. The grafts were seen to become extensively revascularized by the host circulatory system, magnocellular neurones in the grafts often lined up alongside these blood vessels, and much of the capillary network in the graft was fenestrated (Scott & Sherman, 1984). Additionally, neurophysin-positive neurones in the grafts were seen to project into the median eminence of the host brain, although this antibody identifies oxytocin as well as vasopressin cells. Thus any functional effects of the grafts could be mediated by specialized neurovascular connections either in the grafts or in the host median eminence.

A similar pattern of reorganization has been seen in the hypogonadal (HPG) mouse by Krieger *et al.* (1982, 1985). In this mutant strain, there is a deficiency in gonadotropin-releasing hormone (GnRH), resulting in a dramatic decrease in pituitary and plasma levels of gonadotropin, a failure of development of the external genitalia, and infertility. Grafts of preoptic area of the hypothalamus of normal mice to the third ventricle of HPG mice, show good survival and attachment to the floor of the ventricle. Moreover, GnRH-positive cells in the grafts give rise to fibres growing out to the zona externa of the host median eminence. The grafted HPG mice not only showed an increase in brain GnRH concentration, but also a return of circulating gonadotropin and development of the sex organs in both male and female hosts.

A third example of the use of mutant strains for grafting is the elegant series of studies by Sotelo & Alvarado-Mallart (1986) in mice with heterodegenerative ataxia, attributable to degeneration of cerebellar Purkinje cells in early life (the PCD mutation). Suspension grafts of normal embryonic cerebellum were implanted into the cerebella of adult PCD mice, where cell survival and development could be

monitored with a specific antibody raised against Purkinje cells. Not only did the grafted cells survive, but they also migrated away from the graft site to become re-established in the molecular layer of the host cerebellum, where they developed flattened horizontal dendritic trees oriented perpendicular to bundles of parallel fibres. At the ultrastructural level, the graft-derived Purkinje cells received synaptic inputs from climbing fibres and parallel fibres at different (but appropriate) levels of the dendrites. These studies provide some of the best evidence for the capacity of grafted neurones, at least in certain particular model systems, to reform local connections with the host nervous system that are both precise and appropriate for the particular population of neurones.

In the aged brain

In the earlier studies characterizing the optimal conditions for graft survival, it was considered that the age of the donor was a key variable (see above, and Das, Hallas & Das, 1980). By contrast, whereas survival and growth is generally better in neonatal than in adult hosts (Björklund & Stenevi, 1985), the age of the host appears to be relatively unimportant at least in the young to mature-adult age range (Hallas, Das & Das, 1980). However, only recently has the viability of neural grafts in the aged brain been considered explicitly. In the first such study, Azmitia, Perlow, Brennan & Lauder (1981) observed that embryonic raphe grafts implanted into the intact hippocampus of young (4- to 6-month-old) and aged (24-month-old) mice survived, contained healthy 5-HT immunoreactive neurones, and gave rise to a hyperinnervation of the hippocampus, in hosts of either age group. Whereas the extent of the hyperinnervation was somewhat less in the aged than in the young brain, the appropriate laminar distribution of the reinnervation in the hippocampus was similar.

Gage, Björklund, Stenevi & Dunnett (1983*b*) have observed similar effects with dopamine grafts in the neostriatum and cholinergic septal grafts in the hippocampus of aged rats. In both cases, the grafts survived as well as in young rats, although the extent of fibre outgrowth was somewhat less than had been seen in young hosts. However, this comparison was not direct, since the grafts were implanted into otherwise intact aged hosts, whereas the comparison groups of young hosts received explicit deafferenting lesions prior to transplantation. A direct comparison with similarly treated young hosts suggests that the aged brain can not only sustain graft survival as well as the younger brain, but also provide an appropriate substrate for growth of the embryonic cells and fibres. In the studies of septal grafts in the aged hippocampus, however, it appeared that the laminar patterning of cholinergic terminals may be less precisely organized than in the young adult brain (Gage *et al.* 1983*b*). For example, the dense bands of AChE-positive staining above and below the pyramidal cell layer that are a feature of the normal innervation and are re-established by grafts in young rats appeared to be sparse or absent in the graft-derived innervation of the aged brain.

