20. For simplicity, we adopt here a quasi-atomic picture for the resonant satellites of Cu. An alternate model is based is the "ligand-to-metal charge transfer" described, for example, in A. Fujimori, E. Takayama-Muromachi, Y. Uchida, *Solid State Commun.* **63**, 857 (1987), and in the reference therein.
21. The photoelectron energy of the satellite equals the photoelectron energy of the single-electron process, less the excitation energy from $3d$ to $n\ell$, less the electrostatic repulsion between the two holes created in the $3d$ state (the so-called U energy).
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28. We are deeply indebted to the colleagues with whom we collaborated in our studies: M. Onellion, Y. Chang, M. Tang, and R. Joynt of Wisconsin; R. Zanoni of the University of Rome I; N. G. Stoffel, P. A. Morris, W. A. Bonner, and J. M. Tarascon of Bellcore; D. W. Lynch, R. Liu, and A.-B. Yang of Ames; A. J. Arko and R. S. List of Los Alamos; and B. W. Veal, Y. C. Chang, P. Z. Jiang, and A. P. Paulikas of Argonne. Supported by the National Science Foundation, the Office of Naval Research, the Department of Energy, and the Wisconsin Alumni Research Foundation.

Fetal Research

JOHN T. HANSEN AND JOHN R. SLADEK, JR.

This article reviews some of the significant contributions of fetal research and fetal tissue research over the past 20 years. The benefits of fetal research include the development of vaccines, advances in prenatal diagnosis, detection of malformations, assessment of safe and effective medications, and the development of in utero surgical therapies. Fetal tissue research benefits vaccine development, assessment of risk factors and toxicity levels in drug production, development of cell lines, and provides a source of fetal cells for ongoing transplantation trials. Together, fetal research and fetal tissue research offer tremendous potential for the treatment of the fetus, neonate, and adult.

HUMAN DEVELOPMENT OCCURS IN TWO ENTIRELY DIFFERent environments, one prenatal and the other postnatal. Prenatal development encompasses the embryonic and fetal periods, whereas postnatal development involves the passage through infancy, childhood, and adolescence to adulthood. These two environments could not be more different. The safe and nutritive environment of the womb predictably yields to the more hostile existence of life after birth. Nevertheless, the relatively short prenatal existence has always held a fascination for us as we marvel at the apparent recapitulation of our developmental history. Advances in scientific understanding now are at the point where the homunculus of our ancestors' imaginations has given way to an appreciation of the intricate patterning faithfully reproduced by our genetic blueprint. Our ability to intervene prenatally when nature's course deviates has long been limited to the physician's crude palpations and auscultations, methods woefully inadequate to diagnose, let alone treat, fetal problems. Only through persistent scientific inquiry, driven by our inherent curiosity about our development, have we now reached the threshold of prenatal diagnosis and treatment necessary to ensure the mother's safety or save an endangered life. The fetus, once a captive of its own environment, an enigma to be protected but left untreated, finally has gained the status of patient. Accordingly, fetal research itself enters an important new era.

In this article, we review some of the significant contributions of fetal research and fetal tissue research over the past 20 years. It is important to draw a distinction between fetal research, that is, research performed on the living fetus in utero, versus fetal tissue research that focuses on tissues or cells derived from the dead fetus, obtained as a result of spontaneous or induced abortion (*1*). By its very nature, scientific inquiry that involves fetal research or the use of fetal tissues often is obscured in the larger ethical, moral, and legal questions surrounding the use of fetuses, especially human fetuses, in research of any kind. These concerns are not trivial, for they strike at the heart of our moral dilemma regarding abortion, or the use of invasive procedures on a patient (the fetus) who can neither be informed nor grant consent. The resolution of these concerns and the answers to the ethical and legal questions will require honest, open dialogue from all aspects of society before, and if, a consensus is ever forthcoming. Our intent is not to debate whether fetal research should continue; rather, our focus will be on why fetal research and fetal tissue research are done at all, what procedures are feasible, and how this research benefits mankind.

