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PART XV CHAPTER 338

TRANSPLANTATION OF CADAVER TISSUES AND ORGANS

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I do perceive here a divided duty.

Shakespeare: Othello I, 1604

INTRODUCTION:PREROGATIVES, PRIVILEGES AND RESPONSIBILITIES OF THE NEUROSURGEON IN TRANSPLANTATION

The neurosurgeon, uniquely among physicians shoulders two weighty, ostensibly contradictory imperatives: to care for the patient whose brain is devastated by trauma or disease; and when efforts at reversing the inexorable course of cerebral deterioration are unsuccessful and the presumption of human life is untenable, to instruct the grieving family about the possibility of harvesting transplantable organs and tissues. Organs (heart, lung, kidney, liver, etc.) must retain their basic physiological functioning prior to transplantation. The patient who has reached the state of brain death is therefore the source of organs for transplantation. Moreover, such a patient can provide fresh tissue (bone, cartilage, cornea, dura mater, fascia lata, skin). Whereas fresh autogeneic (one's own) tissue transplanted from one part of the body to another is partially or totally viable, allogeneic (same species) tissue is usually processed and thereby rendered nonviable to reduce antigenicity. Because immunological barriers among unidentical members of a species predominately reside on cells, tissues transferred between genetically different individuals should preferentially be nonviable and cleansed of cellular debris.

Moral and legal issues most often surround the transplantation of organs rather than tissues because of the requisite functional integrity of the graft. Tissues, however, can be taken from donors whose circulation arrested some hours before. The criteria for donorship and procedures involved in procurement, processing and distribution differ for organs and tissues. Significant advances in transplantation biology resulting in an accelerating demand for viable allografts and nonviable alloimplants encourage an awareness among neurosurgeons of the possibilities and limits of organ and tissue transplantation and cognizance of the pivotal role the neurosurgeon plays.

For some neurosurgeons the moral dilemma of declaring brain death for the benefit of organ transplantation, while cardiac and pulmonary function contines, is yet unresolved (8). With the technological possibilty of maintaining vegetative body function by artificial means even months after cerebral death (10), the need for statutory laws and moral debate became paramount. Since 1969, 29 states have adopted "brain death" legislation using a dozen different approaches (2). Guidelines for determination of death have been proposed and have included the "Harvard Criteria". A "Uniform Determination of Death Act" has been proposed for passage in all the states which expresses the following: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all function of the entire brain including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards (6)." Acceptable medical standards must be cautiously applied in the presence of drug or metabolic intoxication, hypothermia, in children, and in shock. Whereas there is in general a consensus that irreversible brain death is identifiable and that this state is coincident with death of the patient, there is a minority who view such a position as immoral,that the individual expires only when all vegetative function ceases.

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TYPES OF TISSUES AND ORGANS THAT CAN BE PROCURED, PROCESSED AND TRANSPLANTED

Many consider the neurosurgeon's role only as a handmaiden who provides cadaveric tissues and organs to transplantation surgeons. During the agonal days of a patient's course, the family and neurosurgeon usually develop a close and trusting relationship. When cerebral death supervenes, a neurosurgeon most often is in the most favorable situation to discuss the possibility of organ and tissue transplantation. Whereas for transplantation of organs such as heart, kidney, lung and liver a functioning viscera are mandatory, the harvesting of tissues may be effected within hours after circulatory arrest. Various tissues (cornea, bone, cartilage, skin, dura, fascia) have different biodegradation times and therefore variable periods after cessation of all vegetative function during which they may be harvested. Among the different tissues there are criteria for donorship including age and exclusionary conditions (infections, malignancies, diseases of unknown etiology, etc.). For example, bone must be harvested within 24 hours of circulatory arrest from donors 15-50 years without evidence of a communicable disease, neoplasm, diseases of unknown etiology, or primary bone abnormality.

Enlightened self-interest now dictates that a neurosurgeon be aware of his own stake in the availability of tissue (12). Viable organ transplantation is unlikely ever to be within a neurosurgeon's prerogatives. However, viable tissue transplantation (the autograft) is commonplace. Nonviable implants of allogeneic dura mater, fascia lata, and bone are very benefical resources in neurosurgical practice today. Although allogeneic peripheral nerve grafts (formerly called homografts) are not used because of their low success rate, fresh autogeneic peripheral nerves are used in reconstituting long peripheral nerve defects. Freeze-dried dura mater and fascia lata are used to restore defects in dura overlying the brain or spinal cord. These implants gradually become replaced with fibroblasts and new collagen.

Alloimplants of bone (formerly called homografts) are used for cervical interbody fusions. The quality of these implants can be superior in physical characteristics to autografts taken from the patient's ileum. Moreover the patient is spared a painful donor site. The alloimplant gradually becomes remodelled and thereby viable. The interbody fusion rate using alloimplants equals that with the use of autogeneic grafts in the cervical spine, though the time course for fusion is slightly longer (12). The length of hospitalization is usually reduced because of the avoidance of additional trauma. The volume and dimensions of bone required for posterior lumbar interbody fusions mandate the use of allogeneic bone in that application also. For the neurosurgeon, therefore, an awareness of his critical role in generating transplantable organs and tissues must be augmented by a recognition that available allogeneic tissues will extend his own capabilities.