In these studies, the process of ageing has been considered as providing an implicit lesion (Gage *et al.* 1983*a*), and so the extent and patterning of graft growth will very

much depend on the particular profile of neuroanatomical and neurochemical decline in the individual hosts. However, this cannot account for all differences. A greater variability in graft survival and growth was seen by Gash, Collier & Sladek (1985) when grafting hypothalamic tissue to the third ventricle of young, middle-aged and aged Brattleboro rats. Although some grafts in aged animals were large, healthy and contained many neurophysin-positive magnocellular cells, it was more common to find grafts containing only small neurones which were all neurophysin-negative, and the outgrowth from the remainder was generally sparser than in young or middle-aged hosts. None of the hosts in any age group had received explicit lesions, and so the poorer survival, differentiation and axonal outgrowth of the grafts in the aged brain probably reflect as yet unidentified differences in the trophic and growth-sustaining influences of the host brain over the grafted tissue.

GRAFT FUNCTION IN THE BRAIN

The earliest report of the functional effects of neural grafts was that by Greene & Arnold (1945, as cited in the Introduction). Both human foetal tissue and human glioblastoma cells survived grafting to guinea-pigs, and purportedly stimulated the sexual propensities of the recipients. The means by which the grafts might have had such a stimulatory effect is not clear from their report, although the results are unlikely to be attributable to any direct neural influence since the implants were placed in the anterior eye chamber.

A second, early line of functional research involved the neuroendocrine transplantation studies to the third ventricle of hypophysectomized rats by Halasz, Pupp, Uhlarik & Tima (1963, 1965). Grafted pituitary cells were seen to develop normal hormone secretion only if they were placed in contact with the 'hypophysiotrophic area' of the mediobasal hypothalamus. In such a position, the grafts were seen to compensate several of the neuroendocrine deficiencies induced by hypophysectomy in the host rats.

These early studies were sporadic and did not attract great attention in their time. However, since the conditions for reliable graft survival were outlined in the early 1970s, there has been increasing interest in a systematic study of the functional effects of neural grafts in the adult mammalian brain.

One might address the functional capacity of transplanted neural tissues in terms of different levels of analysis: molecular, biochemical, electrophysiological or behavioural. However, in order to organize the recent proliferation of data on this topic, we will instead describe several model systems in which transplant function has been studied, each at a number of different levels of analysis.

Hippocampal reinnervation

Some of the first systematic attempts to analyse functional influences of transplanted tissues on the host brain were a series of electrophysiological studies by Segal, Björklund and Stenevi. Segal & Bloom (1974) had previously determined that intrinsic noradrenergic neurones of the locus coeruleus exert an inhibitory influence

on spontaneous cellular activity in the hippocampus. Björklund, Segal & Stenevi (1979) then investigated whether a similar influence is exerted by the noradrenergic reinnervation of deafferented hippocampus from locus grafts. Cells in the grafts were seen to be spontaneously active and increased their firing rates in response to ionophoretic application of aspartate. Moreover 20 out of 29 spontaneously active hippocampal cells were inhibited by stimulation of the grafts, similar to the inhibition induced by locus stimulation in the intact animal. The noradrenergic nature of the inhibitory response was confirmed by demonstrating its blockade after administration of the beta-receptor antagonist propranolol.

Subsequent electrophysiological studies have given more attention to cholinergic grafts reinnervating the hippocampus. In the normal rat the cholinergic input from the septum is a driving component for the regulation of the hippocampal theta rhythm, the frequency of which is associated with distinct behavioural states. In anaesthetized animals, Low *et al.* (1982) found that stimulation of grafts that had reinnervated the hippocampus evoked a field response in dentate granule cells, and interacted with cortical inputs to potentiate the synchronous depolarization of granule cells induced by perforant path stimulation. In these studies, however, the abolition of theta rhythm induced by the lesions was not reinstated by the grafts, although rhythmic activity at a higher frequency than natural theta rhythm was seen. In a subsequent, more detailed analysis, Buzsaki, Gage, Czopf & Björklund (1987) have found that the theta rhythm in the normal 8 Hz band can be re-established in fimbria–fornix-lesioned animals with cholinergic grafts, but is only seen when the rats are locomoting, and not when still or engaged in stationary activities such as drinking. Moreover, in this study, the theta rhythms in the two hippocampi were found to be synchronous, which suggests that the grafts themselves were under host control rather than independently driving the reinnervated hippocampus. Since a few animals with control grafts of hippocampal tissue also manifested restoration of theta rhythm, it could be that, rather than providing a primary source of regulatory cholinergic innervation, in this study the grafts were serving to provide a bridge for regrowth of intrinsic host septal neurones into the hippocampus, similar to that first demonstrated by Segal, Stenevi & Björklund (1981).

