NEW DEVELOPMENTS IN NEUROSCIENCE:

NEURAL TRANSPLANTS
AND
NERVE REGENERATION TECHNOLOGIES

ETHICAL ISSUES

FINAL DRAFT

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INTRODUCTION

Emerging neural transplantation and nerve regeneration technologies promise to reverse the course of devastating neurological diseases, as well as correct severe neurological damage or impairment. Such conditions often lay waste to a personal life, arguably destroying the individual person by undermining the capacity for autonomous motor and mental functioning. Since neural grafting involves the surgical intrusion of the brain in order to effect structural and functional changes, the assumption underlying its experimental and therapeutic use is that improvements in the full spectrum of mental functioning associated with the autonomous person can be effected through the alteration of brain structure and/or chemistry. This suggests that what is commonly called the mental is really entirely physical, or at any rate has causes that are entirely physical in nature. Hence, these emerging technologies challenge embedded metaphysical conceptions of the nature of the human self, conceptions which are intimately connected with fundamental beliefs about the nature and components of reality and ultimately, about the meaning of life (Churchland, Paul, 1988).

Reflection on the metaphysical/ontological assumptions underlying neural transplantation might seem an interesting but idle exercise to some. However, these neural technologies presuppose a particular metaphysical stance called materialism, the view that the
human self is essentially and entirely a physical entity, that the mental concepts and language with which we communicate about human behavior refer to nothing real, and that the locus of personal identity is the brain or the brain/body combination unique to each person. Such metaphysical assumptions contradict prevailing cultural conceptions of the nature of the self, personal identity, and of the relations among the mind, brain, and body.

Further, given the prevailing belief that the self or personal identity is intimately connected with the brain and its functioning, the transplanting into the brain of any tissue, from whatever source, must be viewed as a potential modification of the self. For these and other reasons, serious ethical concerns attend human clinical trials, and the potential therapeutic use of these nonvalidated neurological therapies.

In this report, the focal point for the elaboration of the metaphysical and ethical issues raised by neural transplants will be the neural grafting (autograft, allograft, and xenograft techniques) of dopamine-producing tissue into the human brain in order to combat the progress of Parkinson's disease (to be abbreviated 'PD' throughout the remainder of this text), a debilitating neurological condition of unknown etiology but known outcome, namely the neurological deterioration of the patient, which entails the complete loss of motor control as well as dementia associated with mood and personality function. (Gregory, 1987). The PD patient suffers loss of autonomy not because of cognitive deficit per se, but because the area of the
brain responsible for the transformation of cognition and intention to physical activity becomes increasingly impaired. The deterioration and destruction of the dopaminergic neurons of the substantia nigra are causally correlated with the functional losses characteristic of PD. Since levodopa therapy, the pharmacological substitution of dopamine has failed as a cure for PD, research has concentrated on the replacement of the destroyed brain tissue with dopamine-producing tissue that will provide a continuous, on-site supply of the essential neurotransmitter. (Sladek, Redmond, Roth, 1988; Backlund, Granberg, Hamberger, 1985).

Swedish researchers developed extensive knowledge of neural grafting through the study of rodent models, and on the basis of that knowledge, proceeded with human clinical trials of adrenal medullary autografts. Recent research in the United States has focussed on primate models, and human trials have continued, inspired by initial reports of Swedish, Mexican, and British research.

There is considerable controversy over the justifiability (both scientific and ethical) of the move from animal to human trials of adrenal medullary autografts. The Swedish investigators, indisputably the world leaders in this research, apparently made the leap from rodent to human models because anti-vivisection regulations prevented their exploration of primate models beforehand. This suggests that they initiated human trials not because human research constituted the next most rational step in PD grafting research, but
because external considerations directed them to human trials if they were to seriously pursue grafting remedies for PD at all (Backlund, Granberg, Hanberger, 1985).

Significant information has been obtained from primate models, information that many think legitimates greater attention to clinical trials using neural tissue from fetal allografts (Hoffer, 1988) and xenografts (Brundin, Streeker, et al, 1988; Perlow, 1987) than adrenal medullary autografts of non-neural tissue, given the uneven and scarcely encouraging results of adrenal grafting thus far. At minimum, many argue that it is time to take stock of what our human trials tell us, rather than carry on with autografts. At any rate, many feel that there is still a great deal to learn from basic animal research, that more information is needed about the optimal age of the patient, the grafting site (Perlow, 1987), and the the optimal tissue source (Sladek, Redmond, Roth, 1988) and the importance of other factors enabling the graft to survive and grow (Bjorklund, Stenevi, 1985). The grounds of these disputes will be detailed in the section of the report covering research issues.

The majority of the adrenal grafting research in human patient-subjects has involved the transplantation of an autograft (a graft from the patient's own adrenal gland) into the patient's brain. Such a procedure is both arduous and risky, since it requires two major surgeries. Thus far, some patients under sixty years of age have exhibited varying degrees of symptomatic relief, but the underlying
biochemical phenomenon leading to functional improvement remains unclear. Five or six research centers in the United States are engaged in this research, each following its own protocol. There is no coordinated research effort underway in the United States at this time, and there is no organized data gathering procedure in place. Further, there has been no apparent effort to foresee the impacts of neural transplantation on our health care delivery system. Neural grafting to relieve the symptoms of PD is an apt case study for this report, since it is the only disease for which CNS neural grafting has been attempted, and it poses the same philosophical issues as many other nerve grafting and nerve regeneration technologies. Hence, the results of the focus on PD can be extrapolated to these other cases.

The philosophical tradition can be characterized as the history of careful thinking about the nature, meaning, and conduct of human life. As such, it encompasses metaphysical, epistemological, and ethical reflection. In part I of this report, the **metaphysical** issues posed by neural grafting will be systematically presented and discussed. Questions about the nature of the human self, the mind/brain relationship, and the retention of personal identity will be addressed. The linkage between these and other metaphysical concerns many would consider to be religious in nature will be elaborated and discussed. Then, an effort will be made to assess the prevailing public conception of the self, and of the relations among the mind, the brain, and the body. In part II, the **ethical** concerns attending the clincal
trials of neural grafting (including the transitions from animal trials to human trials to human therapeutic use) of neural grafting will be delineated and discussed against the background of the nature and early detectability of PD, the progressive loss of patient autonomy associated with the disease, the epistemological deficits that inevitably accompany clinical and therapeutic practice, and the metaphysical concerns centering on the mind/brain debate elaborated in part I.

The central ethical problem in relation to neural transplantation research and therapeutic use is the development of an adequate quality of life framework enabling the patient-subject to assess the value of this experimental or therapeutic modality relative to alternatives. Such a quality of life framework is essential for negotiating informed consent with patient/subjects and patients (should neural grafting become a recognized therapeutic option). Following a discussion of the metaphysical and ethical issues posed by neural transplantation generally, and the ethical dilemmas associated with the research process itself, a quality of life decision-making perspective will be developed, and the role and responsibilities of institutional review boards will be addressed. Throughout the discussion of this report, issues of justice and the allocation of scarce resources will be discussed as they arise in connection with the human trials and the therapeutic use of neural transplants.
METAPHYSICAL ISSUES

Introduction

Neural grafting involves the surgical alteration of the brain in order to effect functional behavioral changes characteristic of the autonomously functioning person. A discussion of the ethical issues raised by these technologies must begin with an explanation of some of the central issues in the philosophy of mind, an area of philosophical discussion formerly housed in metaphysics but now in the philosophy of science (Dennett, 1978). Two central issues in philosophy of mind are pertinent to neural grafting: the first concerns the nature and relations of the mind, brain, and body; the second, the conditions necessary for the retention of personal identity. Responses to these issues are intended to provide a clear understanding of what appears to be a unique element of reality - the person.

The context for this ontological understanding (i.e., the understanding of a particular kind of being, the person) is the pursuit of an adequate metaphysics (i.e., a complete understanding of the nature and components of reality, and a view about the meaning of life). Since the metaphysical assumptions underlying neural
transplantation contradict culturally pervasive metaphysical assumptions concerning the mind-brain-body connection, and since neural grafting is intended to alter the self by restoring autonomy, significant ethical dilemmas surround its experimental and therapeutic use.

