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Chapter 39

Ethics in Transplantation: Allotransplantation and Xenotransplantation

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In ethics, the terms used need definitions. To start, we consider the meaning of two words: ethics and morals. The use of these two words is not uniform. For some, ethics is the study of behavior between people in relationships in accordance with their cultural values, whereas morals takes into account some wider principles that govern personal behavior, independently of others but often in relation to transcendental principles or beliefs or concept of deity. In this chapter, we use the two words morals and ethics synonymously. This claim is based on the origins of both words—one from ancient Greek (*ethos*) and the other from classical Latin (*mores*)—both meaning the accepted customs and values to which societies and cultures aspire.

As transplantation becomes increasingly globalized, it is important to consider whether the values that are brought to bear on transplant issues are determined by local cultures or are universal (held by all world cultures). There is a lack of uniformity. We claim that all cultures share some values (e.g., it is wrong to abuse children, it is wrong to torture the innocent, and life is of utmost value to each individual). It also is true, however, that some values are held in a different way in different cultures (e.g., individual autonomy versus interests of family, clan, or tribe; the varying intrinsic value of individual lives to the society or culture, as distinct from value to self and the varying respect for individual persons, their personal dignity, and equality before the law). At this time, only some values are held universally, and there is as yet no universal ethical system. These differences are important to intercultural transplantation debates.

DEFINITIONS

Altruism: Actions that are motivated by concern for the well-being of others, sometimes against personal preferences and self-interest.

Consequentialism: See Utilitarianism, including teleology.

Deontology: Also called duty ethics from *deon* (Greek), a binding duty. This theory stresses the intrinsic value of all individual persons, the duty of individual dignity and respect, the value of self-determination, and the cardinal importance of patient autonomy. In secular philosophy, this theory draws heavily on the writings of Kant (1724-1804), and its essence is captured by the claim that individuals should always be treated as ends in themselves and not as means to other persons' ends.

Resource allocation: It is useful to distinguish between three levels: (1) Microallocation refers to the one-on-one encounter between patient and caregiver and is dominated usually by duty-based or deontological ethics. (2) Mesoallocation refers to allocations by program directors, taking into account the needs of programs and individuals. (3) Macroallocation refers to allocation at the levels of government, taking into account wide-ranging social policies. Mesoallocation and macroallocation tend to reflect utilitarian or consequentialist ethics. (A fourth allocative level—mega-allocation—may be used in reference to policies involving international relations and allocations.)

Risk/Benefit: To the deontologist, this ratio (or calculus) refers to the risk taken and the benefit achieved by a given individual in a given situation. It should be distinguished from the concept of risk to the risk taker balanced against the benefit to another, others or society as a whole, although that calculus may have to be made in some situations using a utilitarian approach. A similar conceptual differentiation applies to burden/benefit analysis.

Utilitarianism: The other well-known tradition in ethics. It contrasts with deontology. This is an outcomes-based or consequentialist theory, based on the ethical objective of maximizing utility, or achieving the greatest good for the greatest number. It may use statistical probabilities applied to groups of individuals. The term *teleology* also is used for outcome-based ethics (*telos* [Greek] = end, or goal).

Xenotransplantation: In the human setting, the use of live cells, tissues, or organs from a nonhuman animal source transplanted or implanted into a human or used for ex vivo contact with human body fluids, cells, tissues, or organs that subsequently are given to a human recipient. Xenografts include live cells, tissues, or organs from a nonhuman animal source used for xenotransplantation.

Xenozoonosis: Infection resulting from xenotransplantation, especially of viable perfused organs, in which the risk of generating new viruses exists (e.g., retroviruses). New forms of bacterial and fungus infection may result from mutations.