In parallel with the electrophysiological studies, there have been a number of attempts to investigate whether grafts of cholinergic, noradrenergic or serotonergic tissues might have the capacity to influence behavioural deficits induced by bilateral deafferentation of the hippocampus. Low *et al.* (1982) found that an impairment in learning to find food in the radial arm maze induced by fimbria–fornix lesions was improved by cholinergic grafts to the hippocampus, but only when performance was potentiated by low doses of physostigmine.

Clearer results were obtained in a subsequent study in a T-maze alternation task (Dunnett *et al.* 1982*b*) in which the performance of control and lesion rats was less variable within each group and revealed much more consistent lesion-induced impairments between groups. Cholinergic grafts in the hippocampus, whether made by the solid or the suspension method, provided a highly significant amelioration of the lesion deficit in task learning (whereas noradrenergic grafts were without effect),

and the recovery of individual animals was well-correlated with the extent of acetylcholinesterase-positive fibre ingrowth into the deafferented hippocampus. Subsequent tests of the same animals showed that although the noradrenergic grafts were without effect on this learning task, they did reduce the lesion-induced hyperactivity which was, in turn, not influenced by either type of cholinergic graft (Dunnett *et al.* 1982*a*).

There are now a number of studies confirming these initial results in several different maze tasks. Thus cholinergic grafts reinnervating the hippocampus have been seen to ameliorate lesion-induced deficits in radial mazes (Pallage, Toniolo, Will & Hefti, 1986), T-mazes (Daniloff, Bodony, Low & Wells, 1985) and the Morris swimming maze (Dunnett *et al.* 1982*a*; Nilsson, Shapiro, Gage & Björklund, 1985; Segal, Greenberger & Milgam, 1987). Even more dramatically, there have been two reports that replacement of the aspirated hippocampus itself by grafts of embryonic hippocampus may at least partially ameliorate some of the rats' maze-learning deficits (Kimble, Bremiller & Stickrod, 1986; Woodruff, Baisden, Whittington & Benson, 1987). This suggests a degree of functional incorporation of the grafts into the host circuitry beyond the provision of a diffuse afferent input to an otherwise intact circuitry that might be sufficient to account for the functional effects of noradrenergic and cholinergic grafts. However, resolution of this issue must await a more extensive evaluation of the internal organization and afferent and efferent connections of hippocampal tissue grafts than is presently available.

The nigrostriatal model

Whereas the hippocampal system, with its precise laminar organization, provides an ideal site for anatomical and electrophysiological studies of grafts, the behavioural tests necessary to reveal hippocampal dysfunction all require extensive training. By contrast, the dopaminergic nigrostriatal system is ideally suited for behavioural studies since there exists the neurotoxin 6-hydroxydopamine for its selective destruction, and the behavioural *sequelae* of such lesions are dramatic and simple to assess. Unilateral nigrostriatal lesions produce a sensorimotor asymmetry characterized by spontaneous postural bias to the ipsilateral side and neglect of contralateral space and the contralateral side of the body. Activation of the rats with the dopaminergic stimulant drug amphetamine then produces a marked ipsilateral motor asymmetry in which the animals turn in head-to-tail circles ('rotation') at a rate of 10–20 turns min^{-1} for the 3–4 h duration of drug action. By contrast, a dopamine receptor agonist such as apomorphine induces a similar rate of turning, but in the contralateral direction due to the drug's preferential activation of supersensitive receptors on the lesioned side.

In 1979, two groups independently used the nigrostriatal model to provide the first demonstrations that neural grafts can ameliorate the behavioural effects of brain damage in adult mammals. Perlow *et al.* (1979) showed that dopamine-rich nigral grafts placed into the ventricles of rats with unilateral 6-OHDA lesions can reduce the rats' apomorphine-induced turning asymmetries by approximately 40%, and Björklund & Stenevi (1979) found that similar grafts placed in a cortical cavity

overlying the dorsal striatum could provide a complete compensation of the amphetamine-induced turning. These observations have subsequently been replicated many times (e.g. Freed, 1983; Freed *et al.* 1980; Dunnett, Björklund, Stenevi & Iversen, 1981*a*; Dunnett *et al.* 1983*a*). Drug-induced rotation has been found to correlate well with biochemical measures of the extent of dopamine depletions induced by the lesions and with the extent of graft-derived dopamine fibre reinnervation of the host striatum (Björklund *et al.* 1980*a*; Schmidt *et al.* 1982, 1983), and so provides a reliable means of screening lesions and grafts prior to more detailed functional analyses.