Someone engaged in philosophy of mind stands with one foot outside the debate among our common-sense, intuitively-based view of the mind, scientific psychological theories, and neurobiological theory. From that stance, she articulates the conflicting metaphysical assumptions underlying these alternative theoretical perspectives. In recent years, philosophy of mind has been enervated by developments in the sciences, and so the philosopher’s other foot lies firmly within the scientific domain, evaluating the manner in which evidence provided from within these alternative theoretical perspectives vindicates or compromises certain operating assumptions about the human self and the mind-brain connection. (Dennett, 1978).

The Mind/Brain Debate in Philosophy and Science

Essentially, the mind/brain debate within the philosophy of mind concerns attempts to understand the nature of conscious intelligence by explaining the relationship between the mind and the brain. What is the source of conscious, intelligent behavior? Is the mind something real? If so, what is the mind? What connection, if
any, has it to the physical brain? What role does each play in the production of consciousness and purposeful activity? What is the self? How do the mind, brain, and body figure in the distinctive identity of the individual person? What are the necessary conditions for the possession and retention of personal identity? (Churchland, Paul, 1988).

Most now view research on the mind-brain as an empirical enterprise, or at least acknowledge that empirical study is relevant to answering some of these questions. The goal of such study is to unveil the nature, causes, and effects of mental states and processes. Given the knowledge that structural brain damage and alterations in brain chemistry produce alterations in what we call mental states and processes, it is quite natural to wonder about the extent to which psychological states and processes really are or can be reduced to brain states and processes. To contemplate such a reduction of psychology to neurobiology is to contemplate the development of a unified theory of the mind-brain, in which common-sense psychology (often referred to in the literature as the 'folk psychology'), as well as the more elaborate and experimentally-based theories of scientific psychology, are reduced to neurobiological theory. If such an intertheoretic reduction is constructed, a phenomenon in one theory is said to reduce to a phenomenon in the other. If such a reduction were to be achieved between psychology and neurobiology, it would
follow that mental events are identical with a brain events, or that they really are particular brain events.

Pertinent to this report is the fact that such intertheoretic reductions are often "disruptive of the wider metaphysics." (Churchland, Patricia, 1987). The reduction of folk and scientific psychology to neurobiology would be no exception. Specifically, ontological simplification may result from the identification of one level of phenomena with another. This means that entities formerly believed to be substantial and enduring elements of reality are now dropped from the scheme of things. Unfortunately, such ontological failures often call into question other fundamental metaphysical assumptions people hold. Hence, when one theoretical approach is reduced to another, the ontological fallout may have ethical implications. Such is the case in neural transplantation, since its practice presupposes the possibility of reduction.

The overarching debate in the philosophy of mind, then, is between reductionists (those who argue for the possibility of a unified mind-brain theory, and antireductionists (those who argue for the meaningfulness of our common-sense mental categories because they believe in the independent reality of mental states and processes). The reductionist parties to this debate hold some version of materialism; their antireductionist opponents, either dualism or functionalism.
Dualists hold that there is a distinctive mental aspect of the human being that is not reducible to its physical aspect. Some dualists maintain that there is a nonphysical mind that is a component of the self; other dualists, that the mental aspect of the self consists of nonphysical properties that emerge from the activities of the physical brain. Functionalists construe mental states as functional states of the brain that mediate between sensory inputs and behavioral outputs. The complex physical organization of the brain, along with its physical states and processes, generate functional mental states that are dependent upon, but not identical with (and hence not reducible to) brain states and processes. Thus, functionalism reserves an autonomous domain for scientific psychology.

While one wishes to avoid any illicit philosophical gerrymandering, the differences between dualists and functionalists will be overlooked in this report. It is easiest to convey the important metaphysical and ethical challenges posed by neural grafting by simplifying the discussion to a focus on the disagreement between the reductionist materialists on the one hand, and the antireductionist dualists on the other. Patricia Churchland suggests that "substance dualism and and property dualism are perhaps the most familiar if not the most cogent of the antireductionist reservations, and the best of these arguments certainly jell the most common lay suspicion about reductionism." (Churchland, Patricia, 1988). Thus, since dualism is the culturally entrenched theory of mind that grips popular thinking and is
consistently reflected in language, and materialism is the perspective underlying the use of the new neural technologies, it is entirely defensible to proceed in this way in the present context. This theoretical division is the crux of the matter, so far as a delineation of the ethical issues associated with neural grafting is concerned.

Personal Identity Theory and the Individual Self

A perennial question in philosophy of mind, one that has inspired a host of theories down through the centuries, concerns the nature of the self and the conditions under which the individual remains the same, i.e., retains her unique identity across time. This problem of what constitutes the identity of the individual self and accounts for the self's continued existence might seem to be made more complex by a dualist conception of the self, since there are two aspects of the self to be considered: the mind and the body. A singular materialist conception of the self would seem to vitiate the need to explain the role of both the mind and the body in personal identity, or at least remove the necessity of sorting out the role of the mind in personal identity. However, the problem simply emerges in a new language: which physically based functions ground one's existence as a unique individual? Which functions of the human self are essential to the retention of personal identity across time? The problem has not gone away.
Neural grafting encounters the problem of personal identity just because the transplantation of any tissue into the brain must be viewed as a potential modification of the self. That is, given the intimate connection between the individual self and the brain, the implications of neural grafting for the modification or designing of the self must be contemplated. Neural tissue plays a unique role in the identity or personal characteristics of the individual person. Because of its intimate association with who and what each of us is, unlike cardiac and pulmonary tissue, neural tissue has a special moral status. Hence, its alteration poses dilemmas concerning the nature and preservation of personal identity.

These moral issues are rendered more complex when the kinds and extent of modification of the self are uncertain. Some kinds of alterations in the self, e.g., changes in the capacity to initiate and carry out purposive movement, may be less associated with personal identity than with the full exercising of personal autonomy. However, the transplantation of either non-neural adrenal tissue or neural tissue into the brain, focusses attention on the questions: What tissues, transplanted into what areas, to alter what functions, represent morally justifiable attempts to alter the behavior and functioning of the self? Which of these functional alterations would constitute substantive alterations in personal identity?

The basic fact, that alterations in the brain's structure and chemistry are being made in order to alter central functions of the self,
is morally problematic because (1) the relationship between these central functions and personal identity must be determined; and then (2) interventions altering these functions must be morally evaluated. To accomplish the latter requires a workable conception of personal identity, i.e., a theory about what functions are essential to an individual’s retention of personal identity. For example, if a particular neural implant perfectly restores motor functioning yet results in the permanent erasure of memory, it must be concluded that whatever gains this represented in autonomy (if any), the loss or alteration of the self was scarcely worthwhile.

This suggests that some brain functions are central to who and what each of us is. Neural transplants are intended to alter particular brain functions. Hence, their potential to modify the self in substantial, identity-effacing ways must be confronted whenever surgical intrusion into the brain is contemplated. Such problems are exacerbated when the transplanted tissue is an allograft (neural tissue from another member of the same species), or a xenograft (neural tissue from a member of a different species). Some favor these alternative tissue sources over adrenal autografts on both scientific and ethical grounds (e.g., human fetal allografts, because they appear to work better and require little immunosuppression; and fetal xenografts, because they avoid the ethical dilemmas associated with the use of human fetal tissue)
If the public holds a dualist theory of mind, the theoretical assumptions underlying neural grafting - a materialist theory of mind and a brain-based conception of personal identity - the new neural technologies create a significant need for public education, and for full disclosure for any research or therapeutic use of neural grafting.

The Public's Position: Dualism cum Materialism

Briefly then, dualist theories presume that the nonphysical mind exists and is the source of mental phenomena, that the physical brain exists and is the source of brain events, and that these two systems of the human self are distinct and irreducible. Materialist theories hold that mental states and processes are identical with brain states and processes. The operating assumption of materialist theories is that neuroscience will eventually uncover the brain-based mechanisms and specific neural structures that ground what are referred to as "mental" capacities and activities.

What evidence is there that the popular theory of mind often referred to as "folk psychology" is dualist? Ordinary metaphysical views of the mind accept the reality of mental events. Mental states such as thoughts, feelings, beliefs, and desires are seen as real and irreducible. Even those who are confirmed materialists are more inclined to say that a pain is a "feeling" than a particular pattern of neurons firing. Existing language, derived from a time when there was
little understanding of the neurological realities underlying thoughts, compulsions, and feelings, suggests that in addition to the brain, there is a non-physical mind whose states and processes are introspectively accessed in our own case, and are inferred on the basis of overt behaviors in the case of others. Thus, the language with which people communicate about themselves is about mental states and processes, not about brain states and processes, even though neuroscience has already established compelling correlations between brain states and processes and functional/behavioral outcomes.

