induction of immune unresponsiveness induced by the implantation of various immunogenic materials, such as tissue grafts, into the anterior chamber of the eye. This phenomenon is termed "anterior chamber-associated immune deviation" (ACAID). Data suggesting a possible role of TGF-β in ACAID were presented. Studies of transplantation of neonatal retinas into both the subconjunctival space (a non-privileged site) and the anterior chamber were described. Grafts in the subconjuntival space were rejected readily. Grafts into the anterior eye chamber also did not survive permanently; however, they displayed a range of survival times depending on genetic disparity: Allografts with major MHC disparity survived for 17 - 35 days, while allografts with only minor MHC disparity survived for more than 70 days. Even isografts did not survive permanently. The rejection was unusual, in that inflammation was not seen, even for the allografts. It was suggested that the deterioration of the isografts was caused by transplantation-induced sensitization to retinal antigens.

Sloan and coworkers /132/ presented data on the induction of sensitization to brain tissue allografts by a second graft of donor tissue into the kidney capsule. Removing the second graft five days after it was implanted did not cause an interruption in the reaction to the CNS graft. Thus, CNS immune reactions can be self-sustaining once initiated. It was also noted that there was better survival and less reaction to brain tissue grafts in the brain parenchyma, as compared to grafts in the third or lateral ventricle.

Poltorak and associates /68,111/ found that even when the host animals are systemically sensitized, there are certain strain combinations that resist brain graft rejection. Whereas rejection of grafts from Brown Norway donors was readily induced in all host strains, grafts from Lewis or Fisher 344 donors (both $RT1^l$) survived even after systemic sensitization in many host strains. Conversely, for some strain combinations, including one that did not reject grafts after sensitization (Lewis donors to AO-$RT1^u$ hosts), there was evidence of graft damage even without systemic sensitization. It was also noted that expression of MHC Class I and II antigens did not predict graft rejection, as grafts located in the third ventricle frequently showed strong expression of MHC antigens but were not rejected. It was also noted that cellular infiltration into brain grafts results in rejection only when the infiltrating cells include T-helper and T-cytotoxic lymphocytes, as well as perivascular infiltration. Cell infiltration may also consist of microglia expressing MHC Class II antigens, and this latter form of cell infiltration does not result in graft rejection.

Hickey /59/ (also cf. /60/), in the concluding paper, described a series of experiments on the mechanisms through which T-cells are able to enter into the CNS. The model used involved the use of T-cells derived from Lewis rats, which could be recognized by an antibody specific to the Lewis $RT\text{-}1^{a1}$ MHC molecule. The T-cells were activated by various treatments, and then injected into either Dark Agouti ($RT\text{-}1^a$) hosts, which do not produce the $RT\text{-}1a^1$ molecule, or Lewis hosts. When non-stimulated lymphocytes depleted of lymphoblasts were injected, virtually none were found in the brain following injection. Activation of the lymphocytes using the mitogenic lectin concanavalin A, to induce the cells to enter a lymphoblast phase, allowed the cells to enter the CNS freely, regardless of antigenic specificity of the cells. The peak concentrations of cells in the brain were found between 3 and 12 hours after injection. It had previously been shown that anti-myelin basic protein T-cells produce EAE only if stimulated prior to injection into animals (e.g. /105/). These data may help to explain the fact that rejection of brain grafts can be induced by systemic sensitization, even though T-cells cannot normally gain access to the CNS. Apparently, the reaction of T-cells with the CNS requires activation of the cells in addition to the appropriate antigenic specificity.

A population of T-cells derived from a normal, unstimulated animal will contain a proportion of blast cells. A continuous low level of entry of these lymphoblast cells, with various antigenic specificities, was suggested to continuously "survey" the CNS. After CNS allografts, Hickey /59/ demonstrated the presence of rare donor-specific T-cells in the spleen and lymph nodes of the host. Hickey /59/ suggested that the fact that

these cells are rare, and that even fewer would be in blast phase at any one time, would result in an inability of T-cells with appropriate specificities to "find" the graft. In other words, even though CNS allografts induce a small degree of host sensitization, the level of sensitization is not sufficient to result in graft rejection unless the animal is systemically sensitized or receives a second graft.

The question naturally arises whether allografts can be rejected in non-immunosuppressed hosts, and what circumstances might lead to graft rejection. The ability of brain allografts to survive is ultimately an empirical question; there are several studies which suggest that brain allografts usually survive, but can be rejected in certain host-donor combinations, at least in some circumstances. Hickey's hypothesis /59/ suggests that rejection of brain allografts might potentially be provoked by two factors: either (i) a specific stimulation of the host, resulting in an expansion of the population of donor-specific T-lymphocytes, or (ii) non-specific host stimulation, resulting in a greater proportion of cells in the lymphoblast phase, or some combination of the two. In fact, the relative role of the two factors in sensitization-induced brain allograft rejection has not been systemically studied, as systemic sensitization generally induces both a specific sensitization in addition to a non-specific T-cell activation.

Studies of graft rejection and tolerance have been almost entirely focused on the role of surface antigens, and especially histocompatibility complex antigens. Lampson /79/ reported findings which suggest that, at least under come conditions, even internal antigens may play a role in graft rejection. The enzyme β-glactosidase (β-gal), derived from *E. Coli*, is often used as a cellular marker for studies of genetic alteration of cells. Cells can be made to express this enzyme constitutively by retroviral transfer of the β-gal cDNA. In Lampson's experiments /78/, the 9L gliosarcoma cell line, derived from F344 rats and altered to express β-gal, was transplanted into F344 hosts. F344 animals were systemically immunized with purified β-gal prior to transplantation of β-gal-positive 9L cells into the brain. It was found that prior immunization with β-gal significantly reduced the growth of the transplanted β-gal-positive 9L cells. It was pointed out that T-cells recognize antigen in combination with MHC antigens, rather than free antigen. The complex of MHC with the target antigen might be formed either within the transplanted target cell, or by an antigen-presenting cell after ingestion of the target antigen, culminating in rejection indirectly through a "bystander" type response. Thus, it is possible that non-MHC antigens may provoke graft rejection, even when there is no MHC disparity.

Finally, an observation reported by Ibarra *et al.* /65/ was that acute spinal cord injury markedly reduced the absorption of the immunosuppressant drug cyclosporin A. After oral administration of cyclosporin A, serum levels were markedly reduced in animals with acute spinal cord injury, whereas blood levels of cyclosporin A were increased after intraperitoneal administration. Absorption was normal for both oral and intraperitoneal administration in animals with chronic spinal cord injury. These differences were attributed to delayed gastric emptying (oral administration) and vascular dilatation (intra-peritoneal administration). Altered drug absorption after spinal cord injury would have to be taken account of in any studies of spinal cord injury which require drug administration.

CELL IMPLANTS: USE OF SUPPORT MATRICES AND ENCAPSULATION

One theme expressed in several contexts throughout the meeting was the possibility of the use of support systems for the implantation of cell lines into the CNS. The topic of biomaterials and encapsulation is discussed in an accompanying summary by Sanberg and coworkers /121/. One type of support system involves the use of semi-permeable capsules in which cells are contained and are implanted into the brain. The pore size of the capsules is sufficiently small (approximately 50 kDa) to exclude cells and presumably to exclude large protein molecules and antibodies, thereby providing an immunoprotective effect. Small molecules, such as neurotransmitters and growth factors, can freely diffuse out of the capsules.

New findings regarding transplantation of encapsulated cells included a report on the possible use of pancreatic β-cell lines for GABA-releasing encapsulted grafts /144/. There have been several suggested potential applications for GABA-releasing neural implants, including Huntington's disease, epilepsy, and Parkinson's disease. Pancreatic β-cells are known to express glutamic acid decarboxylase, the GABA synthetic enzyme. Two immortalized cell lines derived from rat and mouse β-cells, designated NIT-1 and RIN, were found to release GABA. *In vitro*, both cell lines were found to survive encapsulation and continued to release GABA. Preliminary data on intracerebral implantation of these encapsulated cells were also reported. If methods for the intracerebral transplantation of cells capable of releasing large amounts of GABA could be developed, it might lead to a number of new applications for intracerebral transplantation.

New data on encapsulated PC12 cell grafts in animal models of Parkinson's disease were also reported /1,36,157-159/. Emerich and coworkers /36/ described a series of preclinical experiments on the development of encapsulated PC12 cells as a potential treatment for Parkinson's disease, including studies on encapsulation techniques, asssessment of biocompatibility and immunoprotection, and functional efficacy. Winn and coworkers /157/ reported that encapsulated PC12 cell grafts could be retrieved from the host brain intact, with the encapsulated cells remaining viable, and producing minimal damage to the host brain. Winn and coworkers /158/ also compared tissue reactions following capsule implantation. Stereotaxic implantation either directly or using a teflon cannula resulted in minimal tissue reaction, whereas biocompatibility was poor when the capsules were inserted using a glass cannula or when sterility was compromised.

A second category of cell support systems seeks to use polymers or protein matrices to support cell attachment without encapsulation. Such systems serve to localize and stabilize cell populations, but do not provide immunoprotection or containment. Where simple diffusion of products from cell to host brain targets is not sufficient to produce a functional effect, enclosed capsules cannot be used. This would be the case where any form of physical interaction between graft and host is required, including invasion of cells, ingrowth of processes, or extension of neurites from grafted cells into the host brain.

Such cell matrices may allow for physical contact between implanted cells and host brain, possibly resulting in synapse formation and cell-cell interactions which require membrane to membrane cell contact. Several of these cell support systems were described and used in experimental transplantation systems. These included implantation of hybridoma cells in a Millipore filter matrix /125/, and studies by Silver in which differences between immature and mature glial cells in terms of their ability to become incorporated into implanted Millipore filters were described /95/. Another support system, employed by Ebendal *et al.* /35/, involved the use of a collagen gel as a matrix for the implantation of NGF-producing cells into lesion cavities in the fimbria-fornix. Woerly /160/ described the use of collagen and methacrylate matrix co-polymers, and described several structural formulations which might be used for transplantation, either by injection of cells into the matrices or by entrapment of cells by rehydration of the polymers in the presence of a cell suspension.

GLIAL CELLS

Silver /95/ described differences betwen the glial reactions which are observed when nitrocellulose Millipore filters are implanted into the brains of immature or mature rats. In general, when these filters are implanted into the brains of immature rats, cells, consisting of microglia and "flat" cells, invade the filters, followed by axons and blood vessels. When these filters are implanted into the brains of mature rats, the implant is instead walled off by a gliotic scar. In host animals 8-14 days of age and older, there is a greater glial fibrillary acid protein (GFAP)-positive glial reaction around the implant, and a much smaller migration of cells into the implant. Thus, the glial reaction tends to wall off the implant from the rest of the brain, rather than incorporating the implant into the brain structure. Also, in older hosts, a

patterned formation of blood vessels, as indicated by laminin staining within the implant, does not take place, the blood vessels are leaky, and laminin is irregularly deposited.

The filters can also be explanted and used as a substrate for cultured neurons. In all cases they support neuronal survival, but there is a substantial difference between the explants from the younger vs. the older host animals in terms of the degree to which they support neurite extension; the implants from the younger animals are several times more effective in supporting the extension of neurites. This difference appears to be related to the expression of proteoglycans, which inhibit neurite growth via a repulsive (non-permissive), but non-toxic, mechanism. These molecules are associated with boundaries between neuronal structures, similar to what has been found for tenascin.