Progress in tissue and organ banking has been furthered by the formulation of guidelines by component councils of the American Association of Tissue Banks (5). These represent consensus minimal standards, the adherence to which is essential for any tissue retrieval, processing and distributional activity. The Food and Drug Adminstration in 1982 has ruled processed bone as a "device", which qualifies under the Federal Food, Drug and Cosmetic Act, Medical Device Amendments of 1976.

METHODS OF STERILIZATION OF TISSUES

Tissues for implantation must rigorously be free of contaminating bacteria, fungi or viruses. Otherwise the recipient would be infected and the goals of transplantation defeated. Criteria for donorship exclude those individuals known to be infected antemortem with any microorganism. There has been known transmission of the rare viruses causing rabies and Creutzfeldt-Jakob disease following corneal transplantation (4,7), as well as the virus of hepatitis transmitted through allogeneic bone (15).

Aseptic procurement of tissues is one method of insuring sterility. Duplication of operating room asepsis is mandatory for such a procurement method. This requires a separate facility for the harvesting of tissue and strict attention to surface decontamination of the cadaver donor. The blood and wound of the donor, along with a percentage of the specimens, are cultured. Any signs of microbial colonization results in discarding all tissue from that donor. With such a practice up to 20% of donors may be rejected (3). Tissue harvested by such methods is then frozen ordinarily at -70°C until use or freeze-dried for preservation. Glass containers for freeze-dried tissue are evacuated and sealed in the sublimator and allow long term storage at room temperature. The shelf life of the resultant product is indefinite, provided the vacuum in the container is maintained. Such alloimplants provide the recipient with an appropriate physical structure or scaffold for remodelling by the host. Whereas cells remain in the form of necrotic debris, all viability is lost with the freezing process and a template of structural proteins, enzymes and other potential antigenic factors are implanted. The genetic disparity between donor and recipient accounts for the slower remodelling rate in the alloimplant as compared to the autograft (graft is used for viable transplantable tissue; implant denotes nonviable transplantable tissue). Under most conditions such an implant will provide a lattice for invasion by host vessels, then gradual remodelling to identical tissue.

The bone alloimplant thus prepared provides a framework for osteoconduction. The potential for osteoinduction, or the stimulus for conversion of migratory, frequently perivascular mesenchymal cells to become bone forming cells, is generally lost in the aseptically precured frozen or freeze-dried alloimplant (13). However, freezing or freeze-drying does reduce the immunogenicity of the implant.

Through the last several decades methods have been advanced to sterilize bone after harvesting. The aim of such efforts has been not only to insure sterility, but also to increase the available donor pool of transplantable bone and dura. Thus these tissues can be harvested in any facility without aseptic technique and the bone secondarily sterilized. Moreover, processing techniques potentially could result in an implant with superior osteoinductive potential.

In bone decontaminated by boiling, autoclaving, irradiation, immersion in antibiotics, bacteriocidal and bacteriostatic agents, the rate of incorporation is impaired by interference with the bone morphogenetic protein (14). Proteins are denatured by these physical and chemical methods of sterilization. Gamma irradiation requires a minimum of 2 Mrads exposure for bacteriocidal effect and much higher for virucidal properties. At these levels the physical and biochemical integrity of structural proteins in the tissue is compromised (14).

The bacteriocidal action of ethylene oxide (EO), an alkylating agent, has been known since 1949. This gas has been generally used for decontaminating heat- and moisture-sensitive devices and instruments. With the successful use of EO in sterilizing dura mater already known, investigators demonstrated the effectiveness of EO in penetrating cortical bone and decontaminating it, after which EO and its reaction products in tissue (ethylene chlorohydrin and ethylene glycol) were removed by prolonged freeze-drying (14). In an experimental study the biological response of such EO sterilized implants in canine skull was comparable to that obtained by implants aseptically procured and freeze-dried alone, and was essentially osteoconductive. In contrast sterilization of bone with chemicals directed toward reducing immunogenicity but with preservation of the bone morphogenetic protein clearly resulted in a superior product in that it was osteoinductive (13).

Future research in tissue grafting will focus on preparing implants which at once anatomically reconstruct the lost part, while preserving osteoinductive properties associated with the fresh autograft. This involves reducing immunogenicity by extracting lipids and cell membrane lipoproteins, autodigesting bone through endogenous intra- and extracellular enzymic activity with preservation of the bone inductive protein, and surface decalcification to promote revascularization of the implant and exposure of the intrinsic morphogenetic protein(s).