Further, the Judeo-Christian heritage and prevailing religious beliefs suggest that persons are endowed with a non-material soul that somehow survives the death of the body. This reinforces the view that there is something more to the human self than a physical body housing a brain, and that that something more is of substantial and enduring significance because of its tight link to personal identity. Since the individual self is believed to survive the death of the body, the body plays no apparent role in the retention of personal identity: the body may be the basis upon which an individual is identified and reidentified in the present life, but it is not who that individual is in an ontological sense. Personal identity is tied to the non-material mental aspect of the person, not to the physical aspect.

The prevalence of dualist conceptions of the self raises a concern about how neuroscience ought to proceed with clinical research and therapeutic practice, if the theoretical assumptions underlying neural
grafting are drastically at odds with the lay person's theory about the mind/brain connection. Clearly, patients may choose to reject this new treatment modality for metaphysical reasons. Because of this, concern with promoting patient understanding and eliciting patient preferences must become an important element in the negotiation of informed consent.

In some respects this dilemma can be demonstrated to be only a seeming one, even though it must be taken very seriously in the negotiation of informed consent at both the experimental and therapeutic levels. Divergences between the lay person's theory of mind and neurobiological theory have arisen before: neural grafting is not the first development in modern medicine to challenge the prevailing lay theory of the mind/brain relation. And by some inexplicable process of accommodation, the public has come to terms with the use of various neurological practices presupposing the materialist stance.

For example, the public has accepted the use of the brain death criterion for declaring death. This means that they have accepted the equation of the permanent absence of brain life with the death of the person. On this basis, they have also accepted the practice of harvesting organs from a respirator-supported brain dead patient. Clearly, the lay person's attention has been shifted from the observable "life" functions of respiration and heartbeat to the life-supporting function of the brain. Somatic functioning, or the grossly
observable functioning of the body, has been displaced by brain functioning as an accurate indicator of the ongoing presence of life.

There is, however, an instructive exception to the general public acceptance of the brain death criterion. Recently, the Bioethics Commission of the state of New Jersey recommended that the state legislature adopt a determination of death statute that deviates from the United States' Uniform Declaration of Death Act by its inclusion of a conscience clause for those whose metaphysical/religious views commit them to a somatic conception of human life and death. One might argue that such policy provisions are the stuff or the staff of life in a pluralistic society. But the general lesson such policy maneuvers suggest for neural grafting is that ethical procedures require metaphysical sensitivities. Thus, any informed consent procedure must speak fully to the metaphysical commitments underlying the use of such therapeutic modalities.

There are further examples of the public's apparent ability to function with two theories of the mind/brain relation. Although a headache is a pain in the head, and the feeling of pain is directly verified only introspectively, one takes pills to relieve it, tacitly acknowledging that some inner feelings have underlying physical-chemical causes that can be tinkered with by calculated physical-chemical interventions. In a related vein, many people resort to psychiatrist-prescribed psychoactive drugs which hype up specific neurotransmitters, in order to manage situationally-induced
depression which has somehow lowered the production of these neurotransmitters, while they adapt to a new life-situation. In ordinary language, they manage the intensity of one emotional state (depression), while they work at reconstructing personal stability on new terms.

Despite these interesting examples, it is perfectly clear that the dualism associated with common-sense psychology is far from becoming merely a Sunday-morning and deathbed way of conceiving of oneself. Nor, for that matter, is it an inefficacious approach to understanding and modifying human behavior. It has already been pointed out that language is heavily dualist, and so communication proceeds in a dualist framework. More telling than this however, folk psychology functions effectively in two important ways: it enables people to construct meaningful explanations and predictions of human behavior, and on this basis to select and adjust their behaviors toward each other in appropriate ways. In short, it functions as any such theory should: it enables them to understand themselves and each other sufficiently so that they can formulate goals, devise means to achieving them, and reassess goals and means if appropriate behaviors are not forthcoming. So there is a sense in which common-sense, intuitively-based psychology cannot be deemed faulty, even though it is not a highly detailed, hierarchically organized set of hypotheses like a scientific theory is. (Dennett, 1978).
Explanation and prediction become more demanding, however, when behavior is aberrant, whether the result of chemical imbalance, disease, structural damage to the brain, or external factors impacting the mechanisms underlying behavior. In such cases, the mechanisms of scientific psychology and/or neurobiology may become especially useful for explanatory and predictive purposes. But this is not to say that folk psychology is essentially flawed.

Moreover, it appears to be the case that when the public is educated about the underlying neurobiological phenomena and their relation to the functioning of the body as a whole, and there are no insurmountable metaphysical impediments among their basic beliefs, they are generally willing to operate on materialist assumptions, whether they are conscious of doing so. Obviously, we have seen a remarkable transformation in the public understanding of the role of the brain and central nervous system in consciousness, the retention of personal identity, character traits, and behavior.

Thus, it seems that the public is in a time of transition, or has at least arrived at some modus vivendi between dualist and materialist assumptions, such that there should be no general resistance to the new neural technologies for the treatment of PD and other neurological disorders. However, given the metaphysical commitments underlying these technologies, it must be assumed that there is great need for public education as well as for a precise eliciting of patient preference while negotiating informed consent.
Those working in mental health and in neuropsychology must take the task of educating their patients and the public to heart as new neurological interventions are developed. The extent to which patient preferences and values are to be honored in public policy decisions must be debated and decided. For example, if a patient refuses an established life-saving neurological intervention because it conflicts with her theory of mind, should such a decision be honored consistent with the principle of patient autonomy? Finally, the issues of the legitimate use of neurological interventions to improve or modify the self must be addressed.
DEVELOPING A QUALITY OF LIFE PERSPECTIVE

Introduction

Like other biological and medical technologies, neural grafting and transplantation represent important new possibilities and powers to alter and improve hitherto fixed conditions of human lives. The goal of neural grafting in PD patients is the restoration of motor control, a fundamental condition for the exercising of personal autonomy. In recent years, quality of life reasoning has emerged as a dominant element in the ethical justification of the development of biomedical technologies and of their use in specific cases. Along with this, the importance of patient autonomy has been acknowledged: the patient is now recognized as the central moral authority, and hence as the source of quality of life judgments, in medical decisionmaking.

Quality of life reasoning in biomedical ethics has been most fully developed in relation to questions about sustaining, terminating, or shortening human life. Hence, it is encountered in discussions of defective newborns, unwanted pregnancies, chronic debilitating and/or painful illness, lingering and painful
terminal illness, and persistent vegetative state. Ideally, a quality of life ethic is appealed to as a justification for the subjective judgment, "My life is (is not) worth living." And it is on the basis of this judgment, then, that specific action choices are made with respect to sustaining, shortening, or terminating life. When such a judgment must be made on behalf of another, emphasis is placed on reaching a decision the individual would have reached on her own behalf (Buchanan, Brock, Gilfix, OTA, 1986; Drane, 1985; Dyer, 1982; Fletcher, Dommel, Cowell, 1985; Jameton, 1985; Lappe, 1978; Meisel, 1985; Meinick, Dubler, 1985; Miller, 1982, 1985; Paschall, 1985; Sundram, 1988; Tibbles, 1985; U.S. OTA, 1987).

There is an obvious difference between these sorts of cases - those relative to which the quality of life model has been most thoroughly developed - and the sorts of cases in relation to which neural grafting and transplants are contemplated. First, one is no longer asking whether a particular life is worth living, but whether a particular kind of therapeutic modality ought to be explored and developed; and if so, whether a particular intervention ought to be elected by the individual patient-subject. Second, the characteristics of the disease, and the nature of the modalities involved, as well as their intended and possible outcomes, establish the specific framework for quality of life reasoning, thus determining what
considerations become relevant as quality of life indicators for
decisionmaking at either of these levels.