The role of glial maturity in this phenomenon was investigated by incorporating young or old astrocytes into the filters, and then transplanting the glia-containing filters into the brain. When filters containing mature glia were transplanted, a GFAP-immunoreactive scar formed in the surrounding medium, and there was blood-brain barrier leakage and poor blood vessel formation. When immature glia were implanted with the filters, the GFAP-positive scar in the surrounding medium did not form, and there was normal formation of blood vessels with much less leakage of the blood-brain barrier. It was also noted that the cells did not migrate out of the implants.

Similar phenomena are observed even if conditioned media from mature vs. immature astrocyte cultures are used to impregnate the filters, rather than the cells themselves. When the filters are impregnated with conditioned medium from immature astrocytes plus mature astrocytes, the regrowth is inhibited and resembles that which is seen with mature astrocytes alone. This again confirms that these phenomena are caused by an inhibitory property of mature astrocytes, rather than a stimulatory property of immature astrocytes /95/.

Geller /92/ described experiments on the effects of bFGF on extracellular matrix expression in astrocyte cultures. bFGF was found to increase tenascin expression and decrease expression of laminin. bFGF treatment of astrocyte cultures reduced neuronal adhesion. Following neuronal injury, it may be that the action of growth factors plays a role in inhibiting recovery and synaptic restructuring. In some cases, this type of extracellular environment may inhibit graft integration into the host brain. Simply transplanting cells into the brain in such a neurite-inhibiting environment may not be sufficient to result in functionally significant restructuring. Several papers, in fact, discussed aspects of the effects of the local glial environment or microenvironment on graft-host connectivity /18,24,44/. For example, Castro *et al.* /18/ found that there were substantial differences in connectivity between cortical grafts and host brain, when the grafts were placed into excitotoxic cortical lesions, as compared to aspiration cavities. Dellman and Carithers /24,25/ found that neurosecretory axon regeneration required living glial cells; cryotreated neural lobe or sciatic nerve grafts did not support neurosecretory axon regeneration, as compared to intact neural lobe and intact sciatic nerve.

A related study was presented by Nieto-Sampedro and coworkers /98/, who employed the technique of coating tissue culture dishes with plasma membranes isolated from normal or gliotic brain tissue. Membranes from the gliotic tissue were found to inhibit neurite extension. The inhibitory activivy was found to be present in a proteoglycan, which was sensitive to digestion with glycosaminoglycan lyase. A core protein with 48 kDa molecular weight was found to undergo a large increase in injured brain tissue and was able to inhibit neurite extension, and to induce neurite retraction when added to cultures in soluble form. This factor was distinct from neurite inhibitors contained in myelin, and was localized to microglial membranes by immunostaining.

GENETIC ENGINEERING

Several topics related to genetic engineering were presented in sessions throughout the meeting. For example, Glorioso /49/ presented a detailed summary of the obstacles to the use of viral vectors derived from Herpes Simplex viruses (HSV) for insertion of genes into CNS cells, as well as information on possible solutions. These viruses

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the β-galactosidase gene will also be expressed and can be used as a marker. In the retina of this mouse strain, β-galactosidase is expressed in the ganglion cell layer, part of the inner nuclear layer, and the inner and outer plexiform layers. When used for transplantation to the retina, labelled cells could be identified using this method. It was pointed out that, since not all donor cells express β-galactosidase, not all transplanted cells could be identified using this method, although a fraction of the transplanted cells could be identified clearly. Kershaw *et al.* /72/ employed tsA58 transgenic mice /71/ as a source of tissue for transplantation, and found that the grafts developed normally, without forming tumors. Other related techniques, involving derivation of cells from transgenic animals, are likely to be applied in transplantation models in the future.

NGF, CO-GRAFTS, CHOLINERGIC SYSTEMS, AND ADRENAL MEDULLA TRANSPLANTATION

Studies of adrenal medulla transplantation, methods for delivery of NGF to the brain, co-grafts of peripheral nerve segments, and other effects of trophic factors have become so interlinked that it is impossible to discuss these issues separately. Thus, studies of delivery of NGF into the brain by genetically-altered cells have potential applications for use in cholinergic systems, and related methods may also be used for delivery of other trophic factors (see section on trophic factors, above). However, several studies of NGF delivery presented at the meeting were directed at enhancing the survival of adrenal medulla grafts, and the entire topic of NGF delivery into the brain, along with related methods, will be discussed in the context of adrenal medulla transplantation.

Adrenal medulla grafts:

Unisicker *et al.* /146/ discussed growth factors found in adrenal chromaffin cells. Growth factors and cytokines which are found in adrenal chromaffin cells include interleukin (IL)-2, IL-6, insulin-like growth factor (IGF)-1, IGF-2, transforming growth factor (TGF)-β1, TGFβ2, TGFβ3, bFGF, aFGF, and a CNTF-like molecule. The contents of chromaffin cell granules include, in addition to catecholamines, ATP, chromogranin, and peptides. Release of catecholamines and chromogranin can be induced using carbachol. Unisicker described the use of a chromaffin cell-conditioned medium assay to measure the promotion of survival of neurons. Carbachol-induced release of catecholamines was found to be parallelled by a release of trophic activity. Verapamil blocked all three (catecholamines, chromogranin, and trophic activity release) similarly.

bFGF is found in chromaffin cells; it is localized to the granules, not the cytosol. This is surprising, because bFGF lacks the signal peptide needed for release. Although bFGF gets out of the cells, the mechanism of release is not known. Unisicker has not been able to show stimulated release of bFGF. It was found that whole chromaffin cells contain two bFGF-immuoreactive molecules, with molecular weights of 32 and 46 kDa; granules contain the 46 kDa form almost exclusively. bFGF is 18 kDa. This 46 kDa molecule is biologically simlar to bFGF, but seems to be a different molecule. Adrenal medullectomy causes death of preganglionic spinal cord neurons which innervate the adrenal medulla. Growth factors which can prevent this cell death and are present in the adrenal medulla include bFGF, as well as TGFβ3, TGFβ2, and the CNTF-like molecule.

Chromogranin A is present in the adrenal medulla in large amounts. It was affinity purified using a monoclonal antibody. Purified chromogranin A was found to have trophic activity for dorsal root ganglia neurons. Surprisingly, this trophic activity was increased seven-fold by boiling. Additional increases in trophic activity were obtained by further purification; the trophic activity was highest in a 28 - 32 kDa molecular weight band. After purification, its efficacy was similar to that of NGF. This activity was not blocked by several monoclonal antibodies, including NGF antibodies. However, chromogranin A produced by 3T3 tranfected cells did not have trophic activity. Possibly there is some additional processing which takes place in the adrenal medulla which is required for the trophic activity.

In the mouse MPTP-lesion model, bFGF was found to protect against dopamine depletion when applied at the same time or shortly after MPTP. Although it has a protective effect, it did not restore depeletion when applied long after MPTP. TH is also protected; TH-immunoreactive fibers recover only immediately adjacent to the bFGF-impregnated gelfoam, but TH activity recovers bilaterally. It was noted that bFGF binds strongly to glial cells /146/.

Studies on the mechanisms of action of adrenal medulla grafts were described by Becker and Curran /8/. These experiments focused on two topics: first, the relationship between effects of adrenal medulla grafts and changes in striatal dopamine metabolism, and second, the possible role of changes in blood-brain barrier permeability in the functional effects of adrenal medulla grafts. Adrenal medulla grafts have been shown to cause blood-brain barrier permeability /116/. Curran and Becker /22/ showed that the behavioral response to adrenal medulla grafts, especially the reductions in amphetamine-induced rotation, are associated with an increase in permeability of the blood-brain barrier to dopamine. Additional studies by this group /142/, comparing adrenalectomized and normal rats with unilateral 6OHDA lesions of the SN, have shown that adrenal medulla grafts appear to function through at least two separate mechanisms to decrease apomorphine-induced rotation. The first, which is abolished by adrenalectomy, appears to be associated with increases in blood dopamine and is similar for animals that receive grafts of adrenal medulla and sciatic nerve or sham transplantation. The second is a specific effect of adrenal medulla grafts, which is similar in adrenalectomized and normal animals. Since decreases in amphetamine-induced rotation, rather than apomorphine-induced rotation, appear to be related to changes in blood-brain barrier function, it appears likely that adrenal medulla grafts can induce changes in behavior through more than one cellular mechanism.

A theme which was developed throughout the meeting was the possibility of improvements in the efficacy, as well as the survival, of chromaffin cells in transplanted adrenal medulla. Transplantation of adrenal medulla is an area which has been motivated by two ultimate goals; first, the treatment of Parkinson's disease /41,50/, and second, the use of adrenal chromaffin cell implants for the treatment of intractible pain /117,119/. Studies related to Parkinson's disease will be discussed in more detail below, and studies in chronic pain will be described in the concluding section on new models and applications.

A thorough review of the effects of adrenal medulla autografts, including the multi-center trial and registry data, was presented by Goetz /50/. Although positive effects of adrenal medulla grafts in patients with Parkinson's disease have been reported without the use of any of these additional methods to enhance cell survival, the effects of these grafts are relatively modest. There were substantial improvements for up to one year, but several of the symptoms which had shown earlier improvement began to deteriorate after extended periods. Most of the beneficial effects disappeared after two years. There was, however, a significant increase in total "on" time, which remained significantly improved four years after transplantation. One unanswered question is whether the increase in "on" time represents a simple change in the temporal pattern of on-off cycling, as opposed to an improvement in function which is perceptible to the subjects only during certain periods of the on-off cycle. It is conceivable that patients interpret periods of improved function as "on" time, rather than as improved function during "off" periods.

Garcia-Flores /45/ has also conducted long-term studies of patients with adrenal medulla grafts, and reported data which were generally consistent with the results reported by Goetz /50/, notwithstanding differences in methods of evaluation. Whereas Goetz /50/ reported on overall mean changes in performance scores, Garcia-Flores /45/ concentrated on the responses to treatment in individual patients. Four-year follow-up data were available for 17 patients. Of the original 24 patients in the study, five had died and two others were lost to follow-up. Two patients showed a substantial long-term improvement; these patients were distinguished by early age at onset of the disease (24 and 41), and neither had received regular L-DOPA treatment. Parenthetically, it might be

mentioned that these characteristics are consistent with a possible diagnosis of striatonigral degeneration (see section on "substantia nigra grafts"). Four additional patients showed no improvement as compared to baseline disability, but did not show progressive deterioration, suggestive of a possible slowing in the progression of the disease. The remaining patients showed no apparent effect of the transplantation procedure, and in these patients there appeared to be a normal continuing disease progression. In addition, numerous surgical and medical complications were seen. These included some suggestions of possibile deleterious effects of the adrenalectomy, such as decreased cortisol, increased incidence of diabetes mellitus, and a possible reduction in stress tolerance. In this latter study /45/, therefore, beneficial effects of adrenal medulla transplantation were detected, but substantial long-term improvement was seen only in a minority of patients, who were atypical.

In the seven published autopsies, few or no surviving chromaffin cells have been found. These clinical data taken together suggest that: (i) at least some of the effects of adrenal medulla grafts may be due to non-specific mechanisms which do not require chromaffin cell survival; (ii) technical improvements which result in increased cell survival may lead to improvements in the performance of these grafts clinically, and (iii) the high frequency of side-effects is a major problem for this procedure. Nonetheless, adrenal medulla transplantation continues to be attractive, in part because it eliminates the problem of obtaining fetal tissue.