ETHICAL PRINCIPLES IN TRANSPLANTATION

In many issues in health care, there is apparent conflict between the two principal ethical theories[8]—deontology and utilitarianism. Neither theory can be exclusively applied; both serve to bring relevant ethical perspectives into debate of difficult issues. In transplantation, because of the severely limited resource of available transplantable organs, transplant teams, while being aware of their deontological obligations to each patient, are forced to draw more on utilitarian considerations in making allocative decisions. Considerable ethical tension is created by this mesolevel obligation to utility (greatest good for the greatest number) because of the tendency for it to override duty owed to each individual as a unique person, at the microallocative level.

Justice comes into play insofar as we try to treat like cases alike (the principle of equity). In organ allocation, the principle of distributive justice also is at play, wherein the sickest (who have the most to gain, i.e., by a lifesaving procedure) are prioritized according to established criteria.

In the final analysis, properly informed and obtained public opinion is the arbiter of practice, and physicians are obliged to explain to the public what they do and to obtain its assent. In this process, the various public media also play an important role in informing and obtaining public opinion.

ORGANS FROM DECEASED DONORS

Ethics Issues in the Determination of Death

Medical, ethical, religious, legal, and political issues influence notions and criteria of death. Different societies accept more easily some definitions of death than others. In Japan, most transplants are from non–heart-beating donors, although the country introduced a law in 1997 enabling organs to be removed from brain-dead donors under strict conditions.[113]

Brain Death by Neurological Criteria

Since the 1970s, there has been a general acceptance that the criteria for death from cerebral causes are valid (see Chapter 6). The process was initiated by a Harvard Medical School consensus in 1968,[9] and there is near-universal acceptance that a person is dead when there is irreversible loss of function of the entire brain, including the brainstem.[109] This definition recognizes that a body may be dead even though the heart is beating and the circulation is maintained with a blood pressure that is adequate for organ perfusion. This definition means that the animate and the vegetative parts of the brain must be irreversibly nonfunctional.[93] This concept can be difficult for families to understand and accept, especially when their recently brain-damaged loved one is warm to touch and has an evident heartbeat and other functions. It is a measure of public trust in the medical profession, in which the media has played an important part, that families can accept the diagnosis of brain death, despite these contextual and conceptual difficulties.

Despite widespread agreement, there are authors who dissent, pointing out that a rigorous definition of loss of all brain and brainstem function implies loss of vasomotor tone, temperature control, and diabetes insipidus. This dissension may be more a legal problem than a medical one, but it is a problem nonetheless.[52,105,111,112]

Death of the Cerebral Cortex Alone

Frequently, individuals experience brain damage that is insufficient to destroy brainstem function, although all cerebral cortical function is lost. By currently accepted legal definitions for brain death, these individuals are not dead. They differ markedly from brain-dead individuals in that they may breathe spontaneously; have a gag reflex, and may undergo apparent sleep-wake brain cycles with opening and closing of the eyes but without seeing, and are unable to exhibit meaningful relations with the outside world. This state, when present for more than 6 months, is termed persistent incognitive vegetative state. Some experts believe that such entities are no longer to be thought of as functioning organisms because they no longer possess "coordinated integration of two types of function: organic and mental. If these two are irretrievably disjoined, then human life no longer exists."[111] For this opinion to prevail, we need to move from a whole-brain–oriented definition of brain death to a higher brain–oriented definition. This definition may come about in the future if the diagnosis of irretrievable loss of all higher brain functions becomes more precise and certain. Presently, most people consider patients in a persistent incognitive vegetative state to be alive.

Although there may be ethically defensible circumstances in which life-supporting systems may be discontinued, this is a separate issue from claiming that patients in a persistent incognitive vegetative state are already dead. Patients in a persistent vegetative state are not deceased donors.