Hence, the nature and impacts of the underlying disease
as well as the nature and impacts of the neurological
technologies must be pondered. What quality of life
considerations are relevant to decisionmaking concerning the
development and use of neural grafting and kindred
technologies for the treatment of neurological disorders like
PD? Neural grafting promises to alter the nature of the self by
reinstating the capacity for autonomous movement. The
impacts of these interventions can be so great as to alter the
emotional states, and arguably the very identity of the self
(Merz, 1988; Lewin, May, 1988). Interventions with such
impacts have been developed and attained general therapeutic
use before: psychosurgery, electroconvulsive shock therapy,
psychoactive drug therapy, and now neural transplantation.
The latter interventions are contemplated in cases in which
chronic neurological disease or injury to the central nervous
system causes loss of motor control, often to the point of the
total freezing up of limbs, or paralysis. Patients who experience
this loss of motor control and function do not necessarily
experience any loss of cognitive awareness or capacity. Hence,
there is a close analogy to the alarming condition of "locked in"
syndrome among some stroke patients. What variables are
relevant to quality of life decisionmaking regarding (1) the pursuit of research, and (2) participation in research, for a disease so devastating to its victims?

It is important to distinguish these two tiers of quality of life reasoning in the present case, and to remain clear about the issue under discussion at any given point. For example, some would claim that the devastating nature of PD is such an important qualitative feature of the research situation that prevailing standards for progressing from animal to human trials ought to be less rigorously applied, and accordingly that informed consent procedures should facilitate rather than complicate the process of acquiring suitable subjects for this research. Others regard this as the subversion of the scientific method; some as ethically suspect in the extreme. But the point is that quality of life reasoning occurs on the research level in answer to the question: Is this research justified by the results in animal and human models thus far?

Quality of life reasoning also occurs on the part of the individual patient-subject in answer to the question: Is participation in this research reasonable, based on my basic beliefs and values, given the certainties and uncertainties of benefits and harms associated with it and its alternatives? Assuming that research is justified by its anticipated impact on the quality of human life, an effort must be made to delineate
the sorts of information prospective patient-subjects require in order to make a truly informed choice to participate in research or to elect the treatment from among other therapeutic options. In *Guidelines on the Termination of Life-Sustaining Treatment and the Care of the Dying*, representatives of the Hastings Center write:

...'quality of life' [is] an ethically essential concept that focuses on the good of the individual, what kind of life is possible given the person's condition, and whether that condition will allow the individual to have a life that he or she views as worth living.... By allowing patients and their surrogates to make choices that consider 'quality of life,' we diminish the risk of forcing lives of pain, indignity, or overwhelming burden on those who are helpless.

As this statement implies, it is a firmly entrenched principle of medical ethics that such decisions are the patient's to make, based on quality of life reasoning relative to the patient's own values and preferences. But the patient must be equipped to make such a decision by being provided the sorts of information relevant to quality of life choices, and assisted in the process of clarifying and articulating their values and preferences relative to the treatment option offered them.

A pertinent question seems to be, have we enough experience in quality of life reasoning to say that we have an adequate model for reasoning in the present case? Is there an adequate quality of life model to outfit us for the present
discussion of the quality of life impacts of this treatment modality in general and in specific cases? The redesigning of the individual through the reinstating of the capacity for autonomous motor control seems to bear some kinship to the sort of radical redesigning associated with some genetic engineering endeavors to treat genetically-based disorders. However the kinship is not a close one: in the treatment of genetic disorders, the alteration is before the fact, prior to the expression of the gene; in the treatment of neurological disorders like PD, it is after the fact, once the disease has begun its insidious progress. Thus, perhaps a new model for quality of life reasoning needs to be developed in the context of neural grafting, the purpose of which is the restoration of motor control which plays a central role in each individual's autonomy and uniqueness.

Quality of Life Reasoning: Its Nature and Necessity in the Present Context

Given the centrality of quality of life reasoning to the resolution of many of the ethical issues arising in the conduct of neural grafting research, and its therapeutic use in individual cases, an understanding of what a quality of life ethic is and how reasoning proceeds in accordance with such an ethic are essential pieces of background information.
The notion of quality is used in both a descriptive and a prescriptive way relative to the conditions of human life generally as well as individually. One can speak of the qualities of an individual without attaching any sort of evaluation to them: e.g., "Jones is a manipulative person," where being manipulative is a descriptive property or quality of Jones' personality that may in fact serve him very well in life. But in the statement, "Jones' life is unhappy because of his manipulative personality," the implication is that a life lived in non-manipulative ways is a better life than Jones' life. A quality of life judgment based on a quality of life ethic is a prescriptive statement reflecting either the qualitative state of an individual life (its relative worthwhileness or worthlessness to its possessor), or the value of a situation vis a vis humanity generally. Thus, quality of life judgments are made about individual lives, but they are also made about situations that impact the quality of life of humanity at large, as in the statement, "The development of penicillin has improved our quality of life by reducing the impacts of devastating diseases and infections."

For any such prescriptive quality of life judgments, there is a presumed context of things or states of affairs humans value. There are many things that human beings value. The notion of a qualitatively good life is comprised of
many variables, and the variables as well as the respective weights assigned each variable vary from person to person, and even from culture to culture. The absence of one or a few of these variables is not a sufficient basis for concluding that life is not worthwhile for its possessor. The decision that enough of the relevant variables are absent, or perhaps that just one is absent in sufficient degree to justify the judgment that life is no longer worth living, is a judgment that can only be made relative to an individual with a particular past, present, and possible future, or a particular human group with a particular past, present, and possible future. Consistent with the overarching principle of autonomy, the ethical presumption is that the individual or the group in question is the authoritative source of such a judgment, and thus the author of its own destiny, unless it can be demonstrated that the conditions for exercising autonomous choice are absent. Parenthetically, the therapeutic value of developing patients' capacities for full participation in treatment decisions has now been experimentally established (Kassirer, 1983; gelman, 1988; Greenfield, Kaplan, Ware, 1985).

Quality of life reasoning is easily identified, which is to confuse it, with sanctity of life reasoning. Each of these can be identified as a distinct ethic: that is, each is a distinct and clearly definable approach to reasoning through an ethical
dilemma. Although they are different ethics, they are related to a common ethical principle, the principle of respect for human life. The ethical notion that human life is especially deserving of respect initiates in the metaphysical/ontological insight that human beings have the capacity for existence as persons, a capacity distinguishing them from other animal species.

The sanctity of life ethic holds that the nature of human life provides a virtually absolute defense for the preservation of human life. On this view, life is considered an intrinsic good, regardless of its value to its possessor. By contrast, the quality of life ethic holds that life is an instrumental good, and that its good is a function of its value to its possessor. Thus, some conditions of existence may be judged unacceptable for humans from a quality of life standpoint. Although both of these ethics are importantly linked to the principle of respect for persons, they often yield conflicting decisions in the same case, in part because of the kind of good life is thought to be, but also because of the distinctive considerations entering into the ethical reasoning associated with each (Reich, 1978).

The sanctity of life ethic is an instance of deontological ethical theory, an approach to ethical reasoning that appeals to one or more ethical principles and rules to resolve ethical dilemmas. The source of the principles and rules making up a
particular deontological ethic may be human reason, a divine being, or some other origin regarded as authoritative. If one reasons deontologically in order to resolve a moral dilemma, essentially one tries to determine if a particular act falls under a particular moral principle or rule. If it does, then it is a morally justified act. Since the sanctity of life view holds the general principle that human life has intrinsic value, it concludes that it deserves absolute protection and preservation, apart from considerations of the quality of life.

The Ten Commandments are a familiar example of a simple deontological ethic of rules. The authoritative source of this ethic is presumed to be God. The rules that make up this ethic designate specific elements constituting the content of the moral life (e.g., honesty, fidelity) that are to be appealed to to determine how one ought to act. In contrast to the Ten Commandments, there are more developed examples of pluralistic (i.e., multiple rule) deontological ethics that consist of a complex system of specific, hierarchically ordered, moral rules. Thus, they provide more guidance in the face of tough ethical dilemmas than do, say, ten rules unranked in their order of importance.

By contrast, quality of life reasoning is essentially consequentialist in nature. This means that the action-decision is based first on a determination of the consequences of
alternative acts, and then on an assignment of degrees of value and disvalue to each set of consequences. Obviously, such an assignment rests on prior decisions about what is valuable and disvaluable, and so a set of values underlies the evaluations one makes of the consequences of alternative actions. Since the quality of life ethic is consequentialist, then, it presupposes a conception of the conditions under which life is and is not valuable to its possessor, and then assesses the conditions of a life relative to those values. Such reasoning can be done in a generic way, about human beings generally. Thus, it can be the basis for a quality of life assessment of the development and therapeutic use of the new neurological technologies. In addition, this reasoning can be engaged in in a person-specific way, thus serving as the basis for an individual's quality of life judgments about whether to elect to undergo a particular experimental and therapeutic treatment.