Nigrostriatal lesions, in fact, induce a wide syndrome of impairments and subsequent studies have investigated which are amenable to graft-derived amelioration. Among the spontaneous deficits, spontaneous and tail-pinch rotation, side bias in maze exploration, contralateral sensory neglect, and the akinesia induced by bilateral lesions can all be reversed by nigral grafts (Dunnett *et al.* 1981*a*,*b*, 1983*a*). Also the deficits in some learning tasks dependent upon nigrostriatal integrity, such as conditioned rotation or intracranial self-stimulation, are also reduced by the grafts (Dunnett, Whishaw, Jones & Isacson, 1986; Fray *et al.* 1983).

In these cases, it has been found that graft placements are critical for their functional effects. It is necessary to place the graft into the specific forebrain terminal region that is responsible for the control of the particular behavioural function or task. Thus, rotational and motor asymmetries can be ameliorated by grafts positioned to reinnervate the dorsal neostriatum, the area which receives corticostriatal inputs from somatomotor cortex, whereas lateral neostriatal innervation is critical for recovery of sensory neglect, and reinnervation of the ventral striatum or nucleus accumbens for recovery from akinesia (Dunnett *et al.* 1981*b*, 1983*a*). Nigral grafts placed outside dopamine terminal fields, e.g. into the substantia nigra or the lateral hypothalamus, survive but are without any detectable functional effects (Björklund *et al.* 1983; Dunnett *et al.* 1983*a*).

There remain, however, a number of functional deficits which have not been successfully ameliorated by nigral grafts in single or multiple graft placements. These deficits include the aphagia and adipsia induced by bilateral nigrostriatal lesions (Dunnett *et al.* 1983*b*), disruption of motor coordination in a skilled paw-reaching task following unilateral nigrostriatal lesions (Dunnett, Whishaw, Rogers & Jones, 1987*b*), and the failure of normal hoarding behaviour following nucleus accumbens lesions (Herman *et al.* 1986). It seems likely that, whereas reinnervation of a deafferented terminal area is sufficient to restore functional control of some behaviours, others are dependent upon control of afferent information relayed *via* the substantia nigra which is not provided by ectopic grafts placed in striatal terminal areas.

In the case of the nigrostriatal system, the behavioural analysis has generally preceded electrophysiological and biochemical levels of assessment of graft function. Recently, Arbuthnott, Dunnett & MacLeod (1985) have identified, by antidromic activation, cells projecting from nigral grafts to innervate the host striatum. In rats in which the amphetamine rotation response was compensated, both dopamine-like and

nondopamine-like units were identified, whereas in uncompensated rats all units had spontaneous waveforms and conduction velocities of the latter type. Moreover, in this study, electrophysiological evidence was obtained of an afferent input to the grafts by orthodromic stimulation of locus coeruleus, raphe nucleus and neocortex, although these inputs have not yet been confirmed by anatomical tracing techniques.

Post mortem biochemical measurements have also been made of changes in dopaminergic synthesis and release from the grafts. As indicated above, the lesions induce extensive dopaminergic depletions (97 % or greater forebrain loss) which are substantially, but never completely, restored by the grafts (10–15 % by a single graft, but up to 50 % in some rats with multiple suspension graft deposits). The lesions induce a number of compensatory processes in residual dopamine neurones, which increase their rates of dopamine synthesis and turnover. Schmidt *et al.* (1982, 1983) have found that both solid and suspension nigral grafts restore synthesis and turnover rates to close to normal levels in the regenerating dopaminergic terminals, in parallel with the extent of regrowth of the new dopaminergic input of the host striatum. These biochemical changes were found to be accompanied by a return of metabolic activity, determined by the radioactive 2-deoxyglucose method, to normal levels in the reinnervated areas (Schmidt *et al.* 1981).