Anencephalic Infants as a Source of Organs

Anencephalic infants resemble patients in the persistent incognitive vegetative state in that they have no higher brain or neocortical function. Some experts hold that anencephalic infants "do not have the minimal biological substrate as the basis for sentience, a necessary condition for being alive as a person" and might be used as donors if law and public policy were framed to recognize that.[17] Others disagree, however, holding that the legally recognized brain death criteria are also the only valid moral criteria.[67,115] Experience is limited. We do not yet have societal

understanding and agreement concerning the moral status of anencephalic infants.[89]

Donation after Cardiac Death (Non–Heart-Beating Donors)

Attention has been drawn, in Europe[37] and in North America,[61,120] to obtaining organs from the original source of transplant organs, before the establishment of brain-dead criteria—bodies after death from cessation of heart beat (>90% of individuals who die in hospitals). In some places, non–heart-beating donors now account for 10% to 40% of all donations.[16] (Preemptively excluded are individuals dying with disseminated cancer or infection.) Long-term results for kidney transplants from this source are comparable to those from brain-dead sources.[77]

According to the Maastricht classification,[60] there are five main categories of non–heart-beating donors. Categories 1 and 2 are termed uncontrolled, referring to donors who die suddenly and unexpectedly. Categories 3 and 4 refer to controlled situations, where death of the donor is expected, usually after the withdrawal of life-sustaining measures.

1. *Dead on arrival*: Individuals who are dead on arrival at emergency departments (e.g., from severe head trauma), some of whom provide viable organs.
2. *Unsuccessful resuscitation*: Individuals who experience cardiac arrest outside the hospital where cardiopulmonary resuscitation is initiated by the ambulance crew. The patient is brought into the hospital, and resuscitation efforts are continued by the hospital team. If unsuccessful, the team initiates the non–heart-beating donor procedure.
3. *Awaiting cardiac arrest*: Individuals dying in intensive care units where a prior decision was made with the patient and with the family that extended life measures, such as life support of various types (e.g., stomach tubes, tracheal tubes, assisted artificial ventilation), would be withdrawn, and that death would be allowed to happen in a natural fashion.
4. *Cardiac arrest while brain dead*: Patients who have been declared brain dead or are in the process of being diagnosed as brain dead in the hospital and experience cardiac arrest.
5. *Cardiac arrest in hospital inpatient*: New category added in 2003.

The debate on non–heart-beating donors has highlighted the difficulty of finding a specific moment to declare death. It may be more appropriate to think of death as a process rather than a finite event. Further debate has focused on the appropriate length of time to elapse after asystole before declaring the death of the potential donor. Different protocols call for durations ranging from 2 to 10 minutes.[25]

Respect for the Dead Body

The act of procuring organs presents particular challenges for health care professionals who are otherwise engaged in the care of living patients (organ recipients). Health care professionals may need help to deal with the emotional challenges surrounding procurement. The normally deeply felt human value of respecting the dead may become eroded in such difficult situations. Nurses feel moral distress about instituting therapies that are for the benefit of another person (the recipient).[86,101] In this situation, the patient's prior consent to donation outweighs the harm associated with organ procurement.

New Duties Owed by Health Care Professionals

Duty Owed by Health Care Professionals' Duty to Provide Organs

Now that organ transplantation is established as a medical treatment for heart, liver, and kidney failure, patients who are selected for transplantation waiting lists have established an expectation to be provided with the organ they need. This expectation places a moral obligation on physicians, nurses, and health care administrators to provide as many organs as possible, although this obligation does not yet seem to be accepted proactively into the codes of professional ethics. Individuals who support transplantation also have an obligation to support measures—a duty shared with the public at large—to encourage everyone to make their wishes known, in advance, with respect to organ donation. These wishes may be recorded in documents such as health cards, advance directives, or living wills. Some jurisdictions use presumed consent, whereas others do not (see later). The important issue is that families are aware of a potential donor's wishes regarding organ donation.

Duty Owed to Declared, Intended Donors and Their Family Members

Individuals who agree to leave their bodies to be used for transplantation or their family members who permit it create responsibilities for health care professionals. These responsibilities include making optimal use of organs procured and distributing them according to just principles of allocation, as outlined subsequently. Society does not extend to donors the right to say to whom the organs should go, unless there are close relatives in need. This limitation of their entitlement recognizes the wider societal principle of not permitting discrimination on the basis of sex, ethnicity, race, or age.