Basic studies: Methods to improve performance

The improvement of chromaffin cell graft performance and survival was addressed in several experimental studies. One of the most consistent themes was the enhancement of chromaffin cell survival by methods which are intended to increase the delivery of NGF to chromaffin cells. These studies took several forms, involving delivery of NGF through chronic pumps /46,102,103/, co-transplantation of cells genetically modified to deliver NGF /20,107/, co-grafting of peripheral nerve or other tissues in combination with chromaffin cells /4,23,85,90,151,156/, and the development of methods to enhance penetration of NGF through the blood-brain barrier /43,51/. Some of these methods, including co-transplantation with peripheral nerve fragments, and direct delivery of NGF into the brain using mechanical pumps, are being employed in clinical trials of adrenal medulla transplantation in humans.

Cunningham *et al.* /20/ reported on the genetic modification of Type 1 astrocytes purified from rat cerebral cortex to constitutively express mouse β-NGF. These genetically-modified astrocytes release NGF into the medium at a rate more than 10-fold higher than comparable non-modified astrocytes. Effects of co-transplantation of these astrocytes with adrenal chromaffin cell suspensions were examined. Chromaffin cells transplanted alone resulted in survival of a mean of 221 ± 129 TH-immunoreactive cells after 10 weeks, as compared to 99 ± 5 cells in animals with adrenal medulla plus normal astrocytes, and a mean of 1168 ± 143 surviving TH-positive cells in the animals that received adrenal medulla plus NGF-modified astrocyte grafts. The chromaffin cells in the NGF-astrocyte co-graft group also showed an increased expression of a neuron-like phenotype, including a large soma and extension of TH-positive processes.

Along the same lines, Patterson and coworkers /107/ described the use of fibroblasts genetically engineered to produce NGF for co-transplantation with adrenal medulla. When adrenal chromaffin cells were transplanted into the striatum of adult rats in combination with these NGF-fibroblasts, the chromaffin cells expressed microtubule-associated protein (MAP)-2, NGF receptor, neurofilament, and TH. The cells exhibited greatly enlarged soma size and extensive process development. The number of surviving TH-positive cells was increased 2.5-fold as compared to chromaffin cells co-transplanted with normal control fibroblasts. As in other studies of NGF effects on adrenal medulla grafts, the outgrowth of processes was largely confined to within the graft.

An additional advance in the possibility of enhancing chromaffin cell survival by co-transplantation was reported by Date and coworkers /23/, based on studies which had shown that transection of peripheral nerve increases the

synthesis of NGF (e.g., /58/). Chromaffin cells were transplanted into the brain either alone, or in combination with sciatic nerve that had either not been previously transected, or that had been transected one day previously. The number of surviving chromaffin cells was increased approximately two-fold by the non-transected nerve, and increased about three-fold by the co-grafts of nerve that had been previously transected. Measurements of TH immunostaining intensity adjacent to the grafts showed that the adrenal medulla + pretransected nerve grafts increased immunostaining in the 0.3 mm x 0.3 mm segment of host striatum immediately adjacent to the grafts, but not further away. The immunostaining intensity was increased, as compared to the adrenal medulla-only animals, by both the pre-transected and non-pretransected nerve co-grafts. This represents a possible further refinement of the peripheral nerve co-grafting method, which is potentially applicable to clinical studies.

An interesting potential method for delivering NGF to the brain by conjugation to an anti-transferrin antibody was described by Granholm and coworkers /43,51/. This method could be applicable to promoting the survival of adrenal medulla grafts, in addition to other possible applications of NGF or other growth factors which require delivery to the central nervous system. The effects of NGF delivered by this method were measured by changes in the size of intraocular grafts of fetal septal tissue. The blood-brain barrier was shown, by exclusion of Evan's blue dye, to have developed in these grafts. Stain was found in blood vessels in the host iris and in the grafts, but not in the graft neuropil. Animals received either NGF alone, NGF-antibody conjugate, antibody alone, or no treatment by a single injection every two weeks. It was reported that grafts in animals treated with the NGF-antibody conjugate grew significantly larger. These grafts also expressed more NGF immunoreactivity and a larger number of choline acetyltransferase immunoreactive neurons than grafts in the controls. NGF concentrations in brain were measured, and preliminary results also suggested some elevation.

Gash /46/ discussed preliminary findings of the effects of infusion of NGF followed by autotransplantation of the adenal medulla in an MPTP-lesioned primate. This study employed a bilateral infusion model, in which MPTP was infused separately into both carotid arteries. In contrast to the unilateral MPTP infusion, or systemic injection of MPTP in which both sides are simultaneously and similarly lesioned, the bilateral model allows for the possibility of the animal to recover from the first set of lesions before the other side is lesioned via the second carotid artery. In this first animal tested, a catheter was placed into the putamen to infuse NGF, and one week later adrenal medulla autografts were placed around the catheter. The NGF infusions caused an increase in motor activity, analagous to decreased bradykinesia, and an improvement in ratings of motor impairment. The adrenal medulla grafts did not produce a substantial additional effect. The ratings slowly deteriorated when the NGF infusions were discontinued. Thus, in this first animal, the improvement observed was related more to the NGF infusions than to the transplantation of adrenal medulla (also cf. /19/). This finding, although so far reported for only a single animal, is reminiscent of the report by Pezzoli *et al.* /110/ in which NGF infusions increased the efficacy of adrenal medulla grafts, but were similarly effective when combined with grafts of other types of tissue, such as adipose tissue or peripheral nerve.

An additional study on adrenal medulla grafts in primates, reported by Bakay and coworkers /4/, examined co-grafts of adrenal medulla and sural nerve, as compared to controls that received sham surgery. Following unilateral MPTP administration, Parkinson-like symptoms were evaluated by a variety of techniques. These techniques included rotational behavior and an operant assessment of movements task, in which time required for an animal to activate a touch-sensitive screen in response to a visual cue was measured. The co-grafts caused an 84% decrease in apomorphine-induced rotation, as compared to a 52% decrease in the sham-operated controls. The decreases were seen over the course of 3 months after surgery, and were stable for up to one year. Improvements in movement times were seen in the co-grafted animals and in only one of the sham-operated controls. Although this study did not compare co-

grafts to adrenal medulla-alone grafts, it does suggest that adrenal medulla/peripheral nerve co-grafts can produce behavioral improvements in hemiparkinsonian primates.

Several clinical studies addressed the issue of improving the performance of adrenal medulla grafts. One possibility, which has largely been ignored in the basic literature, is the perfusion of adrenal medulla prior to transplantation /86,87/. Perfusion of adrenal medulla prior to transplantation will remove blood cells which may promote graft rejection, and might accomplish some of the same goals as isolation of chromaffin cells prior to transplantation, as reported by Schueler and coworkers /123/. Lopez-Lozano /86,87/ described clinical studies in which patients received grafts of adrenal medulla which had been perfused with a calcium and magnesium-free buffer. Patients who had received perfused adrenal medulla grafts had been followed for up to three years, and were found to have shown improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Scale over the course of the first seven months after tranplantation. From seven months to three years after transplantation, some patients maintained the improvements, and for others the improvements were slowly lost, although the overall mean scores were fairly stable over the seven month to three year follow-up. Data reported by Lopez-Lozano /85,86/ on co-grafts of adrenal medulla with peripheral nerve suggested that the major difference from the grafts of adrenal medulla alone was that the phase of gradual improvement lasted longer, for approximately 9 - 12, instead of seven, months after surgery.

Watts and coworkers /150,151/ reported on initial results from three patients (ages 45 - 55) who had received adrenal medulla/intercostal nerve co-grafts. Patients received grafts into two sites in the caudate and one site in the putamen. Patients developed slightly increased dyskinesias, and otherwise tended to show improvements which were somewhat variable. In patient number two, a substantial improvement in relative "on" and "off" times was noted. There was no change in the third patient, who had been followed for only three months. On timed motor tests, patients number one and two were improved somewhat in pronation/supination, hand/arm movements, and a stand/walk/sit test, but only slightly improved in finger dexterity.

Data from Madrazo and coworkers /90/ on four patients, ages 41-51 years, who had received adrenal medulla and peripheral (intercostal) nerve co-grafts, were presented by Franco-Bourland. Although some improvements were seen in all patients, in three of the four the improvements in UPDRS scores were considerably less than the mean improvement seen in a series of 18 patients who had received adrenal medulla-only grafts. These improvements were said to be similar to the improvements seen in poorer responders to adrenal medulla-only grafts. Substantial improvement, similar to the mean improvement in patients with adrenal medulla-only grafts, was seen in only one patient. Taken together, the three studies /85,90, 150,151/ do not provide, at least up to the present time, strong support for the possibility that the clinical effects produced by the co-grafting method are more substantial than the changes produced after adrenal medulla grafts alone.

The final presentation, from Olson *et al.* /103/ presented by Hoffer, described a possible alternative method for improving the clinical effects of adrenal medulla grafts by combining the grafts with infusions of NGF. Data from three patients were presented. The first patient, who has already been described in a published paper, showed some prolonged improvements /102/. In a second patient, there were some improvements, including a dampening of "on"-"off" cycling, but these had disappeared after about six months. In a third patient, who had so far been followed for only about six weeks, there were substantial improvements in walking, standardized tests of motor function, and Brightschaft potentials on the operated side. These patients will continue to be monitored.

In addition to the possibility of increasing chromaffin cell survival and effiicacy by co-grafts or NGF administraton, two additional techniques to increase chromaffin cell survival were described. A very interesting study /76,123,124/ demonstrated convincingly that purified bovine chromaffin cells survived transplantation much better than a mixed

cell preparation from bovine adrenal medulla. Bovine adrenal medulla cells were dissociated and transplanted into the striatal parenchyma of rats immunosuppressed with cyclosporin A. Purifed chromaffin cells were prepared by Percoll gradiant separation and differential plating. Three different cell preparations were employed: (a) The mixed preparation of bovine adrenal medullary cells; (b) the purified chromaffin cells, and (c) a reconsituted preparation, consisting of both chromaffin cells and the other medullary cells. It was found that cell survival was greatly superior in the purified chromaffin cell preparation, as compared to both the original mixed cell preparation and to the reconstituted preparation of chromaffin cells plus non-chromaffin cells.

Another technique, described by Dubach *et al.* /28,29/, involved the transplantation of adrenal medulla tissue in elongated "ribbons", using a method which allowed the tissue to be delivered into the brain so that the tissue was in contact with host brain along its entire length without deformation /30/. Behavioral effects of the grafts were examined in primates using a rotational behavior model /28,29/ which involved assessment of behavioral changes in individual subjects with time-series analyses. Transplantation of adrenal medulla using earlier methods, which result in poor tissue survival, did not cause significant decreases in rotational behavior. There were no improvements in behavior in the first two animals receiving adrenal medulla grafts by the ribbon method; however, in four subsequent animals which received more widely distributed ribbon grafts with longer total graft lengths, there were significant behavioral improvements. The behavioral improvements were associated with the total length of the graft ribbons. Thus, a relatively simple surgical technique which increases graft-host contact resulted in greatly improved tissue survival, reinforcing the conclusion that adrenal medulla grafts can produce behavioral changes which are related to the number and distribution of surviving chromaffin cells /29/.