Prenatal Diagnosis

Fetal research plays a vital role in the continued ability to diagnose a variety of fetal disorders, from genetic inborn errors in metabolism to congenital malformations (Table 1). Approximately 150,000 children in the United States alone, representing 3 to 5% of all live births each year, are born with congenital abnormalities (*2*). Ultrasonography, a noninvasive procedure that permits visualization of the fetus without apparent risk to fetus or mother, is one of the most important diagnostic advances available to the physician (*3*) and is used as an aid for the accurate guidance of instruments. Ultrasonography is also used to assess fetal movements and gross fetal malformations. For example, neurological defects such as anencephaly, spina bifida, and hydrocephalus can be diagnosed with ultrasonography. Heart defects, which occur on the order of 1% of all live births (*4*), and various obstructive disorders of the gastrointestinal

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or urinary tracts also may be visualized with this noninvasive approach.

In contrast, early diagnosis of inherited chromosomal abnormalities, fetal disease, and metabolic deficiencies require invasive intervention. Amniocentesis, the withdrawal of amniotic fluid, has dramatically changed the physician's ability to diagnose, counsel, and implement treatment (*5*). The assessment of chromosomal abnormalities, amniotic infections, fetal lung maturation, and the severity of hemolytic disease related to Rhesus (Rh) factors is now possible; however, most amniocentesis is used for cytogenetic studies (*6*). In addition to direct chromosomal analysis, recombinant DNA technology now makes it possible to diagnose a large number of genetic disorders. Presently, more than 4000 disorders in man are known or suspected of being due to a single gene mutation, and as many as 300 gene mutations in humans may be X-linked (*7, 8*). By means of recombinant technology, many gene mutations may be identified either directly or with the use of restriction fragment length polymorphisms (RFLP). Disorders such as Huntington's disease, Duchenne muscular dystrophy, sickle cell anemia, hemophilia, and cystic fibrosis have been diagnosed by the use of RFLP. Inborn errors in metabolism also may be assessed by culturing fetal cells suspended in the amniotic fluid sample and subjecting their resulting gene products to enzyme analysis assays. Although prenatal diagnosis of most inborn errors of metabolism are made by analyzing the gene product, several direct determinations of unique metabolites in the amniotic fluid sample are also possible (*9*). For example, hexosaminidase A, the deficient enzyme of the autosomal recessive disorder Tay-Sachs disease, can be diagnosed directly (*10*). Endocrine disorders such as adrenogenital syndrome are diagnosed during the prenatal period by direct assay for the elevated levels of 17α-hydroxyprogesterone in amniotic fluid (*5*). Amniocentesis also is a vital diagnostic procedure for the detection of neural tube defects, such as spina bifida, encephalocele, and anencephaly. These neural tube defects, for example, affect about 1 to 2 in 1000 live-born infants in the United States and Canada (*6*). These defects result from the failure of the embryonic neural tube to close, and their diagnosis relies on the determination of elevated levels of α-fetoprotein, a glycoprotein normally found in fetal serum (*9*). The α-fetoprotein leaks through the membrane covering such neural tube defects and accumulates in the amniotic fluid and maternal serum (*6*).

One significant drawback of amniocentesis is that it usually is not performed before 15 or 16 weeks gestation, and any final diagnosis dependent on cell culture must be delayed an additional 2 to 3 weeks (*3, 6, 9*). Moreover, the rate of pregnancy loss relating to amniocentesis is approximately 0.5% in the United States (*11*). Earlier diagnosis of chromosomal abnormalities is possible by using ultrasound-guided chorionic villus sampling, which may be performed as early as 8 weeks gestation. Chorionic villus sampling, although valuable for gathering karyotyping data at earlier gestational ages, does pose a slightly higher risk of fetal loss than amniocentesis (*12*).

Fetoscopy, that is, percutaneous transabdominal uterine endoscopy, provides additional advantages for prenatal diagnosis. Anatomical malformations may be directly visualized, and fetoscopy may be used to obtain blood or tissue biopsy samples (*6, 9*). Since 1983, a newer sampling procedure for obtaining fetal blood samples, called percutaneous umbilical blood sampling (PUBS), has proved valuable for diagnosing fetal hemolytic disease and a number of genetic disorders (*13*). During PUBS, an ultrasonographically guided needle is inserted directly into an umbilical vessel to withdraw a fetal blood sample. The procedure may be performed on an outpatient basis, does not require maternal sedation, and is safer for the fetus than fetoscopy (*13*). Nevertheless, PUBS is still considered an experimental procedure and should only be performed at selected medical centers (*13*). Procedures that involve collecting amniotic fluid, blood, urine, or other body fluids are used to diagnose almost 100 genetic diseases that result from single gene mutations (*8*). Tissue biopsies are especially valuable in prenatal diagnoses when chorionic villus sampling or amniocentesis results are equivocal, and for gathering information about multifactorial inherited congenital anomalies not easily or readily diagnosed by chromosomal or biochemical abnormalities present in the amniotic or other fetal fluid samples (Table 2).