In parallel with these *post mortem* observations, Zetterström *et al.* (1986) and Strecker *et al.* (1987) have measured spontaneous release and metabolism of dopamine from nigral grafts by *in vivo* dialysis. Whereas in the lesioned striatum dopamine release was reduced by 95–98 %, this was restored to between 40 % and 100 % of normal levels in the vicinity of the grafts. Moreover, dopamine release was markedly stimulated by peripheral injection of amphetamine, and inhibited by apomorphine, in the grafted rats, proportional to the response in normal animals, whereas the drug had no effect on the rats with lesions alone.

These different studies, taken together, suggest that nigral grafts influence many of the behaviours disrupted by nigrostriatal lesions by means of reinnervation of the host brain with a new dopaminergic innervation, which is both spontaneously active and can be modulated either pharmacologically or under some afferent control from the host brain. As suggested above, it is likely that those behavioural measures which are not restored by the grafts are dependent upon some other classes of afferent control, presumably mediated *via* neural inputs to the substantia nigra, which do not gain access to the grafts in their ectopic location. Although this interpretation has not been confirmed, placement of the grafts into the region of the denervated nigra (where new afferent connections can be established from the host brain) in combination with procedures to stimulate the grafts to re-establish axonal connections with the distant striatum might resolve this issue. Aguayo *et al.* (1984) have recently demonstrated the feasibility of this approach by using sciatic nerve grafts to form a bridge between mesencephalic placements of nigral grafts and the host striatum. The peripheral nerve medium then supports extensive axonal elongation and dopaminergic reinnervation of the striatum, which can sustain partial compensation of amphetamine rotation (Gage *et al.* 1985), but the use of this surgical

procedure has not yet been examined on functional tests that have been resistant to single-graft approaches.

Neuroendocrine mutant models

The functional viability of neural grafts has been considered in mutant rodent strains as an alternative to making explicit lesions in the host animals. The first such report was that by Gash & Sladek (1980) to the effect that intraventricular hypothalamic grafts in Brattleboro rats, replacing the deficient population of vasopressin neurones, have the capacity to ameliorate the polyuria and polydipsia which is a key feature of homozygotes. Although these initial results generated a lot of interest, this particular model has proved hard to replicate. Subsequent studies suggest that when functional effects are obtained the grafts may be inducing host cells to synthesize vasopressin rather than acting by a mechanism of neuronal replacement (Richards, Morris & Raisman, 1985).

The hypogonadal model described earlier has proved more robust. GnRH release from cells in the graft is associated with a rise in plasma gonadotrophin and the reinstatement of gonadal development. Thus, ovarian and uterine weight in females, and testicular and seminal vesicle weight in males are increased substantially from the non-developed state of the homozygote (Gibson *et al.* 1984*a*; Krieger *et al.* 1982). The most dramatic features of the reinstatement of normal development were in fact seen in the female host mice in which vaginal opening and the return of pituitary FSH and plasma LH were accompanied by the return of normal sexual behaviour (Gibson *et al.* 1984*b*). Ten female rats were paired with stud males 10 weeks after transplantation and all were found to have vaginal plugs, indicative of successful copulation, seven became pregnant and six gave birth to live and healthy litters. Although the pregnancy failure rate is slightly higher than normal, the return of viable endocrine and behavioural sexual function in the majority of these hypogonadal mice provides a dramatic demonstration of the potential of neural grafts.

Models of ageing

The process of ageing includes a decline in the functional capacity of many different central neurotransmitter systems and the onset of a wide range of behavioural incapacities. As such, studies of neural transplants in aged animals have been considered within the context of their potential to overcome the consequences of implicit (in contrast to explicit, experimental) lesions (Gage *et al.* 1983*a*). Gage, Dunnett, Björklund & Stenevi (1983*c*) compared the effects of cholinergic grafts in the hippocampus and dopaminergic grafts in the neostriatum on aged rats' motor coordination abilities. The dopaminergic grafts were able substantially to compensate the age-related deficits in the animals' ability to balance and walk along narrow raised bridges. A nonspecific, activational interpretation of graft function was excluded in this study, since the same grafts had no effect on the aged rats' reduced locomotor activity or impaired muscle strength. In this study the cholinergic grafts had no effect on motor performance, but were effective, in subsequent studies, in

ameliorating spatial learning impairments of aged rats (Gage *et al.* 1984; Gage & Björklund, 1986*a*). In a related study, Collier, Gash, Bruemmer & Sladek (1985) have recently reported that noradrenergic grafts of embryonic locus coeruleus, implanted in the hippocampus of aged rats, also have the capacity to reduce rats' age-related impairments in passive avoidance tests of memory capacity.