It appears essential that a quality of life ethic exist as a corrective to a sanctity of life ethic when biology and medicine achieve their present levels of control over human destiny. Otherwise, our primary ethical principle becomes a technological imperative by default. The technological imperative would read: Where the extension of human life is possible, attempt to develop any conceivable technology, and apply it whenever possible. One need not waste space
discussing the deleterious impacts such an ethic would have on human and environmental life. Indeed, there is abundant evidence of the misfortunes attending the unbridled technological imperative wherever one turns.

The sanctity of life ethic arose in an era when life was generally presumed to be the gift of a divine being, and when (in spite of its divine origin) life was "short, nasty, and brutish," and often subject to wanton destruction. In that era, the central problem was to affirm the equal value of all human lives as a step toward the protection and preservation of life.

While there is little evidence that respect for human life has become the cardinal moral tenet on this planet, the raison d'être of medical research and practice is the improvement of health and the extension of life (in language to be introduced later, the extension of "quality adjusted life time"). Incredible medical progress has arisen in the ethical context of the sanctity of life principle, and only fairly recently have the professional codes governing medical practitioners been examined in light of the unreasonable practices a strict adherence to the sanctity of life ethic requires in the age of machine medicine. Problems arise when this ethic is not rethought relative to the new reality of extensive control over the shaping of the conditions and duration of individual lives.

The quality of life approach to moral reasoning has
emerged as an alternative to the sanctity of life approach in an era in which many of the conditions of human existence (including features of our genetic endowment) are under human control. It provides a vantage point from which to assess the ethical issues surrounding neural grafting, given the latter's impact on the self and intended improvements in the quality of life of multitudes of seriously afflicted persons.

It is, however, critical to preserve the essential insights of each of the ethical perspectives just discussed. Because of its essential nature, human life has an intrinsic value grounding its unconditional respect (a version of the sanctity of life ethic); and because of its essential nature, human life is (not) worth living from the standpoint of the individual whose life is in question under conditions that it is up to the autonomous individual to choose (a version of the quality of life ethic).

Enough has been said about the differences between sanctity of life and quality of life reasoning to distinguish them. From here on out, the focus will be on the ethical issues arising in relation to the research development and potential therapeutic use of neural grafting as a treatment for Parkinson's disease. Since the problem of negotiating informed consent is a problem spanning both the research and therapeutic uses of neural grafting, it will be addressed in a separate subsection. In that section, the primary goal will be to
elucidate the features of consent negotiation essential to enabling patient-subjects and patients to make well-founded quality of life decisions to participate in research or to select neural grafting from among alternative therapies.

ETHICAL ISSUES IN RESEARCH

Introduction: Basic Ethical Principles

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (henceforth referred to as the Commission) identified three foundational ethical principles that should underlie the design and conduct of all biomedical and behavioral research with human subjects. These principles include respect for persons, beneficence, and justice (U.S. DHEW, The Belmont Report, 1978). The difficulty with any such general principles is to determine what they mean, and hence actually require in practice, particularly when they ground conflicting and mutually exclusive courses of action. Nonetheless, a working understanding of the meaning of these principles can be provided that should be sufficient in the present context to ground the discussion of the specific ethical concerns associated with neural grafting research.
First, the Commission held that the principle of respect for persons requires that "individuals should be treated as autonomous agents," and that "persons with diminished autonomy and thus in need of protection are entitled to such protections." (U.S. DHEW, The Belmont Report, 1978). Second, the principle of beneficence is interpreted by the Commission to require researchers to do no harm on the one hand, and to maximize possible benefits and minimize possible harms on the other. Finally, justice is interpreted by the Commission to require care in the selection and use of vulnerable subjects and populations, equal access to the fruits of research, and the use of subjects who are at least possible future beneficiaries of the results of the research. Essentially, justice appears to center on the matter of fairness in the allocation of the benefits and burdens associated with research.

While the central ethical directives for human research are to be respectful, beneficent, and just, this goes little distance in clarifying how to be respectful, beneficent, and just in the present context. Each context poses different dilemmas of respect, beneficence, and fairness. Hence, research on neural grafting raises its own unique dilemmas of respect, beneficence, and justice. Each of these dilemmas will be taken up in this portion of the report.
Research on Neural Grafting for Parkinson's Disease

Animal Research

With these very general understandings of the central ethical prescriptions underlying therapeutic research on human subjects, let us look more closely at neural grafting research and Parkinson's disease. It is generally assumed that a new therapeutic modality should be thoroughly researched in animals before clinical trials in humans are undertaken.

This usual progression of research has been impacted by two factors, each of them significant to the ethical assessment of continued research on adrenal autografts. First, a naturally occurring model of PD has never been observed in non-human animals. Animal research has been based on chemically-induced PD in rodent models (Backlund, Olson, Seiger, 1987; Fishman, 1986; Brundin, Bjorklund, 1987; Bjorklund, Lindvall, Isacson, 1987; Brundin, Strecker, Widner, 1988; Brundin, Strecker, Lindvall, 1987). Following the discovery of MPTP-induced PD in non-human primates, a new and fruitful model for primate research has been developed (Sladek, Redmond, Roth, 1986; Sladek, Redmond, Collier, 1987; Morisha, 1987; Kordover, Notter, Teh, Gash, 1987; Bakay, 1987; Sladek, Collier, Haber, 1987; Perlow, 1987). Secondly, however, there are
ethical proscriptions against primate research in several countries. As a result, research has moved from rodent trials directly to human trials, most notably in Sweden. The initial human trials with adrenal autografts in some countries appear to have sparked trials in other countries, including the United States.

While any move from animal to human trials is based on an educated leap of faith, in the present case the usual progression from non-primates to primate to human trials did not occur. Now that significant new research has been conducted in primates, researchers are in a better position to assess the wisdom of conducting further adrenal autografts rather than fetal allografts or xenografts (Hoffer, Granholm, Stevens, Olson, 1986; Perl, 1987; Backlund, Granberg, Hamberger, 1985; Gage, Wolff, Rosenberg, 1987; Bartus, 1987; Shoulson, Fahn, Langston, 1988).

Some believe that the lack of a naturally occurring model of PD in non-humans alters the ethical necessity of proceeding with research in the usual order (exhausting all relevant animal models before experimenting in humans). It is important to keep the point about the non-natural occurrence of PD in animals in perspective. To be valid, an animal model of a disease does not need to occur in nature. What is most critical is that the animal model duplicate the conditions of
destruction of the same part of the brain resulting in the same behavioral deficits. Our induced-toxicity models of PD in non-humans do this job very well, and so our animal model for PD research is a solid one. The interesting departures of the drug-induced model from the naturally occurring model of PD center on the rapidity with which PD is induced and then treated in the former case. The chronic progression of PD in humans, with the impacts that progression has on other areas of the brain is not duplicated in the animal models. But this is an insufficient ground for arguing that animal research in this area is essentially limited. Drug-induced PD in non-humans is an excellent basis for research, and many investigators argue that there is a great deal more to be learned, particularly through primate studies, that is important to learn before any further clinical trials in humans are conducted (Redmond, et al, 1988; Perlow, 1979; Perlow, 1987; Siadek, Redmond, Roth, 1986).

In the United States, where primate research is continuing, it is important to clarify what basic scientific information some researchers feel ought to be gained in primates before stepping up human trials. Some are opposed, arguing that animal studies have yielded as much information as can be reasonably expected, and that what is known legitimates the cautious undertaking of human therapeutic trials.
There is an ethical issue, then, surrounding the value of further animal studies before human trials continue. The principle of respect for persons requires that persons not be used as subjects until sufficient animal research has been completed. Yet the further value of animal studies is disputed.

This suggests that criteria for the transition from animal to human research are needed in this case, and presumably in others as well. Several years ago, those involved in kidney transplants reached a similar disagreement. Often basic researchers feel that there is more to be learned, and therefore human trials are premature. Clinicians, sensitive to the severity and hopelessness of the patient's condition, judge that enough information has been gained through basic research to justify human trials. Presumably, the perspectives and goals of those doing basic and applied research inform their conclusions. Each side has its effective arguments to offer.