Although so far preliminary results of clinical co-grafting studies are not especially promising, there are several techniques which have been described for improving the functional effects and survival of adrenal medulla grafts which could be employed clinically. These give several possible avenues for improving the performance of these grafts, perhaps even including optimizing the method by combining various methods such as improved surgical technique /28-30/, purified chromaffin cells or perfusion /86,87,123/, and co-grafting /23,156/ or possibly a method for delivery of NGF /20,46,102,107/. Such an approach might very well result in dramatically improved graft performance.

SUBSTANTIA NIGRA GRAFTS

Information presented at the meeting pertaining to substantia nigra (SN) grafts ranged from basic studies of the development of dopaminergic cells to long-term studies of clinical efficacy.

Basic studies

Several presenters reported on the effects of growth factors on *in vitro* characterization of the properties of human ventral mesencephalon /19,26, 128/. For example, Dong *et al.* /26/ reported that treatment of primary cultures of human second trimester fetal mesencephalon with bFGF or with a combination of bFGF and NGF caused an increase in the number of neuron-specific enolase immuno-reactive cells, with no change in the number of GFAP-positive cells, and a two-fold increase in catecholamine content. NGF alone had no effect, but potentiated the effect of bFGF.

Although the development of rodent dopaminergic cells has been studied extensively, there has been relatively little work on the development of human dopaminergic mesencephalic neurons. Silani and coworkers /128/ studied the development of human fetal ventral mesencephalon from 6 to 11 weeks. Neurite extension from TH-immunoreactive cells took place from 8 to 9 weeks; at 8 weeks *in vivo* the cells began to form a crescent-shaped structure; by 9 weeks the dopaminergic afferentation of the striatum begans to form, and by 11 weeks most TH-positive neurons had developed processes. The ratio of neurons to GFAP-positive astroglia was approximately 0.7 to 1, and the number of TH-

SN lesions. Animals were held, so that only the contralateral forelimb was supporting the animal's weight. It was shown that the animals were unable to initiate steps with their contralateral forelimb, but when the animal was moved forward manually, the contralateral limb was able to step to keep pace. The ipsilateral forelimb was able to step normally. Amphetamine and apomorphine both increased the stepping rate of the ipsilateral forelimb, but the contralateral forelimb was unable to initiate steps even after amphetamine or apomorphine. Thus, during rotational behavior tests when the animal is allowed to move freely, the contralateral limb makes only catch-up steps, which is the cause of the turning behavior. In amphetamine-induced rotation, the ipsilateral limb tends to make movements in the ipsilateral direction, while in apomorphine-induced rotation, the ipsilateral limb tends to make crossing movements in the contralateral direction. It was noted that, in animals with unilateral SN lesions, "The ipsilateral forelimb is capable of initiating stepping movements that have major weight shifting consequences whereas the contralateral forelimb almost exclusively makes reactive steps to regain support of a displaced center of gravity..." /122/. Thus, these behavioral findings tend to validate the rotational behavior model as an indicator of Parkinson-like akinesia or bradykinesia; nonetheless, these data suggest that measurement of the ability of the contralateral forelimb to initiate stepping movements would be an important means of assessing the potential efficacy of various therapeutic modalities in the unilaterally-lesioned rat model.

Taylor and coworkers /143/ presented data on the relationship between the initial severity of Parkinson-like symptoms induced by MPTP lesions in primates and the degree of spontaneous recovery and functional improvement induced by SN grafts. Each of 70 animals was assigned a score of "0" to "4", based on ratings and measurements of behavioral impairment following MPTP administration. The score of "0" was used for normal, untreated subjects, and "1" represented subtle deficits in object retrieval but not gross motor deficit. Scores of "2" through "4" represented increasingly severe parkinsonian motor impairment. The more severe the initial deficits, the less rapidly the animals showed spontaneous recovery. Monkeys with ratings of "1" showed spontaneous recovery within one month, while animals with scores of "4" did not recover during 5 months of assessment. Improvements after SN transplantation were observed in category "1", "2", "3", and "4" subjects. Improvements were not seen after control surgical procedures. Category "4" subjects tended to have medical complications and were difficult to maintain; SN grafts were found to increase the percentage of category "4" subjects which survived for more than three months. Thus, there was evidence of functional improvements in primates receiving SN grafts into the caudate nucleus, but control procedures including sham surgery, transplantation of cerebellum into the caudate nucleus, and transplantation of SN into the cortex did not produce improvement.

Prior studies by Brundin and coworkers /14,15/, using grafts of dissociated human mesencephalic cells, had found that tissue from human donor embryos of more than 11 weeks of fetal age were not effective when transplanted into immunosuppressed rats. In these experiments, tissue from donors of age 6.5-9 weeks was effective, while tissue from 11-19 week gestational donors was not. The cut-off age for human fetal donors must therefore be around 9 weeks for dissociated cells. It was generally assumed, however, that it would be possible to use slightly older donors, possibly 10 or 11 weeks, if solid grafts were used. This assumption was based on data suggesting that rat tissue can be approximately one day older when using solid tissue grafts /129,140/. A paper was presented by Freeman *et al.* /42/ in which this question was studied directly, using xenografts from human donors to immunosuppressed rat hosts. Donors ranged from 4-5 weeks (7 - 9 mm crown-rump length) to 10.5 weeks of fetal age. Data were evaluated in terms of survival of TH-immunoreactive cells and host reafferentation. It was found that dissociated cell grafts survived best when the donors were between 5 and 8 weeks of age (E34 to E56). Poor cell survival was obtained when the donors were older than 9 weeks (E65). For solid tissue grafts, however, E37 donor tissue resulted in only modest cell survival. The best cell survival was obtained with donors between 6 and 9

weeks (E43 to E65). No survival was obtained for grafts older than E72, or slightly greater than 10 weeks. These data provide the first direct comparison of solid and dissociated cell grafts in terms of age requirements for cell survival, and confirm previous data suggesting that tissue no older than 9 weeks for dissociated grafts and 10 weeks for solid grafts must be used. If anything, these data suggest that the age limit for solid tissue grafts is somewhat earlier than previously thought. It seems probable, therefore, that tissue of fetal age 11 weeks or greater is not likely to reafferent host striatum when used for clinical studies.

One issue which is a concern regarding the use of fetal SN grafts in human patients, is whether the grafts may be damaged by drugs - especially L-DOPA - which are routinely administered to patients with Parkinson's disease. Steece-Collier and coworkers /135,136/ reported that L-DOPA impairs the survival and neurite outgrowth from primary dopaminergic neurons in tissue culture. Effects of chronic L-DOPA treatment on SN grafts, made by injection of solid fragments of SN directly into the striatum, were also examined. Morphological development of the TH-immunoreactive neurons seemed to be impaired, in terms of neurite development and size of the neurons, although the number of surviving neurons was not decreased. Steece-Collier /136/ presented additional data on the effects of L-DOPA treatment on SN grafts. It was found that the effects of SN grafts on amphetamine-induced rotation, measured six weeks after transplantation, were greatly diminished in animals that had received chronic administration of 50 mg/kg of L-DOPA i.p., twice per day, as compared to saline-treated controls. The administration of L-DOPA was discontinued after six weeks. In the saline-treated controls, the decreases in rotational behavior were maintained when retested at 12 weeks. In the L-DOPA-treated animals, six weeks after withdrawal there was a non-significant reduction in rotation, although not to the level of the controls. When data from individual animals was examined, it appeared that there was a tendency for recovery in half of the animals, but the other half of the animals did not recover. Van Muiswinkel and coworkers /147/ found that, although L-DOPA treatment of dopaminergic neurons in culture induced signs of degeneration (a loss of dopamine uptake), this effect could not be duplicated by chronic administration of a D_2 receptor agonist. It thus remains a strong possibility that the efficacy of SN grafts may be impaired by L-DOPA treatment, at least under certain conditions (also cf. /10,147/). Discontinuation of the L-DOPA treatment may not invariably result in the reversal of this impairment.

There was also some consideration of methods to improve the effects of SN grafts, using animal models. Collier and coworkers /19/ described experiments showing that sciatic nerve co-grafts enhance the effects of SN grafts. Co-culturing experiments with fetal neurons, and studies of polymer-encapsulated sciatic nerve in aged animals in combination with SN grafts, suggested that sciatic nerve produces substances with trophic effects on dopaminergic neurons. Experiments by Yurek *et al.* /163/ examined the possibility that the efficacy of SN grafts could be enhanced by using both intranigral and intrastriatal SN grafts, and reported that animals with grafts in both regions showed a more rapid recovery than animals with grafts in only the striatum. Sladek and coworkers /131/ examined the effects of combined fetal SN and striatum in primates. Although neuronal survival was not markedly enhanced by the co-grafting procedure, there were increases in dopamine concentrations adjacent to the grafts, suggestive of a possible recovery of host dopaminergic systems. Taken together, these three experiments /19,131,163/ suggest that it may be possible to improve the efficacy of SN grafts by various procedural or surgical modifications.

Gervais and Vawter /48,148/ presented information related to the development of ethical guidelines and the unique concerns related to the transplantation of fetal tissue. One set of guidelines which may serve as a model is the cadaveric donation framework. These guidelines treat the fetus as a cadaver but do not, however, address the possible concerns or role of the mother as a donor. Additional provisions may be needed related to the special circumstances of fetal transplantation, to provide for protection of both the fetus and the mother. Details of the guidelines that have been proposed or set up for various countries were

described and compared. These guidelines, in general, tend more toward treating the mother as a living donor. A major issue is the provision for varying degrees of insulation in information transfer, regarding the separation of donors, researchers, and patients. Another issue is the possibility of modifications to the abortion procedure that would be required for tissue donation, including testing of blood and tissue. It was suggested that a complete set of guidelines for fetal tissue transplantation would include aspects of both the cadaver donor framework as well as the living organ donor framework.

Clinical trials

Data on two human patients with MPTP-induced parkinsonism who had been followed for two years after receiving fetal tissue grafts were presented by Widner /154/. Each of the two patients was transplanted with a large amount of tissue, consisting of the ventral mesencephalon from 6-7 human fetuses. Following the surgery, patient #1 was maintained on a stable dose of L-DOPA, while the dose of L-DOPA for the second patient had to be decreased by 75% due to side effects. Gait, as measured by number of steps, was substantially improved in patient #1. Patient #2 did not have a severe gait problem, and in this patient the grafts produced no changes in gait. Rigidity improved slowly over the two year observation period, and continues to show a trend toward improvement. Stop-start movement speed also showed a similar pattern of slow improvement over the course of the two year observation period. This unique study of transplantation in MPTP-induced parkinsonism may comprise an important bridge between animal and human studies. For example, interpretation is not complicated by continuing progressive degenerative changes which occur in idiopathic Parkinson's disease. Such continuing changes not only complicate the measurements of outcome, but also could conceivably result in progressive damage of the implanted tissue. Another advantage of MPTP-induced parkinsonism in humans for the study of transplantation is that the degenerative disease process present in the patients' brains may be relatively less widespread.

Three patients reported by Dymecki and coworkers /34/ received fetal tissue grafts from 11-12 week getstational donors into the head of the caudate nucleus using a method similar to the Madrazo /91/ technique but with a specially designed instrument. These patients had been followed for 30, 20, and 12 months. Improvement according to a number of parameters was observed starting 3 to 6 months after surgery and was sustained for the entire observation period. This study included assessments of motor performance using timed tasks; for example, there were improvements in foot lifting, pronation/supination, and finger dexterity of the order of 30 to 50%. Percentage of the day spent in "off" phase decreased from 55% before transplantation to 17 - 18% from 9 to 30 months after transplantation.