There are now several studies, therefore, confirming that neural grafts can ameliorate aged animals' impairments in a range of behavioural functions, in the absence of explicit lesions. These observations provide an experimental, as opposed to simply correlational, basis for associating decline in particular central neurotransmitter systems with particular patterns of deficit in ageing. Specifically, it is apparent that in any particular test, such as the spatial navigation task employed by Gage *et al.* (1984) and Gage & Björklund (1986*a*), only a subset of the total population of aged animals manifest a decline in performance, and it is in these animals alone that grafts of the appropriate type ameliorate performance. By contrast, in as yet unpublished studies, we have seen that grafts into intact young animals or unimpaired aged rats have little functional benefit, and in particular do not provide 'supernormal' levels of performance.

Complex neural circuits

All of the model systems so far considered involve neural circuits that are relatively diffuse or regulatory in their normal function. Thus, grafts of hypothalamic tissues in mutant rats might restore neuroendocrine function by relatively nonspecific diffusion of the active neurohormones into host parenchyma followed by uptake into the host circulation. Nevertheless, the functional grafts are seen to establish an anatomical connectivity that exceeds such minimal expectation, peptidergic axons being seen to grow into host median eminence and re-establish specialized contact zones with fenestrated capillaries. Similarly, since some aspects of the dopamine-deficiency syndrome in rats can be reversed by the anti-Parkinsonian drug L-DOPA or by receptor agonists such as apomorphine (Ljungberg & Ungerstedt, 1976; Marshall & Gotthelf, 1979), dopamine-rich grafts might be functional simply by diffuse release of the neurotransmitter into the deafferented host neuropile. It appears that the functional effects of catecholamine-rich adrenal medulla tissues are indeed mediated by such a diffuse-release phenomenon. Nevertheless, the anatomical and electrophysiological observations on functional dopamine grafts suggest that embryonic dopamine neurones re-establish precise and appropriate connections with the host brain, which may be important for their efficacy.

It has therefore been of interest to consider whether neural grafts can have any functional effects following damage to neural systems that are more precisely arranged in a topographic, 'point-to-point' organization for the relay and transformation of specific patterned information.

In 1983, Labbe, Firl, Mufson & Stein reported that grafts of cortical tissue could restore rats' abilities, following prefrontal cortex lesions, to learn a complex maze task that involved alternating their responses to the two side-arms of the maze between each trial. This study generated considerable interest because it appeared to

suggest that the functional neocortex can be replaced by transplantation. However, the authors were cautious in their interpretation, particularly because the grafts were effective in reversing lesion-induced impairments within several days of surgery, whereas graft–host connections take several weeks to become established. Dunnett *et al.* (1987*a*) have therefore confirmed that recovery in maze-alternation can take place in this model system, but only if the lesion surgery, graft surgery and behavioural testing are conducted within a 2-week period. At longer times of graft survival the effect is no longer apparent and can, in certain circumstances, actually further impair the animals' maze learning abilities. This suggests that the acute functional benefit provided by cortical grafts implanted in animals with cortical damage is attributable to diffusible influences of the newly grafted embryonic tissue over the course of lesion development and recovery in the brain-damaged host, rather than to the incorporation of the grafts into the host neural circuitry. Direct support for this alternative interpretation is provided by Kesslak, Nieto-Sampedro, Globus & Cotman (1986) who found that the transfer of cultured astrocytes or wound-derived trophic factors in Gelfoam could have a similar beneficial effect, with similar time constraints, to that of grafted embryonic cortex.

However, recent experiments in another topographically organized system indicate that patterned functional connections can be restored by neural tissue implants. The whole cortical mantle projects in a topographic manner onto the neostriatum from where outputs converge, *via* the globus pallidus and the pars reticulata of the substantia nigra, on both the pyramidal and extrapyramidal motor systems. Deckel, Robinson, Coyle & Sanberg (1983) first showed that grafts of striatal primordium could restore normal levels of locomotor activation in hyperactive rats with neurotoxic striatal lesions. Such lesions also disrupt cognitive tasks, such as the maze-alternation abilities under prefrontal cortical control, described above. In two subsequent studies, these cognitive impairments in rats with striatal lesions have also been found to be ameliorated by striatal grafts (Deckel *et al.* 1986; Isacson, Dunnett & Björklund, 1986). Furthermore, the grafted striatal tissue is seen both anatomically and behaviourally to be subject to dopaminergic control from new afferent connections from the host nigrostriatal system (unpublished data), and perhaps to reform some efferent connections with the host globus pallidus and substantia nigra (Pritzel *et al.* 1986). Although the extent to which the functional recovery in this model system is dependent on particular aspects of the grafts' incorporation into the host circuitry has not yet been resolved, at present the striatal model is the system in which the functional regenerative capacity of neural grafts appears to be most pronounced.