Table 1. Examples of noninvasive and invasive procedures used to diagnose or treat fetal disorders. Details are provided in (*3, 6, 9, 47*).

Noninvasive	Invasive
Patient history	Amniocentesis
Uterine size	Chorionic villus sampling
Fetal activity	Percutaneous umbilical blood sampling
Fetal heart rate	Fetoscopy
Ultrasonography	Blood or tissue biopsies
Estimate age	Structural abnormalities
Evaluate growth	Fetal therapy
Detect gross malformations	Blood transfusions
Determine multiple gestation	Drug administration
Determine sex	Surgical intervention
	Fetal cell transplants

Diagnostic procedures such as those described above are possible because of technical advances developed from fetal research. Refinements of these procedures are first developed in suitable lamb or nonhuman primate animal models and then judiciously introduced into the clinical setting (*9*). Additionally, a number of biopsy procedures are being developed and perfected. For example, blood, skin, or liver may be biopsied by the use of fetoscopy. About 100 enzyme deficiency disorders can be diagnosed from cultured fibroblasts, and another 100 deficiencies are diagnosed from specific cell types obtained from fetal tissue biopsies (*8*). However, before these invasive procedures become standard clinical practice, they must be carefully tested for their safety and effectiveness in clinical volunteers. To illustrate this point, some enzyme deficiencies can only be diagnosed from fetal liver cells. Needle biopsies of the fetal liver are possible, but questions concerning liver damage, intraperitoneal bleeding, or fetal injury surround this procedure. The answers to these questions were obtained by experimenting with fetal liver biopsy procedures on fetuses of patients undergoing second-trimester abortions (*9*). The biopsy procedures were successful. Consequently, enzyme deficiencies such as glucose-6-phosphate deficiency, which occurs in von Gierke's disease and is related to the liver's ability to store glycogen, may now be diagnosed (*9*). Similarly, several rare enzyme deficiencies of the urea cycle, for example, carbamyl-phosphate synthetase and ornithine transcarbamylase, may be diagnosed from fetal liver biopsies (*14*).

Research on the fetus is essential before diagnosed disorders can be treated. The efficacy of vaccines, such as the rubella vaccine for the prevention of German measles, or the titration of drugs can only be tested in pregnant women. The fetus is not an innocent bystander if maternal treatment necessitates medical intervention. Virtually all commonly used drugs with the possible exception of insulin, heparin, dextrose, and thyroxine pass through the placenta to varying degrees (*15*). Therefore, the safety of medications such as hormones, diuretics, anticonvulsants, anesthetics, and analgesics must be tested first in utero to determine their effect on the fetus. Moreover, fetal disorders such as cardiac arrhythmias are responsive to antiarrhythmic drugs such as digitalis and may be treated directly while in utero (*9, 16*). In instances where substances do not cross the placenta, or do so poorly and at low levels, medications or nutritional supplements may be administered directly into the amniotic fluid

Table 2. Diagnostic and therapeutic benefits and application of fetal research and fetal tissue research. A more complete listing of specific benefits and applications may be found in (*1, 3, 47, 48*).

Fetal research	Fetal tissue research
Amniocentesis	Cell growth—normal and abnormal
Blood transfusions	Cell line development
Chorionic villus sampling	Cell plasticity
Drug therapy	Drug testing
Fetoscopy	Fetal cell transplantation
Percutaneous umbilical artery sampling	Immunology
Pregnancy management	Karyotyping studies
Ultrasonography	Vaccine development
Ventriculoamniotic shunts	
Vesicoamniotic shunts	

where oral ingestion and gastrointestinal absorption by the fetus can occur.

Surgical Intervention

For those disorders affecting a single organ system or resulting from an isolated congenital malformation, unencumbered by multifactorially inherited abnormalities, surgical intervention may provide the most promising prognosis. Obstructive hydrocephalus and urethral obstruction are among several anatomical malformations amenable to surgical intervention in utero.