Hence, it appears to be ethically advisable to confront more directly the matter of developing criteria for the transition to human trials for such a devastating disease. A crucial aspect of the attempt to devise criteria would be the isolation of essential information, information that could be gained from animal studies and would spare human subjects the physical, emotional, and possibly the economic expense of a trial and error approach to curing PD. To provide an adequate
ethical justification for proceeding with human trials requires, at minimum, the argument that there is nothing better (i.e., more beneficent) to do in face of the devastations of PD than to undertake research to establish the efficacy of neural grafting in humans, designing and conducting limited protocols attempting to minimize risk to the greatest extent possible.

Problems lie at two levels then: the scientific and the ethical. The scientific question centers on the value of further animal research. The ethical questions concern (1) the moral relevance of that scientific dispute given what has been learned in animal trials already, and given the serious nature of PD; and (2) (assuming the continuation of human trials) the ethical conduct of human research under conditions of uncertainty. The second of these ethical questions presumes that uncertainty generates dilemmas concerning the allocation of human, medical, and research resources, because uncertainty exacerbates the difficulty of devising adequate methods for treating persons respectfully.

**Human Clinical Trials**

Opinion is divided on the matters of whether and how to proceed with human trials. In December, 1988, the American Academy of Neurology (AAN) issued its position statement on adrenal autografting. This document reports that minimal
benefits have resulted in clinical trials, that the theoretical basis for the procedure has been established in animals but not in humans, and that other (presently unknown) factors in addition to the transplanted dopaminergic tissue may be essential to the success of the graft. For these reasons, the AAN counsels restraint: "In this instance, human therapeutics may be running ahead of careful studies of transplantation in now-excellent models of Parkinson's disease in primates." (AAN, 1988). The efficacy of adrenal grafts has not been demonstrated, hence the AAN recommends that any further research take place at highly specialized research centers only.

Apparently, the AAN is not recommending a moratorium on clinical trials. It is, however, recommending a greater degree of control over the research process. Some adopt a stronger position than this, arguing that enough is known to conclude not only that human research has outrun animal research, but also that recent results in primate studies lend support to the abandonment of adrenal grafts in favor of fetal allografts or xenografts (Merz, 1988; Sladek, Redmond, Roth, 1986; Perlow, 1987).

Others suggest a moratorium on further research while we proceed with "careful long-term follow-up" of the transplants already performed in human subjects (Lancet editorial, 1988). Sladek has suggested that there are
fundamental scientific problems with adrenal grafts because "it is so difficult to transform adrenal chromaffin cells into nerve cells" (Merz, 1986).

In view of these differences, an ethical argument appears imperative to establish that human trials constitute the most beneficent alternative under the circumstances. How might this argument go?

There is no treatment for PD and apparently no hope for spontaneous remission. From a quality of life perspective, neural grafting is the only therapy on the horizon that offers any hope for the patient with Parkinson's disease. Once the disease symptoms begin to appear, the patient will progress through an embarrassing, frustrating, terrifying period of gradual and debilitating loss of motor control, eventually deteriorating into a condition of frozen limbs. Thirty to fifty per cent of PD patients exhibit dementia late in the disease. The PD patient may be a reduced to the status of a comprehending brain within an unresponsive body, thus unable to communicate in even rudimentary ways. What moral obligations exist to do human research that might help such patients, even though a basic understanding of the neurological realities underlying their possible improvement through neural grafting techniques is still not in hand?
The goal of helping such patients seems meritorious: a disease that promotes suffering and disability of such magnitude, a disease that reaches extensively and increasingly into our population, a disease that costs us dearly in terms of loss of human productivity and expensive patient maintenance and support cannot be ignored. Hence, it might be argued that the value of further animal studies is uncertain, and that since animal and human trials have shown minimal if any significant success, human trials ought to be conscientiously and cautiously undertaken.

Joynt and Gash conclude their scathing rebuttal of this position in this way: "We believe that attention should be focused on analyzing objectively the human studies that have been done and accelerating research programs employing animals to resolve the scientific issues prerequisite for rational clinical trials" (Joynt, Gash, 1987). Animal research can settle the causes for the uneven results of adrenal grafts thus far, determine the extent of surgery necessary, determine the optimal grafting site, and promote understanding of the mechanism of action of the graft. These appear to be such fundamental concerns that the use of humans to determine them must be exhaustively scrutinized.

The purpose of presenting these alternative perspectives on further human trials of adrenal grafts has been to highlight
competing values. It must be added that the costs of applying therapeutic breakthroughs in neural grafting will be high, and this economic reality must be factored into the ethical equation when the decision is made to go forward with human experimentation.

Uniformity of protocols, mandatory versus voluntary reporting of data, and availability of research findings to all researchers

Assuming that proceeding with human trials is ethically defensible at this point in time, or whenever it is determined that it is ethically defensible to proceed with human trials, further ethical issues immediately present themselves. Should human clinical trials proceed as they now are, cautiously, at separate research centers in accordance with a variety of research protocols? Or should a centralized, multi-center approach be undertaken, and a data base created that will serve as a mechanism for the finer tuning of research as it progresses? Which approach is more respectful of research subjects? Which approach is more responsive to the needs of those afflicted with PD?

The principles of respect, beneficence, and justice (for the pool of subjects selected and for PD patients to be benefitted
by the results of research) require that maximal information be obtained from the least amount of research in the shortest period of time. This is not a simple concern with efficiency; it refers to the conditions of data gathering and utilization essential to the moral use of patient subjects. This suggests that multiple research centers using non-uniform research protocols may be an ethically problematic arrangement in the context of this research. The formation of a comprehensive data base, the constant monitoring and interpreting of data, as well as the constant adjustment of information given to patient-subjects in informed consent negotiations in light of data received to date, appear initial necessities when research is knowingly undertaken under conditions of uncertainty. The proper handling of the research process results in the ethically defensible use of our human, medical, and research resources. In effect, then, these are matters of the ethical allocation of resources relative to neural grafting research, given that this research is laden with humanly significant uncertainties and potential.

While research can proceed at private centers in accordance with diverse research protocols, this appears to be an inefficient approach if research on a particular disease is deemed an important national health priority. The present state of research on neural grafting for PD is proceeding
inefficiently, and arguably at the moral expense of patient-subjects. Dissemination of information about procedures and results is slow and unreliable, and there appear to be uneven results among researchers. Under the present system, it will be a long time before all of the information obtained in these separate studies can be digested and utilized. If neural grafting has therapeutic potential, it will be a long time before this is conclusively determined, and it will be an even longer time before the transition is made from clinical trials to therapeutic use. Moreover, many more PD patients will have to be enlisted as subjects. The human, medical, and research costs of the present research arrangement are, and will continue to be, very high.

While this may not suffice as an argument for a multi-center uniform protocol, it suggests the importance of considering mandatory data reporting and a more centralized approach to data gathering and monitoring, so that research findings can be made available to all researchers as rapidly as possible.

**Selection of subjects**

Existing federal regulations in human experimentation require that the selection of subjects be fair and equitable in order to insure that the benefits and burdens of research be
fairly and equitable distributed (Levine, 1986). To meet the requirements of this principle of distributive justice requires careful attention to the status of the poor relative to the clinical and therapeutic use of neural grafting. Given the prevailing pay as you go mentality, the poor and uninsured lack equal access to this treatment modality unless economic provisions are made for their participation in research and receiving of therapy. Further, a dilemma of distributive justice surrounds the selection of categories of PD patients for research: What category should have priority in the selection process - the sickest patients with the most advanced cases of PD, or those most likely to improve as a result of the grafting procedure (Moody, 1985. It is not enough simply to appeal to the greater promise of neural grafting in younger patients, given the results in animal trials, to settle this dilemma. Younger PD patients face a difficult risk/benefit calculation that the more advanced patient does not: while the younger patient may show maximal benefit from grafting, they must undertake the greatest risk, for the side effects and unknown risks, as well as the long term prognosis must be chanced against the reasonably solid prospect of many good years of effective and productive living without the graft.

Regardless of the approach taken to resolve these distributive justice quandries in relation to the selection of
subjects, like every victim of a serious disease, PD are highly vulnerable: the fact that they have an incurable, devastating disease inclines them to try anything that might help them. Hence, their approach and selection as subjects must be done with their extensive vulnerability in mind in order to assure that the negotiation of informed consent is a meaningful process.