Duty Owed to Donors and Their Families to Preserve Their Option to Donate or Not to Donate

It is recognized that individuals or families have a right to give their organs should death come unexpectedly. The possibility of preserving the option for families to donate is inherent in newly suggested protocols for individuals who die suddenly and unexpectedly—non–heart-beating donors.[2,53] This also is known as donation after cardiac death. It may be acceptable ethically to subject the body of someone who has died recently and unexpectedly to preconditioning agents and techniques (e.g., vascular cannulation for cold perfusion) to preserve for the family members the option to donate organs for transplantation,[68] even though this involves touching the dead body without prior consent from a family member.

Duties Owed by Health Care Administrators and Government Officials to Patients Awaiting Transplantation

Public education by means of publicity programs promoted by government or transplant-related agencies is one measure

for obtaining organs from deceased donors. This measure promotes public altruism. Several studies indicated that despite a high percentage of the public being in favor of using organs from deceased donors for transplantation, low organ availability rates were caused partly by poor collaboration by health care professionals who are *not* involved in transplantation. Required request, required consideration, and required notification policies have been introduced widely, especially in North America, to improve collaboration, although initial improvements in obtaining organs have not always been maintained. Other measures to facilitate the process are organ removal permission statements on driver's licenses, tax returns, or other repeatedly used public documents. These measures also require support by public education for optimal participation.

There is debate on the use of systems of organ procurement referred to as opting-in (consent not assumed but sought at time of death) and opting-out, or presumed consent (consent mandated by law whereby procurement occurs based on an assumed consent, unless the individual has registered that consent is denied). Belgium and Spain are leaders among the countries that successfully practice presumed consent; the United Kingdom, Canada, and the United States have opt-in systems. In Europe, with the support of the Ministers of the Council of Europe, more attention than elsewhere has been turned to convincing the public that organs should be used without permission of next of kin or prior designation by the deceased. Presumed consent legislation permits those who do not accept this assumption to opt out of the scheme by placing their names in a registry, which must be consulted before taking organs.

Evidence suggests that opt-out systems are effective in increasing organ procurement, especially in Austria and Belgium.[58] Since enacting presumed consent legislation in 1986, no more than 2% of the population of Belgium has registered an objection to having organs donated.[51] In France, Spain, and other European countries with presumed consent legislation, physicians often require family permission even when not required by law. It is possible that such legislation is more acceptable in societies that are more homogeneous, although Singapore may be an exception. Since changing to a system of presumed consent, Singapore's rates of donation from deceased donors have increased significantly.[57] In a study of 13 Asian countries, Singapore had the highest rate of kidney donors at 21.4/1 million population.[110]

Spain achieved a 2004 procurement rate of 34.6/1 million population[91] by means of a centralized, coordinated in-hospital system, with individuals specially trained in detecting prospective donors and approaching families to obtain permission.[65] The 2004 rate is consistent with Spain's trend of continued increase in annual procurement. The 2002 donation rate was 33.7/1 million population—a number that far exceeded rates in other parts of Europe, which range from 10.4 to 24.3/1 million population donors.[21] The Spanish success may be partly due to the built-in financial incentives given to the hospitals, physicians, and coordinators involved in organ procurement.[62] Another contributing factor may be that many of the coordinators are themselves hospital intensive care specialists, nephrologists, or anesthesiologists,[18,65] although they do not coordinate for the donors who had been their own patients before death. To some individuals, these issues raise the question of conflict of interest. For these reasons, the model may not be adopted easily by other countries that lack the same level of social cohesiveness and trust.