Obstructive hydrocephalus, a condition that occurs with an incidence of about 5 to 25 per 10,000 births and is characterized by dilation of the brain's ventricular system due to the obstruction of the normal cerebrospinal fluid (CSF) pathways, leads to significant brain compression and neurologic dysfunction. The surgical insertion of a ventriculoamniotic shunt with a one-way valve that permits the release of CSF into the amniotic fluid offers one possibility for decompressing the brain (*17*). Obstructive uropathy and the resulting damage to the developing kidney also may be corrected by the surgical placement of a suprapubic drainage catheter. The catheter is guided into the distended fetal urinary bladder by the aid of sonography, and the accumulated urine is drained into the amniotic fluid (*18*). These surgical procedures, and others still under development, were made possible because suitable animal models were available (*19*). This experimentation is difficult because only larger animal species such as rabbits, lambs, or nonhuman primates can be used. The animal models for obstructive disorders such as those discussed above mimic the clinical condition and replicate closely the human pathophysiology. The monkey is particularly useful for these studies because, like humans, the pregnant monkey uterus is susceptible to premature labor and late gestational miscarriage (*9*). However, suitable animal models for most human genetic and metabolic disorders do not exist.

The Future of Fetal Research

The benefits of fetal research include (i) the development of vaccines, (ii) advances in prenatal diagnosis, (iii) detection of anatomical malformations, (iv) assessment of safe and effective medications, and (v) the development and refinement of in utero surgical therapies. Animal models have been essential in the advancement of most of these applications and are vital for determining potential risks before clinical applications. Frequently, appropriate animal models are not available or are inadequate for risk assessment. In these instances clinical fetal research becomes important; many diseases and malformations occur during fetal development and if the problems can be addressed early, often before birth, the neonate stands a much better chance of living a normal life. Current federal regulations limit fetal research to only those procedures that pose "minimal risk" to the fetus or that can be of direct therapeutic benefit to an endangered fetus (*1*). Perhaps, until we fully explore the ethical issues surrounding fetal research, this is an appropriate standard. Nevertheless, advances continue to be made in laboratory animal experiments and in countries where the potential benefits of clinical fetal research are regarded as outweighing the potential erosion of ethical standards (*20*). Clearly, there has been a decline in the number of investigators willing to face criticism consequent to conducting clinical fetal resarch in spite of the potential benefits generated by such studies (*1*). Thus, fetal research at present appears to have plateaued and may advance only slowly until the larger questions affecting social responsibility are addressed.

Fetal Tissue Research

Fetal tissue research differs from fetal research in that it involves studies on fetal cells rather than on living fetuses. Fetal tissue research has benefited a number of biomedical areas by providing cell lines to study gene regulation, pattern formation during embryogenesis, and model systems for cell interaction and function. Vaccines, such as the polio vaccine, have been developed in fetal tissues, and a variety of studies on cell growth and regulation have led to an understanding of chromosomal abnormalities, cancer and tumorigenesis, and cellular immunology (Table 2). These advances are possible because of some of the unique characteristics of fetal cells. They have the ability to rapidly divide and grow in culture, are pluripotent with respect to their developmental lineage, may be cryopreserved and subsequently reanimated, have lower antigenicity, and will survive and grow if transplanted into a supportive host environment.

Fetal cells are used to establish cell lines that provide model systems with which to study events in cell differentiation and growth. In vitro and in vivo analyses of stem cell lineages are instrumental in helping researchers better understand complex cell interactions during normal and abnormal fetal development (*21*). The process of culturing and growing fetal cells has been used by molecular biologists to understand gene regulation, protein synthesis, and other cellular mechanisms. Genetic engineering experiments have advanced to the point where investigators can now immortalize cells and develop gene constructs that can be used to design cells that express specific functional or secretory activities (*22*). Additionally, fetal cells are used to replicate human viruses that may be used to develop and test vaccines (*23*). The rapidly dividing fetal cells of the central nervous system are used to test their susceptibility to the acquired immunodeficiency syndrome (AIDS) virus, studies crucial for determining the rate of infection of fetal cells to maternally transmitted AIDS (*24*). Finally, fetal cells are used to screen new pharmaceutical agents to determine their risk as teratogens or carcinogens. These experiments are essential before clinical trials may be undertaken. One need only recall the thalidomide episode of the 1960s as a grim reminder of the value of careful fetal screening before patient use. Maternal intake of the sedative thalidomide early in pregnancy, as reported in Germany and England, led to an unusually high incidence of limb-reduction deformities (*25*). Once thalidomide was recognized as the causative agent, it was withdrawn from the market, but not before an estimated 3000 malformed infants were born (*26*).