At the present moment, however, ethylene oxide is most effectively used for decontamination of bone, dura mater, and fascia lata. Documentation of the removal of EO and its reaction products must be proven. Prolonged freeze-drying (lyophilization) of tissue sterilized with EO to a residual water content of less than 5% provides the basis for long-term storage and removes these chemicals from the tissue. Appropriate bacteriological controls must accompany this method of preparation.

DISPARITY BETWEEN SUPPLY AND DEMAND: PROBABLE SOLUTIONS

There is a critical shortage of transplantable organs and tissues in the United States. Such a shortfall is the limiting factor in the renal and heart transplants now being done in America. As improved immunosuppressive agents become available, this serious deficiency of functional kidneys, hearts and other organs will become even more acute and a problem demanding a solution. There is an estimated 20,000 patients of appropriate age in the United States who annually suffer irreversible brain death in the absence of infections or malignancy prior to arrest of circulation (9). In 1979, 3000 renal transplants were performed; however, transplantation is the preferred option for about half of the 50,000 Americans undergoing dialysis. Cadaver kidney and heart graft survival is now up to 70% for two years (9). This disparity between the need and availability of transplantable organs on the one hand and the actual efforts to recruit and harvest on the other is a source of grave concern and exasperation.

Moreover, all organ donors should also be sources of tissue. Most neurosurgeons do not request extended permission to retrieve all transplantable tissue along with viable organs, despite the obvious need and benefit allogeneic tissues provide those practicing this specialty. There is an enormous demand for freeze-dried dura mater, fascia lata, and bone that is unsatisfied. These tissues are commonly used for reconstructing pachymeningeal defects and fusing the cervical and lumbar spine. The foremost obstacle to fulfilling the need for tissue is the reluctance on the part of physicians to promote donorship and the reservations of surviving relatives toward this ultimate gift.

All 50 states have now adopted the Uniform Anatomical Gift Act which allows the donor's wishes to be binding after death. Whereas 70% of the general public and an identical percentage of physicians favor organ donations, only 1.5% of individuals in one state elected to sign a driver's license donor card (9). Programs directed at public awareness and instilling a sense of responsiblilty toward transplantation among physicians are absolutely essential. The usual impetus toward promoting donorship of organs and tissue comes from those active in transplantation. The entire community benefits, however, from their activities, which are closely allied with the generally more accepted practice of blood donation.

Solutions to the problem of insufficient organs and tissues will probably be legislative, educational and organizational. In some countries donor recruitment has been enhanced by providing laws for routine salvage of tissues and organs except where there is prior objection by the decedent or next of kin. This presumed consent legislation now is in effect for cornea donorship in at least two states. County coroners frequently impede donorship by their need to establish the cause of death. Laws which stipulate their responsibility in this new era of transplantation would facilitate and mandate their cooperation. Simplification of their duties by providing one number for them to call (rather than multiple notifications to different teams) would undoubtedly enhance their willingness to serve the cause of transplantation. Further, state laws to require adults to stipulate on their driver's license donor card "yes" of "no" would facilitate more tissue donorship.

Repetitive educational programs to promote the awareness of the public and physicians further are essential. The adverse consequences of rivalry among transplantation teams confuse the public and will fragment the thin thread linking community understanding and approval of tissue and organ donation. General news media representation of the successes in this field must be supported by conferences for physicians and nurses within hospitals.

State organizations to stimulate donorship, review and propose enabling legislation and establish guidelines and scientific practices are essential. A hospital surveillance system where potential donors are identified and a nurse-coordinator serves as an intermediary between the attending staff, transplant team and the family substantially increases the recruitment of organ and tissue donors (9).

LEGAL AND ETHICAL ISSUES

New technologies in transplantation and life support systems have raised complex philosophical, legal and ethical issues. Neurosurgeons are central in this debate, for they most often care for the individual who dies of central nervous system trauma, hemorrhage or tumor. The surgeon who strives mightily to preserve the life of a patient and minister to the family's needs must accept failure of his efforts at the time bioethical considerations of organ and tissue donorship supervene. Legal criteria exist for pronouncing death based on total brain destruction in over half the states. The biological basis for this is generally accepted in the medical community once irreversible cessation of brain function has occurred. In moral terms, however, it has been troubling to many whether the person continues to exist as long as the circulation persists. Is it appropriate moral behavior to remove from an individual a functioning heart, kidney, lung or liver?

For most physicians the unique nature of the human brain is the substrate which renders the personal identity to the individual. The intellectual principle (soul) or ability to conceptualize distinguishes man from the brute, and is a radical difference in kind rather than degree (1). This rational principle provides form to the body and coexists with it (11). The soul is bound to the material brain for its activities and leaves when the brain is destroyed. When total death of the brain has occurred, human life ends.

Neurosurgical ubiety sets the scene for the possibility of donorship. The challenge is to further the life of another beyond that of the one lost. The privileges of neurosurgery carry the associated responsibility to facilitate the rational transfer of transplantable organs and tissues in the further service of man.

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