When dealing with vulnerable patients, patients made vulnerable by the incurable nature of the disease itself, the issues of the experimental nature of the surgery, the extent of the surgery, the anticipated pain and suffering anticipated from the surgery, the likelihood of benefits and harms, and the extent of uncertainty involved overall, become ethically critical aspects of the informational process. The only way to mediate the impacts of patient vulnerability appears to be to tell the whole truth and nothing but the truth, as well as to develop a manner of presenting information that will not exploit their vulnerability. Studies have been done exploring the impacts of the way information is framed: information on neural grafting that is included in the negotiation for informed consent must be conscientiously framed so that it avoids preying on their vulnerability. Since PD has no cure, the disease itself constitutes a powerful or an undue inducement to consent to research (Newton, 1982; Macklin, 1982). This must be borne in
mind in the design of the approach and presentation to the patient, as well as in the interactions that occur as part of the negotiation process.

Research Design

Other ethical concerns surround the clinical trial procedure to be used. Randomized clinical trials (RCTs) are a standard approach to testing new treatment modalities. The essence of a RCT is that some of the subjects are given another or other standard therapies already established to treat the disease, while other subjects are given the treatment being tested. There is a vast discussion and debate in the literature concerning the circumstances under which RCTs are ethically justified and unjustified. (Mitchell, Steingrub, 1988; Feinstein, 1983; Veatch, 1983; Kopelman, 1983; Marquis, Stephens, Siris, 1988).

In the case of neural grafting research, some of it now being done at private centers is proceeding on the basis of RCTs, and animal research has underscored the value of control groups. Some argue that since there is no alternative therapy with the same potential as neural grafting for PD, and L-dopa has been in use for so long and researched so extensively, there is little to be gained from the existence of a control group alongside the treatment group, and hence no reason to use the
standard, approved method of the RCT. PD patients have
everything to gain and nothing to lose, as does society at large,
by the use of a different research design in this case. This
argument rests on a simplistic grasp of the RCT procedure. The
control subject in a RCT is a control from within the setting of
the RCT, not from outside of the setting of the clinical trial. For
example, the control subject in a primate study to establish the
efficacy of graft placement received the graft in another
portion of the brain, thus demonstrating the differential growth
capacity of the graft, and its ability to grow at the intended
site.

Research in non-humans has involved the use of
autografts, allografts, and xenografts. Thus far, Clinical trials in
humans have either been autografts or human fetal allografts.
The focus of this report is on the ethical issues surrounding
transplanted non-fetal tissue. Allografts and xenografts are
alternatives for PD grafting, and any PD patient contemplating
adrenal transplantation should be informed of the greater
promise many researchers see for human fetal neural tissue
allografts and non-human xenografts of neural tissue. What
ethical concerns are associated with the use of these alternative
sources of neural tissue? There are immunological difficulties
with allografts that do not exist with autografts. Brain implants
of neural tissue raise personal identity questions for which
there are no clear answers, but so do any implants into the brain, since the impacts of surgical intrusion on personal identity are unknown. Adrenal autografts require two extensive surgeries, and thus far show little promise. Xenografts might be thought to elevate the personal identity problem, since it is a cross-species graft (VanBalaban, 1988). Recall the controversy surrounding the transplantation of a baboon heart into a human baby: that was not even a transplant of neural tissue with the latter's potential to alter the identity and capacities of the self.

There are two (perhaps three) levels of questions concerning alternative tissue sources. On one level, the researchers can be asked: On the basis of our (limited) knowledge, which type of graft appears to have the greatest potential in the human? On another level, the ethicists can be asked: What ethical arguments favor or discourage the exploration of alternative tissue sources? On yet another level, patients might be asked to select among alternative available tissue sources, after they have been clearly appraised of the knowledge and ignorance associated with the use of each, and the other information necessary to give informed consent has been provided to them.

Institutional Review Boards
Institutional Review Boards have demanding tasks in relation to neural grafting research. While their role is not to be involved in the policing of the actual conduct of research, they must assure the safety and well-being of potential and existing patient-subjects, as well as adherence to research protocol. This requires close scrutiny of the research protocol itself, as well as of the procedures and instruments used for selecting subjects and negotiating informed consent with them. In clarifying the relationship of the IRB to research subjects, Lackey (1982) suggests that the relationship should be understood as an extension of the parenthood model, wherein the IRB anticipates the needs, interests, and particular vulnerabilities of the subjects. Not only does the IRB seek the optimal treatment of the subjects, but also participates in the determination of criteria for patient selection, and may even rule out the use of human subjects entirely.

The data gathered in the course of research is often complex. Frequently the researcher is also the person who monitors the data as it comes in. Some view this as not only inefficient in highly complex research situations, but also a potential source of bias in the interpretation of data. It is further argued that the subject-advocacy functions of the IRB require different kinds of knowledge and expertise than do data monitoring functions. Hence, it is recommended that the
data monitoring function be given to a specially constituted data monitoring committee (DMC). The DMC is empowered to participate in determinations of the sorts of data to be obtained, and performs an ongoing data monitoring function on the basis of which it recommends protocol revision and addresses relevant policy issues that arise in the course of research (Friedman, DeMets, 1981; Cowan, 1975; Lackey, 1982).

Certainly where research is proceeding under the assumption that uncertainty is being slowly whittled away at (possibly in the absence of any genuine control group), it is easy to construct an ethical argument favoring a sophisticated data monitoring system enabling the continuous fine-tuning of the protocol as well as increasingly greater precision in the explanation of potential harms and benefits to subjects.

Should research be conducted in accordance with a common protocol at multiple participating centers, a centralized data monitoring and data reporting function would appear critical to the adequate protection of human subjects. Moreover, it would mitigate the impact of the debate in recent years over the problem of consistency in IRB decisions. (Goldman, Katz 1982, 1984; Brandt, 1983; Veatch, 1983; Levine, 1984; A. Caplan, 1984). Without entering into that debate here, any system that promotes research yielding comparable results and an ongoing monitoring of data would appear to have the
edge so far as serving the principles of respect, beneficence, and justice, even though this is an unusual approach in the history of clinical research. It might be claimed that neural grafting for such a debilitating disease defends the unusual in this case (vanEys, 1984).

Thus, some research seems ethically to require a centralized approach wherein a common-protocol, multi-center approach is accompanied by the creation of a substantial data base subject to ongoing review, and protocol revision on the basis of data obtained (A. Caplan, 1987). This suggests the creation of a National Advisory Council (Cowan, 1975) or an Ethics Advisory Board to address broader scientific and ethical policy questions.

Whatever research arrangements are in place, the obtaining of informed consent from PD patient-subjects will constitute the primary ethical necessity in enlisting them to participate in research. Here quality of life concerns emerge in full color, for the nature of technologies like neural grafting (presented in the discussion of metaphysical issues earlier in the report) must be comprehended by the patient along with the more customary items required for quality of life reasoning so that the patient will have all information relevant to giving informed consent to participate in this kind of research. This matter will be addressed in the next section.
The core function of the IRB has always been understood to be to assure the safety and well-being of the subject. The performance of this function has been taken to require a full assessment of the potential harms and benefits of the research, where the notions of harm and benefit have typically been attached to hard data like morbidity and mortality rates. As the notions of harm and benefit are typically discussed in relation to the responsibilities of IRBs, they are spelled out in terms of hard data (the hardest datum being death itself, or the mortality rates associated with the treatment and its alternatives). While hard data are certainly relevant to patient's choices, patients need a good deal more to go on if their decisions are to be based on their values and preferences.

In the next section, it will be suggested that there is an important hard/soft data distinction that must be drawn among harms and benefits, and the patient's understanding of each must be as complete as possible if the patient-subject is to be empowered to give informed consent. It will be suggested that in addition to the hard data harm/benefit calculus, the softer notion of life-altering impacts must be incorporated into the negotiation of informed consent with prospective subjects. Decisions to participate in such research require medically-relevant and ethically-relevant data, from the patient's perspective. Thus, informed consent practices must take into
account alternative views of the self, alternative conceptions of the mind/brain/body relationship, and basic metaphysical beliefs related to these views of the human self, as well as the certainties and uncertainties of the risks and benefits of neural grafting.