Other factors may be influencing the Spanish donation rate. Spain accepts a high number of organs from marginal donors. Donors older than 60 years old make up more than 30% of the total donor pool, whereas donors older than 60 years make up 13.3% of the total donor pool in the United States.[18] Part of the Spanish model's success can be attributed to its strategy related to mass media; this includes a 24-hour transplantation hotline where media can obtain information from trained professionals, periodic meetings between journalists and leaders in transplantation, and training in communication for regional and hospital coordinators who deal with controversial issues.[66]

Incentives for Donors and Donor Families

Another controversial area assumes that organ procurement might be increased if incentives were offered to families of individuals whose organs might be procured after death. Suggested incentives fall into two classes: (1) proposals that anticipate death and prepare advance incentives to donate after death and (2) proposals that apply without prior planning to recently bereaved families. The former include creating a futures market,[19] or creating a priority system, such as LifeSharers. Members of LifeSharers agree to give their organs on death to individuals who also agreed to eventual postmortem organ donation. If the organ cannot be matched to a fellow member, it is made available to a nonmember.[107] LifeSharers encourages people to join while healthy by imposing a 180-day waiting period before a new member can be allocated an organ.[11]

The second category includes "ethical incentives," such as reimbursement of funeral expenses,[38] providing postmortem educational grants for bereaved children, or providing other insurance policies that become active only after donation from a deceased donor.[71] This category could include such public acknowledgment of societal indebtedness as the planting of a tree in a park or awarding donor families a medal.[80] All of these incentives have been framed as programs of rewarded gifting.[28] Much more controversial (see later) is the use of cash payments as direct incentives for organ donation. Individuals who oppose all these suggestions believe that they may lead to a lessening of the spirit of altruism in society and a descent into commercialization of organs and usage of the body and lessened societal value in the uniqueness and dignity of the human body. There is widespread repugnance over commercialism in organs from the deceased through sale or purchase, although few oppose compensation for any additional expenses incurred by the family as a result of organ procurement. Efforts to thwart the buying and selling of organs from living donors have been ineffective in many countries, and the practice is increasing.[24]

Duties Owed by Organ Recipients

Poorly defined as yet, the costs and sacrifices involved in providing organs create a moral obligation on the individuals who receive them. In the context of scarcity of organs, how far should issues such as poor adherence to treatment be used in the selection of candidates for transplants?[119] If a recipient needs retransplantation, should his or her failure to comply with antirejection medication or other requirements

preclude their being awarded another organ? Obligations of this type have been formulated poorly for society, but many see it as part of the barely articulated contract that exists between members of society and health care providers when interacting with each other within a publicly funded system.

Issues of Ownership and Authority

Issues in transplantation that seldom are addressed include the following questions: Who owns the organ after it has been procured, before it has been implanted into someone? Who has the authority to establish the rules by which the organs are distributed? What rights do family members have in saying what they want done with their relative's body?

Who Owns the Excised Organ?

The law has not determined who owns a dead body or the organs excised from it. In the Middle Ages in Europe, matters relating to dead bodies were delegated to the ecclesiastical courts (now obsolete) by the civil courts. Inherent in the concept that there is no property value in a dead body, an individual who steals an excised organ from an operating room in one hospital to take and implant it at another hospital could be charged only with trespass. It would be a theft only if that individual had stolen the container for transport purposes. Some experts advocate an end to this extraordinary anomaly[2] when such great value is placed on organs by would-be recipients and the professionals obligated to find them. Apportioning property value and ownership rights to organs from the dead is seen as a big step toward unwanted commercialization, however, which might not be prevented by concomitant legal steps to prohibit market transactions of organs. In the case of *Moore v. Regents of University of California*, a spleen donor initially was refused property rights by the California Supreme Court, but the case was subsequently settled initially by sharing in the profits from the cell line grown from the excised diseased spleen.[39]

Who Should Decide on Allocation from Deceased Donors?