Lindvall /84/ discussed the results of fetal SN transplantation, using dissociated cell grafts, in four patients with idiopathic Parkinson's disease. The two patients with MPTP-induced parkinsonism described by Widner (see above; /154/) were also discussed. Each patient received grafts from several fetal donors. Some of the earlier results from three of the patients have been described in prior publications /82,83/. Patients numbers 3 and 4 both received grafts into the putamen only. Patient #3 has shown significant improvement. Patient #4 especially has shown continued improvement from one to three years after transplantation; this patient now has no "off" periods. Rigidity has decreased, but this effect did not begin to appear until one year after transplantation. Gait was not improved, and tremor has not improved in any of the patients. Thus, there seem to have been some effects, such as decreased rigidity, that were not seen until more than one year after transplantation. Interestingly, the disease process seems to have continued, as measured by decreased fluorodopa uptake in positron emission tomography (PET) scans or by the progressive deterioration in tremor and gait, even while progressive improvement was observed in other measures such as "on"-"off" periods and rigidity. These data suggest that graft function may not be adversely influenced in concert with the progression of the disease, and that SN grafts may produce therapeutically significant improvements in Parkinson's disease.

Freed /39/ reported on clinical changes in patients that had received fetal SN grafts. The first of these patients had been followed for nearly four years. Alternate patients were immunosuppressed or not immunosuppressed. Clinical improvement was observed in 5 of 7 patients overall, most of whom received bilateral grafts into 12 to 14 sites in the putamen, with tissue obtained from a single embryo. Improvements were seen in rapid alternating movements, postural control, speech, and "on" durations, which occurred gradually over the course of several months. In the first patient, there were modest signs of clinical improvement during the first year after transplantation, although walking speed did not improve and in fact was slightly worse during the first year. Between 15 and 45 months after transplantation, however, there was a marked progressive improvment in walking speed. This may have corresponded to evidence of continued transplant development, from ^{18}F-DOPA PET scanning, between 9 and 33 months. The slow, long-term improvement seen in the first patient is a very interesting observation.

Molina and coworkers reported on studies of transplantation of fetal mesencephalic tissue into patients with Parkinson's disease, including long-term studies of 30 patients who had received grafts into the caudate via a transfrontal open surgical approach /94/ and four patients who had received stereotaxic implantation of dissociated cells into the caudate and putamen /93/. In the thirty patients with grafts to the caudate, there were clinical improvements, including changes in "on" and "off" periods, changes in L-DOPA dosages, and changes in UPDRS scores, which persisted for the 26 - 53 months of postsurgical follow-up. The largest changes in UPDRS scores were seen during the first three months after transplantation, following which scores were stable or showed further small improvements for up to three years /94/. The four patients with stereotaxic dissociated cell grafts had been followed for only a few months. For this procedure also, improvement was seen in several measures including, for example, rigidity scores and "on" - "off" fluctuations. Surprisingly, the improvements developed very rapidly, with considerable changes occurring over 2 - 3 months, and some improvements even after 30 days. There was no suggestion of an improvement occurring over a long period akin to that reported by Widner *et al.* /154/, Lindvall *et al.* /84/, or C. Freed *et al.* /39/.

Hitchcock and coworkers /61/ (also cf. /57/) reported on 12 patients that received grafts of ventral mesencephalon from human donors of 11 to 18 weeks gestational age, implanted into a single site in the right caudate nucleus. Note that the age of the donor tissue in this study appears to exceed the optimal range. The range of patient ages was from 41 to 67 years, with 10 of the 12 patients aged 53 to 60 years. All implantation procedures were performed stereotaxically, and the patients were not immunosuppressed. Using the Webster rating scale, which rates motor dysfunction, three of the 12 patients showed improvement after three months which was sustained when retested at 6 and 12 months after transplantation. The other nine patients either showed no change or showed improvement after 6 months followed by deterioration to baseline levels of performance or slightly below. Interestingly, timed tests of motor function showed clear group improvements, in some cases including improvements that were not reflected clinically. For example, in one patient, whose functioning according to the Webster scale improved but deteriorated back to baseline levels from 6 to 12 months, performance on pronation/supination remained improved. Group performance on the pronation/supination test showed a clear tendency for contralateral improvement (cf. /57/). In other experiments, patients received unilateral grafts into the putamen, the caudate and putamen, or bilaterally into the heads of both caudates. In addition, a group of patients that did not receive surgery was followed as a "control" or comparison group, for purposes of comparison with the operated patients. There was no clear indication of superiority of any of the four implantation site regimens. A particularly valuable aspect of this series of studies is that it employed videotapes which were blindly rated by independent neurologists. One patient has died; although results of the post-mortem examination were not yet complete, no TH-positive cells have been found and some TH+ fibers around the graft were seen.

The final paper of the symposium, also on transplantation of fetal SN into human subjects, was given by Redmond *et al.* /112/. This study had several unique aspects, which were in some respects advantages and in other respects were drawbacks. First, this study is the closest approximation to a controlled study to date. Half of the patients served as non-operated controls for one year, following which they received the same transplantation surgery as the experimental group. This does permit a direct comparison between the groups; however, as discussed above, recent data suggest possible effects which take place over the very long-term (more than one year), and the one-year crossover design would not allow these changes to be detected. Second, the tissue used was cryopreserved, which allows for donor-host separation, screening, and scheduling. Tissue was implanted into the caudate nucleus only, and all patients received immunosuppression with cyclosporin for 6 months after transplantation. Patients were videotaped performing timed motor tasks, while wearing a cap and gown to conceal whether they had received surgery or were controls. There were two series of patients; the first received unilateral implantations into the caduate nucleus from one 7-11 weeks gestational donor each. The second series received tissue bilaterally into the caudate nucleus from 1-3 donors of 9-11 weeks gestation. Preliminary results from patients in the first series were reported. There were improvements in the operated patients which were consistent for several tasks, including walking, pronation/supination, foot-tapping, and fist clenching. These improvements exceeded those of the controls. An interesting observation with implications for other clinical studies was that ratings using the UPDRS showed improvements in the operated patients and also in the controls; nonetheless, the improvements in the operated group were somewhat smaller. Also, the controls self-rated themselves as being considerably improved, but the objective raters did not observe as much improvement in the control group.

There was one death, which appeared to be unrelated to the experimental procedure. Histology of this brain revealed that the graft did not have surviving TH-immunoreactive cells and, moreover, that this patient had striatonigral degeneration, not Parkinson's disease. This latter observation can be interpreted as raising an interesting caution. This diagnosis represents a minority of the population of patients with Parkinson's disease. Nevertheless, there are several factors which may substantially increase the probability of including patients with striatonigral degeneration in clinical transplantation trials. It may be that patients with striatonigral degeneration, who are unresponsive to L-DOPA, show a relatively high probability of non-responsiveness to therapy, and a correspondingly high probability of meeting the selection criteria (severe illness, unsatisfactory response to conventional therapy) for inclusion in experimental trials. Although patients with striatonigral degeneration can be distinguished by a poor reponse to L-DOPA, it is often not possible to make this diagnosis reliably except by post-mortem examination (cf. /33/). Patients with striatonigral degeneration are also relatively younger than patients with Parkinson's disease (cf. /73/). In several clinical trials, it has been considered desirable to employ relatively young patients. Several very young patients, in fact, have been employed in clinical transplantation trials. The tendency to include young patients may further increase the probability of including patients with striatonigral degeneration. Although it is not impossible that dopaminergic tissue transplants would improve function in patients with striatonigral degeneration, such an improvement, of course, would not have been predicted from the literature on transplantation in animal models.

This latter study /112/ is certainly a potential model of experimental design for future studies, in terms of the controlled design, blind ratings of quantifiable motor tasks, and consistency which was permitted due to the use of cyopreserved tissue. On the other hand, there were drawbacks to this particular study, including the relatively short (one-year) controlled evaluation period, implantation of tissue into the caudate only, and the use of donors which were in some cases of a gestational age slightly exceeding what appears to be optimal. The development of an effective transplantation methodology is bound to be a complex process which will involve improvements

SN lesions. Animals were held, so that only the contralateral forelimb was supporting the animal's weight. It was shown that the animals were unable to initiate steps with their contralateral forelimb, but when the animal was moved forward manually, the contralateral limb was able to step to keep pace. The ipsilateral forelimb was able to step normally. Amphetamine and apomorphine both increased the stepping rate of the ipsilateral forelimb, but the contralateral forelimb was unable to initiate steps even after amphetamine or apomorphine. Thus, during rotational behavior tests when the animal is allowed to move freely, the contralateral limb makes only catch-up steps, which is the cause of the turning behavior. In amphetamine-induced rotation, the ipsilateral limb tends to make movements in the ipsilateral direction, while in apomorphine-induced rotation, the ipsilateral limb tends to make crossing movements in the contralateral direction. It was noted that, in animals with unilateral SN lesions, "The ipsilateral forelimb is capable of initiating stepping movements that have major weight shifting consequences whereas the contralateral forelimb almost exclusively makes reactive steps to regain support of a displaced center of gravity..." /122/. Thus, these behavioral findings tend to validate the rotational behavior model as an indicator of Parkinson-like akinesia or bradykinesia; nonetheless, these data suggest that measurement of the ability of the contralateral forelimb to initiate stepping movements would be an important means of assessing the potential efficacy of various therapeutic modalities in the unilaterally-lesioned rat model.

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Prior studies by Brundin and coworkers /14,15/, using grafts of dissociated human mesencephalic cells, had found that tissue from human donor embryos of more than 11 weeks of fetal age were not effective when transplanted into immunosuppressed rats. In these experiments, tissue from donors of age 6.5-9 weeks was effective, while tissue from 11-19 week gestational donors was not. The cut-off age for human fetal donors must therefore be around 9 weeks for dissociated cells. It was generally assumed, however, that it would be possible to use slightly older donors, possibly 10 or 11 weeks, if solid grafts were used. This assumption was based on data suggesting that rat tissue can be approximately one day older when using solid tissue grafts /129,140/. A paper was presented by Freeman *et al.* /42/ in which this question was studied directly, using xenografts from human donors to immunosuppressed rat hosts. Donors ranged from 4-5 weeks (7 - 9 mm crown-rump length) to 10.5 weeks of fetal age. Data were evaluated in terms of survival of TH-immunoreactive cells and host reafferentation. It was found that dissociated cell grafts survived best when the donors were between 5 and 8 weeks of age (E34 to E56). Poor cell survival was obtained when the donors were older than 9 weeks (E65). For solid tissue grafts, however, E37 donor tissue resulted in only modest cell survival. The best cell survival was obtained with donors between 6 and 9

SN lesions. Animals were held, so that only the contralateral forelimb was supporting the animal's weight. It was shown that the animals were unable to initiate steps with their contralateral forelimb, but when the animal was moved forward manually, the contralateral limb was able to step to keep pace. The ipsilateral forelimb was able to step normally. Amphetamine and apomorphine both increased the stepping rate of the ipsilateral forelimb, but the contralateral forelimb was unable to initiate steps even after amphetamine or apomorphine. Thus, during rotational behavior tests when the animal is allowed to move freely, the contralateral limb makes only catch-up steps, which is the cause of the turning behavior. In amphetamine-induced rotation, the ipsilateral limb tends to make movements in the ipsilateral direction, while in apomorphine-induced rotation, the ipsilateral limb tends to make crossing movements in the contralateral direction. It was noted that, in animals with unilateral SN lesions, "The ipsilateral forelimb is capable of initiating stepping movements that have major weight shifting consequences whereas the contralateral forelimb almost exclusively makes reactive steps to regain support of a displaced center of gravity..." /122/. Thus, these behavioral findings tend to validate the rotational behavior model as an indicator of Parkinson-like akinesia or bradykinesia; nonetheless, these data suggest that measurement of the ability of the contralateral forelimb to initiate stepping movements would be an important means of assessing the potential efficacy of various therapeutic modalities in the unilaterally-lesioned rat model.