One of the more exciting and promising applications of fetal

tissue research has been the use of fetal cells as therapeutic tools to treat clinical disorders. In one such instance, fetal cells were used to treat another fetus in utero. In June 1988, French physicians Jean-Louis Touraine, an immunologist, and obstetrician Daniel Raudrant treated a 30-week-old fetus diagnosed with a rare, and nearly always fatal, immune deficiency disease (bare lymphocyte syndrome) by injecting immune cells from the thymus and liver of two aborted fetuses into the umbilical cord of the deficient fetus (*27*). This daring clinical experiment was based on the results of animal studies that demonstrated that second trimester fetal liver contains a rich source of hematopoietic stem cells (*28*). At this stage, the donor fetus immune system is not yet developed, so normally histoincompatible stem cells may be transplanted into the immunodeficient host fetus to establish a viable population of reconstituted T cells (*29*). After the birth of this infant, a second injection of cells was given; subsequent blood tests suggest that some of the cells have seeded and multiplied in the infant's spleen, liver, and bone marrow. Although there is hope that this infant will develop a normal immune system, the prognosis is still guarded.

Fetal cells are also being examined in animal studies and clinical trials for their potential to reverse insulin-deficient diabetes mellitus, a disease that affects millions of people worldwide, including an estimated 11 million in the United States (*30*). Animal experiments demonstrate that if fetal pancreas is transplanted before the differentiation of the problematic exocrine cells (which produce the lytic digestive enzymes), subsequent development of the islet cells necessary for insulin production will occur (*31*). However, one limitation for the success of fetal pancreatic transplants has been the presence of significant quantities of immunogenetic lymphoid tissue in the pancreas. Selective cell culturing before transplantation of the pancreas has been successful in removing most of the immunogenetic cells (*32*). If this approach ultimately proves successful, it will be an important advance in this field of transplantation because immunosuppression to avoid graft rejection is undesirable in diabetics who already are at increased risk for infection. Cell transplant efforts such as this highlight the benefits of using fetal cells: their ability to survive and multiply necessitates the grafting of only small numbers of cells; their lower or absent antigenicity eliminates the requirement of tissue matching and immunosuppression; and they are adaptable to the host environment. Although fetal islet cell transplantation is still experimental, initial clinical trials suggest that some patients who have received grafts can produce their own insulin, thus decreasing their requirement of daily exogenous insulin (*33*). However, these results are not universal and a number of questions remain (*34*).

Nowhere else is the revolutionary idea of fetal cell transplantation as a therapeutic tool more evident than as a treatment for neurodegenerative disorders such as parkinsonism or Alzheimer's disease. Because these diseases are progressive and affect millions of people in the United States alone, medical researchers have explored the feasibility of grafted fetal nerve cells to restore damaged neural circuits. The economic impact of these neurodegenerative diseases is significant when one considers the lost productivity, forced early retirement, and costs of therapy and nursing care.

The field of neural transplantation has a long and varied history, but its full potential perhaps was revealed as a result of pioneering studies by Olson and colleagues (*35*). These investigators demonstrated that the anterior eye chamber provided a nutritive and immunologically "privileged site" for the transplantation of cells. Moreover, subsequent experiments showed that grafted neurons could reinnervate a previously denervated target (*36*). However, adult neurons do not divide and, once damaged or lost, cannot be replenished from endogenous sources. Because of this, grafts of fetal neurons were investigated and found to be capable of partially reestablishing damaged neural circuits (*37*). Not only could fetal cells survive and establish neural contacts, but they also had the ability to synthesize and release appropriate transmitter substances (*38*). Additionally, implanted fetal nerve cells could ameliorate specific cognitive (*39*), neuroendocrine (*40*), and motor deficits (*41*). Virtually every region of the central nervous system, from the olfactory neuroepithelium to the spinal cord, can be grafted, with minimal immunological consequence (*35*).