SUMMARY OF MECHANISMS OF GRAFT FUNCTION

Seven years after the first suggestion that neural grafts might have a functionally beneficial effect on the host animal, a rapid expansion of research has established that such influences can indeed be reliably demonstrated. By what mechanism do the

grafts exert their functional effects? A number of answers, involving different levels of complexity of the graft into the host neural circuitry, have been suggested.

(1) Acute influence over recovery of function in the damaged host brain, by provision of neurotrophic and growth-promoting factors.

(2) Diffuse release of essential substances, neurohormones or neurotransmitters into the host neuropile or circulation.

(3) Reinnervation of the host brain by the graft, providing a tonic, diffuse and unregulated (or autoregulated) release of neurotransmitter, but at stable physiological levels.

(4) Bridging grafts, providing a medium through which damaged host neurones can reconnect with deafferented targets.

(5) Reciprocal reinnervation, whereby the grafted neurones reform both afferent and efferent connections with the host brain, and become incorporated within, and under the regulation of, the host neural circuitry.

Each of these levels of explanation can, of course, in turn involve varying degrees of complexity and completeness. Thus, for example, bridging grafts can at one extreme provide a conduit through which regrowth of central axons is promoted, and at the other extreme involve host afferents linking with interneurones in the grafts to make new connections with the hosts that becomes indistinguishable from the level of reciprocal reinnervation. Additionally connections between graft and host may be relatively complete or incomplete in the range of inputs received and output targets reinnervated, and the synaptic morphology and arrangement of new connections may be more or less precise and appropriate to the normal organization.

The discussion of different models of graft function, however, suggests that it is incorrect to think in terms of what is *the* mechanism of graft function. Rather, a multiplicity of different mechanisms is not only possible but also appears to apply in different circumstances. Formulation of the different levels at which function might be subserved provides a framework within which each situation can be discussed, and suggests a range of alternative explanations that need to be considered and experimentally addressed.