Taylor and coworkers /143/ presented data on the relationship between the initial severity of Parkinson-like symptoms induced by MPTP lesions in primates and the degree of spontaneous recovery and functional improvement induced by SN grafts. Each of 70 animals was assigned a score of "0" to "4", based on ratings and measurements of behavioral impairment following MPTP administration. The score of "0" was used for normal, untreated subjects, and "1" represented subtle deficits in object retrieval but not gross motor deficit. Scores of "2" through "4" represented increasingly severe parkinsonian motor impairment. The more severe the initial deficits, the less rapidly the animals showed spontaneous recovery. Monkeys with ratings of "1" showed spontaneous recovery within one month, while animals with scores of "4" did not recover during 5 months of assessment. Improvements after SN transplantation were observed in category "1", "2", "3", and "4" subjects. Improvements were not seen after control surgical procedures. Category "4" subjects tended to have medical complications and were difficult to maintain; SN grafts were found to increase the percentage of category "4" subjects which survived for more than three months. Thus, there was evidence of functional improvements in primates receiving SN grafts into the caudate nucleus, but control procedures including sham surgery, transplantation of cerebellum into the caudate nucleus, and transplantation of SN into the cortex did not produce improvement.

Prior studies by Brundin and coworkers /14,15/, using grafts of dissociated human mesencephalic cells, had found that tissue from human donor embryos of more than 11 weeks of fetal age were not effective when transplanted into immunosuppressed rats. In these experiments, tissue from donors of age 6.5-9 weeks was effective, while tissue from 11-19 week gestational donors was not. The cut-off age for human fetal donors must therefore be around 9 weeks for dissociated cells. It was generally assumed, however, that it would be possible to use slightly older donors, possibly 10 or 11 weeks, if solid grafts were used. This assumption was based on data suggesting that rat tissue can be approximately one day older when using solid tissue grafts /129,140/. A paper was presented by Freeman *et al.* /42/ in which this question was studied directly, using xenografts from human donors to immunosuppressed rat hosts. Donors ranged from 4-5 weeks (7 - 9 mm crown-rump length) to 10.5 weeks of fetal age. Data were evaluated in terms of survival of TH-immunoreactive cells and host reafferentation. It was found that dissociated cell grafts survived best when the donors were between 5 and 8 weeks of age (E34 to E56). Poor cell survival was obtained when the donors were older than 9 weeks (E65). For solid tissue grafts, however, E37 donor tissue resulted in only modest cell survival. The best cell survival was obtained with donors between 6 and 9

weeks (E43 to E65). No survival was obtained for grafts older than E72, or slightly greater than 10 weeks. These data provide the first direct comparison of solid and dissociated cell grafts in terms of age requirements for cell survival, and confirm previous data suggesting that tissue no older than 9 weeks for dissociated grafts and 10 weeks for solid grafts must be used. If anything, these data suggest that the age limit for solid tissue grafts is somewhat earlier than previously thought. It seems probable, therefore, that tissue of fetal age 11 weeks or greater is not likely to reafferent host striatum when used for clinical studies.

One issue which is a concern regarding the use of fetal SN grafts in human patients, is whether the grafts may be damaged by drugs - especially L-DOPA - which are routinely administered to patients with Parkinson's disease. Steece-Collier and coworkers /135,136/ reported that L-DOPA impairs the survival and neurite outgrowth from primary dopaminergic neurons in tissue culture. Effects of chronic L-DOPA treatment on SN grafts, made by injection of solid fragments of SN directly into the striatum, were also examined. Morphological development of the TH-immunoreactive neurons seemed to be impaired, in terms of neurite development and size of the neurons, although the number of surviving neurons was not decreased. Steece-Collier /136/ presented additional data on the effects of L-DOPA treatment on SN grafts. It was found that the effects of SN grafts on amphetamine-induced rotation, measured six weeks after transplantation, were greatly diminished in animals that had received chronic administration of 50 mg/kg of L-DOPA i.p., twice per day, as compared to saline-treated controls. The administration of L-DOPA was discontinued after six weeks. In the saline-treated controls, the decreases in rotational behavior were maintained when retested at 12 weeks. In the L-DOPA-treated animals, six weeks after withdrawal there was a non-significant reduction in rotation, although not to the level of the controls. When data from individual animals was examined, it appeared that there was a tendency for recovery in half of the animals, but the other half of the animals did not recover. Van Muiswinkel and coworkers /147/ found that, although L-DOPA treatment of dopaminergic neurons in culture induced signs of degeneration (a loss of dopamine uptake), this effect could not be duplicated by chronic administration of a D_2 receptor agonist. It thus remains a strong possibility that the efficacy of SN grafts may be impaired by L-DOPA treatment, at least under certain conditions (also cf. /10,147/). Discontinuation of the L-DOPA treatment may not invariably result in the reversal of this impairment.

There was also some consideration of methods to improve the effects of SN grafts, using animal models. Collier and coworkers /19/ described experiments showing that sciatic nerve co-grafts enhance the effects of SN grafts. Co-culturing experiments with fetal neurons, and studies of polymer-encapsulated sciatic nerve in aged animals in combination with SN grafts, suggested that sciatic nerve produces substances with trophic effects on dopaminergic neurons. Experiments by Yurek *et al.* /163/ examined the possibility that the efficacy of SN grafts could be enhanced by using both intranigral and intrastriatal SN grafts, and reported that animals with grafts in both regions showed a more rapid recovery than animals with grafts in only the striatum. Sladek and coworkers /131/ examined the effects of combined fetal SN and striatum in primates. Although neuronal survival was not markedly enhanced by the co-grafting procedure, there were increases in dopamine concentrations adjacent to the grafts, suggestive of a possible recovery of host dopaminergic systems. Taken together, these three experiments /19,131,163/ suggest that it may be possible to improve the efficacy of SN grafts by various procedural or surgical modifications.

Gervais and Vawter /48,148/ presented information related to the development of ethical guidelines and the unique concerns related to the transplantation of fetal tissue. One set of guidelines which may serve as a model is the cadaveric donation framework. These guidelines treat the fetus as a cadaver but do not, however, address the possible concerns or role of the mother as a donor. Additional provisions may be needed related to the special circumstances of fetal transplantation, to provide for protection of both the fetus and the mother. Details of the guidelines that have been proposed or set up for various countries were

described and compared. These guidelines, in general, tend more toward treating the mother as a living donor. A major issue is the provision for varying degrees of insulation in information transfer, regarding the separation of donors, researchers, and patients. Another issue is the possibility of modifications to the abortion procedure that would be required for tissue donation, including testing of blood and tissue. It was suggested that a complete set of guidelines for fetal tissue transplantation would include aspects of both the cadaver donor framework as well as the living organ donor framework.

Clinical trials

Data on two human patients with MPTP-induced parkinsonism who had been followed for two years after receiving fetal tissue grafts were presented by Widner /154/. Each of the two patients was transplanted with a large amount of tissue, consisting of the ventral mesencephalon from 6-7 human fetuses. Following the surgery, patient #1 was maintained on a stable dose of L-DOPA, while the dose of L-DOPA for the second patient had to be decreased by 75% due to side effects. Gait, as measured by number of steps, was substantially improved in patient #1. Patient #2 did not have a severe gait problem, and in this patient the grafts produced no changes in gait. Rigidity improved slowly over the two year observation period, and continues to show a trend toward improvement. Stop-start movement speed also showed a similar pattern of slow improvement over the course of the two year observation period. This unique study of transplantation in MPTP-induced parkinsonism may comprise an important bridge between animal and human studies. For example, interpretation is not complicated by continuing progressive degenerative changes which occur in idiopathic Parkinson's disease. Such continuing changes not only complicate the measurements of outcome, but also could conceivably result in progressive damage of the implanted tissue. Another advantage of MPTP-induced parkinsonism in humans for the study of transplantation is that the degenerative disease process present in the patients' brains may be relatively less widespread.

Three patients reported by Dymecki and coworkers /34/ received fetal tissue grafts from 11-12 week getstational donors into the head of the caudate nucleus using a method similar to the Madrazo /91/ technique but with a specially designed instrument. These patients had been followed for 30, 20, and 12 months. Improvement according to a number of parameters was observed starting 3 to 6 months after surgery and was sustained for the entire observation period. This study included assessments of motor performance using timed tasks; for example, there were improvements in foot lifting, pronation/supination, and finger dexterity of the order of 30 to 50%. Percentage of the day spent in "off" phase decreased from 55% before transplantation to 17 - 18% from 9 to 30 months after transplantation.

Lindvall /84/ discussed the results of fetal SN transplantation, using dissociated cell grafts, in four patients with idiopathic Parkinson's disease. The two patients with MPTP-induced parkinsonism described by Widner (see above; /154/) were also discussed. Each patient received grafts from several fetal donors. Some of the earlier results from three of the patients have been described in prior publications /82,83/. Patients numbers 3 and 4 both received grafts into the putamen only. Patient #3 has shown significant improvement. Patient #4 especially has shown continued improvement from one to three years after transplantation; this patient now has no "off" periods. Rigidity has decreased, but this effect did not begin to appear until one year after transplantation. Gait was not improved, and tremor has not improved in any of the patients. Thus, there seem to have been some effects, such as decreased rigidity, that were not seen until more than one year after transplantation. Interestingly, the disease process seems to have continued, as measured by decreased fluorodopa uptake in positron emission tomography (PET) scans or by the progressive deterioration in tremor and gait, even while progressive improvement was observed in other measures such as "on"-"off" periods and rigidity. These data suggest that graft function may not be adversely influenced in concert with the progression of the disease, and that SN grafts may produce therapeutically significant improvements in Parkinson's disease.

Freed /39/ reported on clinical changes in patients that had received fetal SN grafts. The first of these patients had been followed for nearly four years. Alternate patients were immunosuppressed or not immunosuppressed. Clinical improvement was observed in 5 of 7 patients overall, most of whom received bilateral grafts into 12 to 14 sites in the putamen, with tissue obtained from a single embryo. Improvements were seen in rapid alternating movements, postural control, speech, and "on" durations, which occurred gradually over the course of several months. In the first patient, there were modest signs of clinical improvement during the first year after transplantation, although walking speed did not improve and in fact was slightly worse during the first year. Between 15 and 45 months after transplantation, however, there was a marked progressive improvment in walking speed. This may have corresponded to evidence of continued transplant development, from ^{18}F-DOPA PET scanning, between 9 and 33 months. The slow, long-term improvement seen in the first patient is a very interesting observation.