Although a variety of animal models of neurodegenerative disorders are used by transplant neurobiologists, the nonhuman primate model of Parkinson's disease has provided the greatest incentive for fetal grafting experiments. The selective neurotoxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered to monkeys produces a parkinsonian-like syndrome characterized by rigidity, resting tremor, progressive akinesia, flexed posture, and episodes of freezing during movement (*42*). Moreover, MPTP rather selectively affects the dopaminergic cells of a brainstem region known as the substantia nigra, causing their degeneration in a manner that anatomically and physiologically mimics human parkinsonism (*43*). The loss of the neurotransmitter dopamine from these neurons, which project to target neurons in a large subcortical region termed the striatum, appears responsible for the movement disorders of parkinsonism. Many Parkinson's disease patients, therefore, benefit from the administration of the drug L-dopa, a dopamine precursor, which is converted to dopamine in the brain to replenish the dopamine deficient striatum.

However, L-dopa therapy is ineffective in a large percentage of patients, and other patients progressively become refractory to the drug over a period of 5 to 10 years. Because few pharmacologic options remain for these patients, neural grafting of dopamine-producing cells has been considered as one alternative. Initial studies in rodents with grafted fetal tissue from the mesencephalon brain region giving rise to dopaminergic neurons of the substantia nigra were promising (*41*). The use of fetal dopaminergic neurons appeared obvious because one could replace degenerating cells in the host with cells of like origin that presumably carry the correct genetic programs for dopamine synthesis, cell growth, connectivity, transmitter release, and receptivity.

Subsequent experiments by Redmond and colleagues (*43*) in African Green monkeys that were rendered parkinsonian by MPTP administration confirmed earlier rodent studies and demonstrated the efficacy of fetal nerve cell transplantation in nonhuman primates. Seven and one-half months after transplantation of fetal nigral neurons, these investigators observed significant behavioral improvement, as well as dopamine neuron survival and increased levels of dopamine in the host striatum. The implanted neurons appeared integrated with the host, extending numerous small fibers into the adjacent neural parenchyma. Long-term studies and experiments to determine the specificity of fiber sprouting from the implanted neurons are not yet completed, so caution is warranted (*44*). Nevertheless, current scientific wisdom suggests that fetal dopaminergic neurons presently may be the best tissue source to graft in parkinsonian patients, usurping the use of the adrenal medullary autografts, which exhibit very poor survival in monkeys (*45*) and have minimal effects as used presently in humans (*46*). Several centers around the world, including two in the United States, have already performed human fetal nigral grafts in patients with Parkinson's disease. It is still too early to objectively assess the results.

The Future of Fetal Tissue Research

The benefits of studying fetal cells are many, and the clinical potential for their use as therapeutic tools is just now being realized

(Table 2). Vaccine development, study of human viruses and the development of specific therapies for the treatment of infections such as AIDS, the assessment of risk factors and toxicity levels in drug production, and the initiation of transplantation trials are important and necessary contributions of fetal cell research to biomedical science (*1*). Ongoing animal experiments and a source of human fetal cells are critical for studying fatal blood diseases (sickle-cell anemia, aplastic anemia, and leukemia), or for addressing nervous system disorders including optic nerve damage, degenerative disorders of the brain, and spinal cord damage. On the horizon lies the potential to reverse insulin-deficient diabetes and immunodeficiency disorders and to address cognitive dysfunctions. Current federal and state regulations permit the use of fetal tissues and cells obtained from dead fetuses, and all 50 states have adopted the Uniform Anatomical Gift Act, which sustains this essential need for continued research to advance our scientific knowledge and biomedical applications (*1*). Such advances have brought us to the point where we no longer stand by helplessly in the face of fetal malformations, nor are we left impotent to respond to treatable disorders. With a growing ability to diagnose and treat, with a new-found knowledge to shape and direct developmental events, and with an awareness of how to replace and restore that which is old, we must remain cognizant of the delicate interplay between responsible moral behavior and the desire to maintain and improve the quality of human life.

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49. We thank all of our colleagues involved with our transplant programs, especially D. E. Redmond, D. M. Gash, T. J. Collier, R. H. Roth, and S. N. Haber. Several of the studies cited in the article were supported by USPHS grants PO1-NS24032 and PO1-NS25778, and a grant from the Pew Charitable Trust. We also thank D. Baram for helpful suggestions.