The question of ownership relates to the questions of allocation. At present, although there may be no legislation to support it, it generally is *assumed* that ownership of organs resides in the state, which is *assumed* to have delegated its authority to the institution, and then to the transplantation service. It is widely assumed that the disposition of transplantable organs is not at the whim of the transplantation team simply by virtue of their skill in being able satisfactorily to remove and then implant them.

Principles Used in Organ Allocation in Transplantation

Many principles are used in the just distribution of access opportunities to scarce resources; this includes how deceased donor organs are shared, and how transplant waiting lists are managed.

Ethical Commitment to the Principle of Rescue

Despite possible injustice, we all recognize rescue as an ethical imperative to which we should respond. Sometimes rescue impels action when it is unlikely to provide the optimal outcome. It also brings out the tension created when the consequentialist principle of the greatest good for the greatest number conflicts with the deontological commitment to the quality and dignity of each human life together with the principle of justice that recognizes claims in proportion to need. The seeming imperative to carry out a subsequent organ transplant when the first has failed may present the ethical conflict between rescue and utility.[106] Veatch[113] also recognized that efficiency and equity may conflict in the allocation of organs. Rescue should not be applied to situations that fail to meet the minimal standard of utility, referred to subsequently.

Optimizing the Medical Outcome (Utility Principle)

In transplantation, particularly when setting public policy, actions usually are governed by applying the principle of greatest utility. As decision making moves from the microlevel to the mesolevel or macrolevel, the utilitarian consequentialist ethic increasingly dominates over the deontological ethic. This change explains why ethical conflict seems greater for physicians than administrators because the latter do not have personal relationships with individual patients and hold responsibilities only in the field of public policy. Monaco[70] emphasized that programs should have a minimal threshold for medical utility and make decisions above that threshold. Veatch[113] suggested that the utilitarian's goal should be to allocate the organ to the individual who is likely to gain the greatest number of quality-adjusted life-years from the organ. When all potential recipients meet the minimal threshold of utility, other ethical factors may be used for organ allocative decisions in addition to optimizing medical outcome.

Fiduciary Principle

The fiduciary principle recognizes physicians' duty to care for each patient. Tension often is created between the deontological duty imposed by this principle and some of the other legitimate principles, especially for professionals who may have responsibilities at the microallocative and the mesoallocative levels.

Random Choice (Lottery Principle and Use of First Come, First Served) and Random Factors

The two principles of random choice and random factors have much in common in that the allocative factors are value neutral. Both principles acknowledge that there are factors such as chance, or good or bad luck, that are legitimate in decision making for organ allocation because they affect all people in society in a more or less random, yet equal way. Patients find this randomness acceptable in systems based on an egalitarian principle. In contrast, physicians and transplantation coordinators may be reluctant to place any weight on random choice and random factors because it seems to deny their professional expertise in wielding medical science knowledge. Nevertheless, there are occasions when these principles would be just. Length of time on the waiting list and distance from home to center may be ethically legitimate factors in allocation provided that time of entry to the list is achieved at a comparable time point for each potential recipient, and that distance interferes with ability to accept some opportunities for receiving a graft. In different programs, other value-neutral circumstances may be accepted as weighting factors.

Ability to Pay

Ability to pay has operated largely in health care in previous centuries in all Western countries. Inevitably, it is the dominant principle in most, but not all, developing countries, where transplantation is available mainly for the rich. In a capitalist society based on libertarian principles, such as the United States, ability to pay as a dominant principle would not be unjust provided that a commonly accepted standard of basic care were available to all. Renal dialysis and kidney transplantation in the United States is covered by an egalitarian Act of Congress, which does not extend to other organ transplants. Ability to pay is excluded as a factor in allocation in transplantation in most developed countries, where there is a social commitment to support health care on egalitarian principles.

Social Worth

In an egalitarian system, estimates of social worth are ethically inappropriate and may not be used in estimating good outcomes. One often finds social worth parameters, such as lack of adherence to treatment, lack of family support, undesirable personal habits, or inability to speak the dominant language, masquerading as factors for optimizing medical outcomes, however. In our opinion, these parameters should be recognized for what they are and resisted. These factors may identify areas where patients need support and opportunities for assistance.