Molina and coworkers reported on studies of transplantation of fetal mesencephalic tissue into patients with Parkinson's disease, including long-term studies of 30 patients who had received grafts into the caudate via a transfrontal open surgical approach /94/ and four patients who had received stereotaxic implantation of dissociated cells into the caudate and putamen /93/. In the thirty patients with grafts to the caudate, there were clinical improvements, including changes in "on" and "off" periods, changes in L-DOPA dosages, and changes in UPDRS scores, which persisted for the 26 - 53 months of postsurgical follow-up. The largest changes in UPDRS scores were seen during the first three months after transplantation, following which scores were stable or showed further small improvements for up to three years /94/. The four patients with stereotaxic dissociated cell grafts had been followed for only a few months. For this procedure also, improvement was seen in several measures including, for example, rigidity scores and "on" - "off" fluctuations. Surprisingly, the improvements developed very rapidly, with considerable changes occurring over 2 - 3 months, and some improvements even after 30 days. There was no suggestion of an improvement occurring over a long period akin to that reported by Widner *et al.* /154/, Lindvall *et al.* /84/, or C. Freed *et al.* /39/.

Hitchcock and coworkers /61/ (also cf. /57/) reported on 12 patients that received grafts of ventral mesencephalon from human donors of 11 to 18 weeks gestational age, implanted into a single site in the right caudate nucleus. Note that the age of the donor tissue in this study appears to exceed the optimal range. The range of patient ages was from 41 to 67 years, with 10 of the 12 patients aged 53 to 60 years. All implantation procedures were performed stereotaxically, and the patients were not immunosuppressed. Using the Webster rating scale, which rates motor dysfunction, three of the 12 patients showed improvement after three months which was sustained when retested at 6 and 12 months after transplantation. The other nine patients either showed no change or showed improvement after 6 months followed by deterioration to baseline levels of performance or slightly below. Interestingly, timed tests of motor function showed clear group improvements, in some cases including improvements that were not reflected clinically. For example, in one patient, whose functioning according to the Webster scale improved but deteriorated back to baseline levels from 6 to 12 months, performance on pronation/supination remained improved. Group performance on the pronation/supination test showed a clear tendency for contralateral improvement (cf. /57/). In other experiments, patients received unilateral grafts into the putamen, the caudate and putamen, or bilaterally into the heads of both caudates. In addition, a group of patients that did not receive surgery was followed as a "control" or comparison group, for purposes of comparison with the operated patients. There was no clear indication of superiority of any of the four implantation site regimens. A particularly valuable aspect of this series of studies is that it employed videotapes which were blindly rated by independent neurologists. One patient has died; although results of the post-mortem examination were not yet complete, no TH-positive cells have been found and some TH+ fibers around the graft were seen.

The final paper of the symposium, also on transplantation of fetal SN into human subjects, was given by Redmond *et al.* /112/. This study had several unique aspects, which were in some respects advantages and in other respects were drawbacks. First, this study is the closest approximation to a controlled study to date. Half of the patients served as non-operated controls for one year, following which they received the same transplantation surgery as the experimental group. This does permit a direct comparison between the groups; however, as discussed above, recent data suggest possible effects which take place over the very long-term (more than one year), and the one-year crossover design would not allow these changes to be detected. Second, the tissue used was cryopreserved, which allows for donor-host separation, screening, and scheduling. Tissue was implanted into the caudate nucleus only, and all patients received immunosuppression with cyclosporin for 6 months after transplantation. Patients were videotaped performing timed motor tasks, while wearing a cap and gown to conceal whether they had received surgery or were controls. There were two series of patients; the first received unilateral implantations into the caduate nucleus from one 7-11 weeks gestational donor each. The second series received tissue bilaterally into the caudate nucleus from 1-3 donors of 9-11 weeks gestation. Preliminary results from patients in the first series were reported. There were improvements in the operated patients which were consistent for several tasks, including walking, pronation/supination, foot-tapping, and fist clenching. These improvements exceeded those of the controls. An interesting observation with implications for other clinical studies was that ratings using the UPDRS showed improvements in the operated patients and also in the controls; nonetheless, the improvements in the operated group were somewhat smaller. Also, the controls self-rated themselves as being considerably improved, but the objective raters did not observe as much improvement in the control group.

There was one death, which appeared to be unrelated to the experimental procedure. Histology of this brain revealed that the graft did not have surviving TH-immunoreactive cells and, moreover, that this patient had striatonigral degeneration, not Parkinson's disease. This latter observation can be interpreted as raising an interesting caution. This diagnosis represents a minority of the population of patients with Parkinson's disease. Nevertheless, there are several factors which may substantially increase the probability of including patients with striatonigral degeneration in clinical transplantation trials. It may be that patients with striatonigral degeneration, who are unresponsive to L-DOPA, show a relatively high probability of non-responsiveness to therapy, and a correspondingly high probability of meeting the selection criteria (severe illness, unsatisfactory response to conventional therapy) for inclusion in experimental trials. Although patients with striatonigral degeneration can be distinguished by a poor reponse to L-DOPA, it is often not possible to make this diagnosis reliably except by post-mortem examination (cf. /33/). Patients with striatonigral degeneration are also relatively younger than patients with Parkinson's disease (cf. /73/). In several clinical trials, it has been considered desirable to employ relatively young patients. Several very young patients, in fact, have been employed in clinical transplantation trials. The tendency to include young patients may further increase the probability of including patients with striatonigral degeneration. Although it is not impossible that dopaminergic tissue transplants would improve function in patients with striatonigral degeneration, such an improvement, of course, would not have been predicted from the literature on transplantation in animal models.

This latter study /112/ is certainly a potential model of experimental design for future studies, in terms of the controlled design, blind ratings of quantifiable motor tasks, and consistency which was permitted due to the use of cyopreserved tissue. On the other hand, there were drawbacks to this particular study, including the relatively short (one-year) controlled evaluation period, implantation of tissue into the caudate only, and the use of donors which were in some cases of a gestational age slightly exceeding what appears to be optimal. The development of an effective transplantation methodology is bound to be a complex process which will involve improvements

in procedures and experimental design over the course of a number of clinical trials.

Several reports on transplantation in human patients have employed tissue of a gestational age which exceeds the optimum that would be expected from studies of transplantation of human fetal tissue into rat hosts. Freeman /42/ (see above) presented data which suggest that it is not likely that human tissue older than approximately 10 weeks gestational age would be effective. It is therefore conceivable that the improvement in some of the clinical studies is due to some factor other than graft survival and host brain reafferentation.

On the other hand, it is also possible that synapses are irrelevant for the clinical improvement. This could be the case even for younger tissue which does reafferent host brain and even produces synapses, since improvement has been observed in some studies using tissue more mature than what would seem to be optimal. Since the improvement to some degree (especially for the near-term effects, i.e., up to one year) seems to be generally similar for all of the transplantation techniques, perhaps reafferentation is not important. Another caveat should be pointed out as well: The conclusion that clinical transplantation will require tissue younger than 10 weeks is based largely on studies of human tissue transplantation into rats, *in vitro* studies and examination of human fetal tissue. Although this extrapolation is quite reasonable, the possibility that survival and development of more mature donor tissue can be observed for transplantation of human tissue into human brains, and especially into the brains of patients with Parkinson's disease where unusual trophic interactions may be present, cannot be ruled out entirely.

The one facet of clinical improvement that, so far, has been reported only for transplants using young donor tissue is the very long-term gradual improvement observed between one and three years after transplantation, by Widner *et al.* /154/, Lindvall *et al.* /84/ and C. Freed *et al.* /39/. Each of these studies used donor tissue younger than 10 weeks, which would be expected to be at least capable of reafferenting host brain. Nonetheless, there were other unique aspects of these studies including transplantation into the putamen. It is also notable that, in animals, the functional effects which are observed following SN grafts generally require tissue which is capable of growing new dopaminergic fibers into the host brain. A reasonable hypothesis then, regarding the clinical results, is that the relatively short-term effects, seen up to approximately one year, involve a mechanism other than reafferentation of the host brain, as generally similar effects can also be produced by several types of fetal tissue transplantation and even, at least to some extent, transplantation of other tissues, including adrenal medulla and superior cervical ganglia. A gradually-developing improvement that continues over the very long term, that is, more than one year after transplantation, may be suggestive of effects which involve the development of new connections between graft and host brain. This hypothesis, however, is far from confirmed and will require considerable additional evidence.

NEW MODELS AND NEW POTENTIAL APPLICATIONS

Nakao and associates /97/ presented data on transplantation of superior cervical ganglia (SCG) to the brain in animal models of Parkinson's disease. In rats, SCG from 2-3 day postnatal rats was grown in culture for four to six weeks. For transplantation, these cells were scraped off of the culture dishes and resuspended, but not entirely dissociated. Either SCG cells or sciatic nerve, as a control tissue, was transplanted into the brains of rats with unilateral lesions of the SN. Rotational behavior was gradually decreased over the course of 12 weeks, finally reaching a decrease of approximately 70% as compared to the control group. Excellent examples of grafts with numerous surviving catcholaminergic cells were shown using histochemical fluorescence. Wu *et al.* /161/ also showed that the development of kindled seizures in norepinephrine-depleted rats could be delayed by SCG grafts into the amygdala and piriform cortex. Five animals with substantially surviving grafts showed a greater than four-fold increase in the number of stimulations required to induce seizures,

while no effect was seen in another five animals with poorly-surviving grafts.

In primates, using the MPTP model, long-term improvement in three monkeys was reported. This was accompanied by a slight increase in plasma homovanillic acid /70/. Convincing evidence of long-term survival of the grafts after two years was shown using catecholamine histochemical fluorescence. In the primate studies, although improvement was reported in the animals that had received grafts, there was not a very clear difference between the experimental and control groups.

Itakura also presented data suggesting the possible use of transplantation of stellate ganglia in human patients with Parkinson's disease /69/. Eight patients, 45 to 59 years of age, received unilateral stereotaxic autografts of stellate ganglion, cut into small fragments. No L-DOPA was administered starting one week before transplantation and during the entire follow-up period of 2 to 12 months. Gradual improvements in bradykinesia and gait disturbance were reported in seven of the eight patients. From timed tests of motor function, the improvement appeared to be bilateral. There was a transient worsening of tremor in seven of the eight patients from two to four weeks after transplantation. Other complications of the surgery included probable manifestations of stellate ganglion removal. In one severely affected patient, who did not improve, it was noted that the catecholaminergic cells in the stellate gangion were damaged.

A model presented by Sharp and coworkers /127/ approaches the traditional "replacement" model of neural tissue transplantation from a quite different perspective. Lesions of the frontal cortex induced atrophy of ventroposteromedial thalamic neurons. Within 5 hours of cortical lesions, whisker simulation was no longer able to activate thalamic neurons. Nonetheless, at this time the thalamic neurons were still intact, and cortical tetrodotoxin did not eliminate the ability of whisker stimulation to activate these thalamic neurons. These data suggest that cortical inputs to the thalamus are not directly required for whisker activation of thalamic neurons; but, following cortical removal, the synaptic connections from brainstem to thalamus lose their efficacy. The neuronal death that occurs following cortical removal is associated with thalamic hypometabolism as measured by local cerebral glucose utilization. Transplantation of fetal cerebral cortex into the sites of cortical lesions maintained thalamic glucose utilization and, in some animals, restored the ability of whisker stimulation to activate ventroposteromedial thalamus. It is suggested that the cerebral cortex provides a factor which is required for the survival of neurons in the ventroposteromedial thalamus and for the maintenance of synaptic connections from the brainstem to the thalamus. Cortical transplants may provide this trophic factor, thereby facilitating the maintenance of these brain-stem-ventroposteromedial thalamus synaptic connections.