**Negotiating Informed Consent to Participation in Research and Election of Therapy**

The quality of life impacts of Parkinson's disease have already been addressed. Clearly, significant improvement in the quality of life of PD victims is the goal of neural grafting research. Should this macro-goal be achieved, the excessive toll of PD and related disorders on human happiness and productivity will be dramatically reduced. Such are the dreams of us all. But quality of life concerns must also be addressed as a micro-goal arising relative to each individual patient who is a potential candidate for neural grafting research or neural grafting therapy. In brief, critical to the ethical pursuit of research and conduct of medical practice, is the principle that no treatment be undertaken that the individual has not chosen on the basis of (i) a full understanding of the anticipated impacts of that treatment and alternative treatments on her body, (ii) insight into the kinds
and extent of uncertainties associated with the treatment, and (iii) her assessment of those impacts and uncertainties relative to her fundamental beliefs and values. Sometimes individuals require assistance in the latter aspect of this choice: that is, they need help in articulating and discussing their fundamental beliefs and values relative to the alternatives they face. Only in this way does a person reach a decision that accords with their view of how they ought to live their life, unless they do so utterly by accident.

The decision to receive a particular treatment as part of research or as a therapeutic option is ideally based on the patient's own quality of life reasoning, then. As it was explained earlier, such reasoning relies on a quality of life ethic, a consequentialist ethic that embodies the patient's most basic values and beliefs. Hence, the negotiation of informed consent must reflect the patient's need to have the right kinds of information in sufficient supply to apply her quality of life perspective to it, and thus determine her preference in the matter at hand. Obviously, such information includes a substantial medical/scientific component, as well as what will be referred to as a subjective component. Each of these components are critical to the individual's ability to make a well-founded decision. The use of the label 'subjective' is intended to convey the range of elements that was referred to
earlier as life-altering impacts, impacts that will be personally-experienced by the patient-subject: eg., degree of pain, loss of mobility, impact on awareness, inability to sleep, etc. Some commentators distinguish these two aspects of information relevant to an optimal clinical choice by referring to them as the scientific and the ethical components. (Forrow, Wartman, Brock, 1988). They intend this to represent the division between the 'hard' data associated with our knowledge of the disease and existing treatments and of the procedures to be performed, and the 'soft' data that have more to do with the quality of the patient's experience as a person with the disease undergoing one of the available treatments.

While many have thought that there is no use in attempting to explore the soft or subjective data and to quantify over it, the field of decision theory called decision analysis has been developing relative to the clinical context since around 1970 (Pauker, Kassirer, 1987; Kassirer, Moskowitz, Lau, Pauker, 1987; Detsky, 1987; Sox, 1987). This field has developed in large part because medicine is still being practiced intuitively in a era of complex knowledge and options that pose a wide range of trade-off possibilities. Many patients still let the physician decide what treatment ought to be pursued, but the argument of those developing decision analysis for use in the clinical context is that anyone making
the decision (patient or physician) needs to have a much clearer grasp of alternatives and their potential impacts (Brett, 1981; Feinstein, 1985; Doubilet, McNeil, 1985; Dawson, Arkes, 1987).

Further, if the patient is to be properly empowered to make an informed choice, the physician must actually inform the patient. To do so, the physician must assume a more disciplined approach to the exploration, presentation, and evaluation of treatment options. It goes without saying that patients cannot effectively apply their values and beliefs to a treatment decision unless information is thoroughly presented. Hence, decision analysis, although it was originally intended to clarify treatment options and promote decisionmaking on the basis of all of the relevant hard data available, has now become an essential tool in the promotion of patient choice based on careful quality of life assessments of alternatives on their part.

While some have despaired of incorporating the subjective or soft data into the decision trees associated with decision analysis, others have proceeded to develop instruments for measuring patients' responses to questions concerning soft-data issues. A Medical Outcomes Study Short-form General Health Survey has been tested for reliability and validity in measuring "physical and mental health, social and
role functioning, and other general health concepts for use in evaluating health care." (Stewart, Hays, Ware, 1988).

20 items were selected to represent six health concepts: physical functioning, role functioning, social functioning, mental health, health perceptions, and pain. Physical functioning was assessed by limitations in a variety of physical activities, ranging from strenuous to basic, due to health. Role and social functioning were defined by limitations due to health problems. Mental health was assessed in terms of psychological distress and well-being. The measure of health perceptions tapped patients' own ratings of their current health in general. Pain was included to capture differences in physical discomfort. [Such definitions]...tap positive as well as negative states of health.

Hence, tools have been developed for the recording and meaningful measurement of significant subjective data. Such a tool requires formulation in the context of research on neural grafting, so that patients are fully empowered to make quality of life choices. That is, there seems to be adequate momentum and success in the design of simple quality of life oriented health surveys to begin the design of such an instrument relative to a particular patient population, and to incorporate the results of this survey into the negotiation of informed consent.

To this purpose, a delineation and discussion of the relevant quality of life (QL) variables for the PD patient
considering neural grafting is in order. The central QL indicators of the short-form discussed above are:

(a) physical functioning
(b) role functioning
(c) social functioning
(d) mental health
(e) health perceptions
(f) pain.

The relevance of each of these categories to QL assessments by the PD patient must be established, and additional indicators must be added to the list if they are appropriate. The pertinent question in relation to PD is this: Do QL indicators (a)-(f) adequately capture the nature and range of quality of life concerns besetting the PD patient? Do they provide a thorough listing of QL rubrics in terms of which to assess treatment alternatives for PD?

It will be shown that each of the short-form indicators seems pertinent in the context of PD, but additions to the list will be recommended. First, what is the specific meaning or relevance of each of (a) - (f) relative to the functional deficits associated with PD?

PD is a disorder of middle or late age, and may now be diagnosed long before the patient experiences substantial functional limitations or impairments. Since PD is essentially a
degeneration of the motor control mechanism of the body, alterations in the physical functioning of the individual (a) at the level of motor control, are the initiators of altered capacities in role and social functioning (b) and (c). So, the sorts of motor impairments central to PD must be understood, along with their impacts on the individual’s ability to maintain role and social functioning.

Early features of the disease include mild rhythmic tremors of the limbs while at rest. Complete relaxation or intentional movement may cause the tremors to stop temporarily. The tremor progresses until all movement is affected, including walking, all customary activities, facial expression, and posture. Movement becomes progressively impoverished and reduces to incapacitating rigidity. Swallowing and respiration become impaired, and in the later stages of PD, the added insult of dementia may occur (d).

As the disease progresses, the patient’s psychological distress escalates, further compromising mental health (d) and a sense of well-being (e). The patient’s health perceptions (e) are impacted by the growing experience of loss of capacity to maintain normal life patterns and activities. And the level of concentration increasingly required to carry on the simplest of activities is exhausting and painful (f).
This surveys the PD patient's experience relative to the six QL indicators described above. Clearly, they offer an extensive framework for the patient's consideration of research and therapeutic alternatives, since they focus attention on key aspects of PD. However, they need amplification, particularly in light of the metaphysical issues surrounding neural grafting, and the personal risks associated with grafting but not with traditional pharmacological therapy for PD.

Given the metaphysical implications of neural grafting on the mind/brain/body question as well as the personal identity problem, a further QL rubric,

(g) conception of the self,

must be included. Conception of the self signifies the patient's understanding of the self, including the mind/brain/body connection and personal identity, and to elicit the relevance of that conception to the neural grafting option.

An eighth QL rubric contains relevant patient-specific attributes that bear on the selection of a treatment option for PD because they impact the harm/benefit ratio. Hence,

(h) patient-specific attributes

includes (i) the age of the patient, (ii) the duration of the disease, (iii) the stage of the disease, and (iv) the severity of the disease. Although this category sounds like a catch-all, it is intended to focus attention on factors relevant to the patient's
assumption of the risks attending neural grafting. Many of these risks will have been explained under one of the other QL rubrics, but the patient’s ability to weigh those risks is importantly linked to knowledge and understanding of her present condition and likely future.

It must be understood that for every description of the patient and her experience under each of these rubrics, the task of the researcher is to project, on the basis of all of the available information, the impacts of neural grafting and other therapeutic alternatives for each of the QL rubrics. Given the sensitivity of item (g), the researcher must be trained to elicit interaction with the patient that will clarify the implications of the choices open for her fundamental metaphysical beliefs and concerns.

SUMMARY

This report has elucidated the range of metaphysical and ethical issues surrounding neural grafting research and therapeutic application, and has given special attention to the articulation of features of informed consent proceedings enabling quality of life based decisionmaking on the part of the Parkinson’s disease patient.
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