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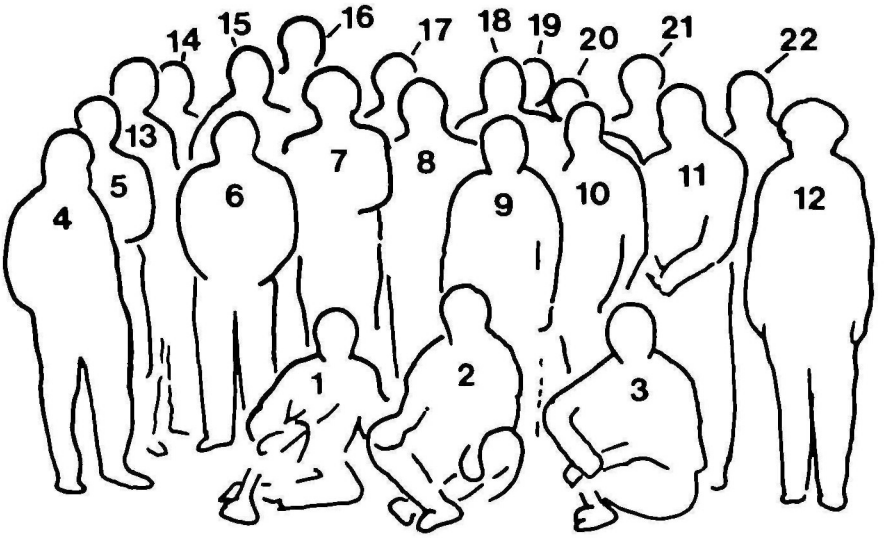
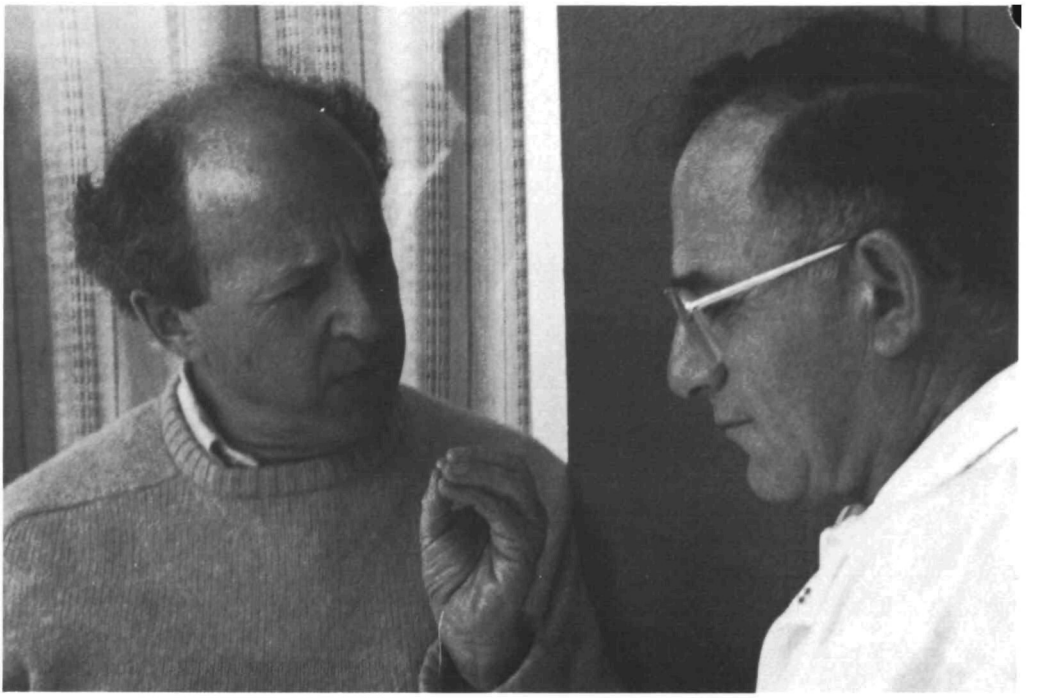
Photographs taken at the Discussion Meeting held at Kolimbari, Crete, in March 1987



1. John Nicholls
2. Eric Shooter
3. Damien Kuffler
4. Jenny Walker (BBC)
5. Elizabeth Howes
6. Itzchak Parnas
7. John Treherne
8. Peter Smith
9. Rolf Heumann
10. Ken Muller
11. Jack McMahan
12. Mary Bunge
13. Steve Dunnett
14. Garth Bray
15. Monte Westerfield
16. Richard Bunge
17. Martin Raff
18. Wesley Thompson
19. Hartmut Wekerle
20. Jeremy Brockes
21. Matthias Chiquet
22. Micha Spira

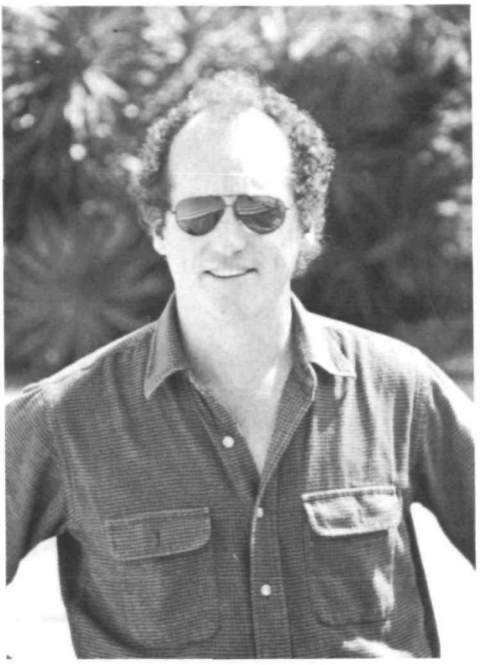
Elizabeth Howes and Jack McMahan

John Treherne, Jeremy Brockes, Micha Spira and Peter Smith



John Nicholls and Itzchak Parnas

Ken Muller and Garth Bray



Damien Kuffler

Matthias Chiquet

Mary Bunge

Richard Bunge

Steve Dunnett, Eric Shooter, Elaine Shooter and Itzchak Parnas

Tom Sears, Monte Westerfield, Martin Raff and Wesley Thompson