Another model of transplantation in cortical injury, described by Bermudez-Rattoni *et al.* /9/ examined the effects of insular cortical lesions on conditioned taste aversion. Lesions of the insular cortex impaired conditioned taste aversion learning, and transplantation of insular cortex into the lesion site produced significant recovery of taste aversion learning in insular cortex-lesioned rats. Transplantation of occipital cortex did not produce recovery. It was found that the insular cortex grafts, but not the control occipital cortex grafts, released acetylcholine in response to depolarization, suggesting a role of acetylcholine release in the behavioral recovery. Afferents from the cortical grafts were found to extend into the host thalamus and amygdala, with these connections developing over a 60-day time course, roughly parallelling the time course of behavioral recovery. Based on the hypothesized role of acetylcholine in the behavioral recovery, effects of NGF were examined. NGF was found to accelerate the time-course of behavioral recovery after insular cortex grafts, but had no effect on the long-term outcome. NGF had no effect alone or when combined with occipital cortex grafts. One interesting aspect of these experiments /9/ is that they suggest a specific neurochemical mediation (i.e., acetylcholine) of a behavioral response to cortical tissue transplantation.

A novel transplantation model described by Sortwell and Sagen /133/ involved the use of

"learned helplessness" and "forced swimming" models of depression. "Learned helplessness" describes a paradigm in which animals subjected to inescapable stress show deficits in their ability to avoid subsequent escapable stress. This deficit can be alleviated by antidepressant drugs. Sortwell and Sagen /133/ found that grafts of either adrenal medulla (to produce catecholamines) or pineal gland (to release serotonin), or a combination of adrenal medulla and pineal gland grafts in the frontal cortex prevented the learned helplessness reponse, but control grafts of muscle tissue had no effect. The "forced swimming" test involves the measurement of immobility induced by forced swimming in a confined enclosure, and is also used as an animal model of depression. Transplantation of adrenal medulla or pineal gland grafts, but not control grafts of sciatic nerve, were found to reduce immobility scores six to eight weeks after transplantation. Biochemical and immunohistochemical studies suggested that both the adrenal medulla and pineal gland grafts survived well. This is a new model which may suggest applications of neural tissue grafting in cortically-mediated phenomena.

Senatorov and associates /126/ suggest that functional graft-host connections may be present which cannot be activated under normal conditions. Among other receptor systems, excitatory synapses in the cerebral cortex may be mediated by the N-methyl-D-aspartate (NMDA) receptor complex, and activation of this receptor is regulated by magnesium ions. When magnesium ion concentrations are increased, greater levels of glutamate occupancy are required for ionic conductance by the channel. To determine whether graft-host connections are present which are "silent" under conditions of normal magnesium ion concentration, cerebral cortex grafts were studied using a slice preparation. Slices containing fetal cortical grafts were examined in lesion cavities and surrounding host cortex. In a medium of standard artificial cerebrospinal fluid (CSF), electrical stimulation of the host brain elicited field potentials in four of seventeen preparations. When the medium was changed to magnesium-free artificial CSF, field potentials were recorded in 10 of the 17 rats. The amplitude and duration of the evoked field potentials were increased in magnesium-free medium, for both graft responses to host stimulation and vice versa. NMDA antagonists decreased the amplitude of the evoked field potentials. These data suggest that connections between transplanted cerebral cortex and adjacent host brain may be mediated by NMDA-type glutamatergic synapses. There is also a possibility that some of these synapses are inactive under normal conditions of endogenous synaptic activation. These data would be consistent with several findings that functional effects of grafts can be enhanced by pharmacological stimulation; for example, when SN grafts are activated by amphetamine administration in animals with SN lesions (cf. /40/), or when nicotonergic drugs are employed to activate adrenal medulla grafts in pain models (cf. /118/).

Transplantation was employed in a model of Down's syndrome, using the trisomy 16 mouse. These trisomy 16 animals do not survive past late gestation, but fetal brain tissue from these animals can survive as transplants in the brains of normal mice. Hohmann and co-workers /63/ reported that these grafts did not show obvious abnormalities, other than a transient increase in the expression of amyloid precursor protein in trisomy 16 grafts as compared to controls, which was seen two weeks after transplantation but had disappeared by one month. Hohmann /63/ also observed abnormal amyloid precursor protein immunoreactivity in the CA3 region of the host hippocampus in many of the animals bearing trisomy 16 grafts. Stoll *et al.* /137/ also failed to find obvious signs of Alzheimer's-like degeneration in trisomy 16 grafts. On the other hand, Holtzman and colleagues /64/ observed time-dependent atrophy of cholinergic neurons within trisomy 16 grafts, using cell suspension grafts into the hippocampus. This atrophy was not a gross or obvious neuronal loss or degeneration, but was manifest as a modest but statistically significant decrease in the size of cell somata (126 μ^2 versus 156 μ^2 for the controls). The small size of the change suggests that it would not be seen unless quantitative meaurements of cell soma size were used. NGF administration was found to reverse this cholinergic neuronal atrophy, in that it increased the size of all cholinergic cell

somata. The effects of NGF were not specific for trisomy 16 grafts, however, in that the size of all cholinergic neurons was increased. These papers are further described in the accompanying report by Geller /47/.

An example of the use of transplantation to study physiological regulatory mechanisms was presented by Murphy *et al.* /96/. These experiments involved the use of normal Wistar rats and a spontaneously hypertensive rat strain to study blood-pressure regulation. Transplantation of the antero-ventral third ventricle region of the hypothalamus, an area which has been implicated in control of blood pressure, from hypertensive to normal rats resulted in chronic blood pressure elevations in normal Wistar rats. The ability of tissue grafts to elevate blood pressure appeared to depend strongly upon donor tissue age. Hypothalamic tissue from E19-20 donors elevated blood pressure for 30 - 60 days, while tissue from younger E15-16 donors elevated blood pressure for at least five months. When the younger E15-16 donors were used, even grafts of cerebral cortex were able to induce blood pressure increases for at least four months after transplantation. These data suggest that the genetic control of blood pressure is anatomically localized, does not involve complex circuits, and that the abnormality may be "transmissable" by transplantation of relatively isolated tissue fragments. As the effect can be transferred by even cortical tissue, the defect may even be a general property of CNS from the abnormal rat strain, rather than a hypothalamic abnormality. This is an example of the use of transplantation to localize primary versus secondary control of neuronal circuit functions /96/.

Studies by several groups have shown that transplantation of the suprachiasmatic nucleus into the hypothalamus of rats with suprachiasmatic nucleus lesions, and consequently disrupted circadian rhythms, can restore circadian rhythmicity. Lehmann *et al.* /80/ described their experiments on this topic. It was noted that the restoration of circadian rhythmicity displays the pacemaker properties of the donor cells, demonstrating that the donor cells themselves continue to express their intrinsic pacemaker activity in the host brain. Another experiment related to functions of the suprachiasmatic nucleus was described by Aravich *et al.* /3/. Animals that are given voluntary access to running wheels, but are placed on a time-restricted feeding schedule, develop a disorder termed "activity-based anorexia", which involves a progressive increase in running and a substantial loss of weight as compared to rats that are placed on a restricted feeding schedule only. This syndrome is aggravated by lesions of the suprachaismatic nucleus or continuous illumination. Immediately after receiving lesions of the suprachiasmatic nucleus, animals received transplants of rostral hypothalamus (containing the suprachiasmatic nucleus) or control grafts of fetal cerebral cortex. After 30 days, the animals were subjected to conditions designed to induce activity-based anorexia; namely, 1.5 h per day access to food and 22.5 h per day access to a running wheel. Susceptibility to activity-based anorexia, defined as a 25% weight loss, was seen in 69% of the controls but in only 31% of the animals with hypothalamic transplants. The animals with the hypothalamic transplants showed a significantly greater food intake than the animals with control grafts of cerebral cortex, and no significant difference in amount of running activity (wheel turns). The animals with hypothalamic transplants, however, tended to run more (not less, as might be expected) than the controls. This is an interesting example of the use of transplantation to examine the neural circuits involved in a model of a neuropsychiatric disorder.

An interesting technique for graft implantation into spinal cord, which might be used in a modified form in other anatomical regions such as cerebral cortex, was described by Grijalva and colleagues /53/. These investigators sought to improve graft-host adhesion by enzymatic manipulation of the site of a spinal cord lesion. Rats received spinal cord lesions by the weight-drop method, and after nine days received fetal spinal cord grafts following aspiration of necrotic tissue at the lesion site. In the experimental group, the lesion site was bathed in a solution of 0.25% collagenase and 0.1% hyaluronidase for 20 min, followed by application of 0.1 M EDTA for 30 seconds. The enzymatic

treatment did not change the total number of animals with surviving grafts, or the total amount of surviving graft tissue. There was, however, approximately a 2.7-fold greater surface of graft-host contact in the animals treated with enzyme solution. In addition to spinal cord, similar methods might be useful in other circumstances where graft-host contact is impaired by scar formation.

Weiss /114,115,152/ presented data on a method to generate cells from the CNS which express neuronal and glial properties by relatively simple manipulations in tissue culture. Cells obtained from the brain under certain conditions can be induced to proliferate in tissue culture under the stimulating influence of epidermal growth factor (EGF), generating groups of cells which they have termed "neurospheres". These neurospheres can be propagated and will continue to divide; however, when they are subsequently grown on coated surfaces without EGF, cells from these neurospheres differentiate to form cells with both neuronal and glial properties. It might eventually be possible to use methods such as these to generate, from the human CNS, glia, neurons, or partially differentiated cells with sufficient neuron-like properties to be useful for transplantation. Although most readily generated from fetal tissue, some such cells can even be obtained from the periventricular striatum of mature animals. These studies suggest that stem cells representing neural/glial progenitor cells continue to be present even in the mature CNS to some extent. Under appropriate conditions, it may be that these cells can be induced to differentiate to form mature neurons or glia.

Possibly the most exciting new development was presented by Sagen and associates /117,119/, who discussed the possible use of adrenal medulla transplants for chronic pain. Sagen first reviewed their findings on the effects of adrenal medulla transplants in animal models of pain, including data showing that these grafts are effective in alleviating manifestations of pain, such as vocalizations and weight loss, in chronic pain models /54,120,149/. Adrenal medulla grafts were tried in terminal cancer patients with severe pain who had a prognosis of six months of less. Each patient received an allograft of 1.5 precultured adrenal medulla into the spinal cord by lumbar cisternal puncture, and immunosuppression by cyclosporin for approximately two weeks. Three patients aged 52-69 years, with carcinoma of the colon and suffering from severe pain, showed substantial improvement, consisting of a lowering of self-assessed pain scores. All three became nearly pain-free between 3 and 16 weeks after the surgery. Each of the three carcinoma patients remained pain-free therafter, and in two cases lived for 11 to 12 months free of pain. Of the other two patients in the trial, aged 41 and 49 years, with breast carcinoma and Gardiner's syndrome, one reported no pain relief, and only transient improvement was observed for the fifth patient. These data suggest that adrenal medulla transplantation may eventually be found to be a significant alternative or adjunct to narcotics for severe chronic pain /117,119/.

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