Lobbying and Using the Media

Another factor that may be unjust but is difficult to resist is the influence of individuals who advance their cause by obtaining greater publicity of their need through the media or a lobbying process. In a libertarian atmosphere of the marketplace, this activity might be termed a competitive edge. With use of the Internet a part of our daily lives, we need to develop strategies to address this in organ donation.[118] One advantage it offers to recipients is it redresses the imbalance caused by nature of the availability of living donors.

Using the Needs of the Program in Allocation

When a program is starting up, it can be ethical to select patients so that initial results are good enough to ensure continued funding. This selection approach should operate only for a limited time and is ethical only if it is publicized as public policy so that potential recipients and their advisors all know of the policy and its limited duration.

KIDNEYS FROM LIVING DONORS

Benefit/Burden Calculus for Living Donors

There always has been an ethical issue in living donors stemming from the injunction *primum nihil nocere*—above all do no harm.[95] Can it be claimed that removing a sibling or parent's kidney is not doing harm? It usually is argued that the good (benefit) that comes to the donor as a result of restoring his or her family member to well-being and renewed life justifies the possible burden borne by the donor. The donor is acting altruistically (acting for the good of another, without primary regard to self-interests) but has this good result as an added compensation.

Living donor kidney transplantation is not without its risks. Donors face a perioperative mortality rate of 0.03%.[76] A study following up with donors who had given kidneys between 1963 and December 1979 (20 to 37 years after transplantation) revealed a few donors develop renal dysfunction or renal failure at some point.[83] It is unclear if this risk is more than in people who have not donated, and there are studies that have shown a survival benefit in healthy individuals who have donated one kidney.[45]

International consensus statements recommend standards regarding the care of living organ donors. These practice guidelines emphasize the elements of informed consent: capacity, disclosure, understanding, and voluntariness.[5,43] In some places, only an emancipated minor (a minor who has undergone a legal process to attain legal adulthood before reaching the age at which they would usually be considered adults) or an adult can make the assessment meaningfully and give informed consent. Minors are rarely used as living kidney donors, but in such instances many jurisdictions insist that only a family court judge or equivalent can sanction the donation.

It is not deemed ethical to balance the possible harms to the donor against the benefit to the recipient; this is considered to be an unethical way of calculating burden versus benefit. Calculated in that way, the ratio could be used to justify the use of mentally incompetent relatives and the reluctant but competent relative. It is necessary that overall donor benefit is present.[100] One must consider the burden/benefit ratio to the donor against the burden/benefit ratio to the recipient. Included in calculating benefit for the donor is the knowledge that his or her kidney would give a better result than is obtainable from a deceased donor kidney[10,87] and relieving the burden of continued dialysis and (in children) further risk of stunted growth.

Increased demand for kidneys continues to outstrip supply.[44,108] The shortage of organs from deceased donors has led to continued use of living donors and a widening of the donor pool. Living donors now include extended family members, friends, acquaintances, and even strangers.[64] This expansion of the living donor pool has raised further debate on whether the emotional connection between donor and recipient should influence the degree of risk that the living donor undertakes.[88] Research indicates that transplantation is the best treatment for most patients with end-stage kidney disease,[94] and generally the longer a patient is on dialysis, the poorer the outcome after transplantation.[48]

Commerce in Human Kidneys, Especially from Living Strangers

One very controversial area in organ transplantation is the ethical probity of exchanging viable kidneys for money or other forms of payment. Before considering that aspect, there are several less challenging issues, which involve some form of altruism. The key factor seems to be donor (vendor) motivation.

These issues may be analyzed by considering the motivation of donors or vendors of their own kidneys. Other stakeholders in these transactions are recipients of commercially obtained kidneys, entrepreneurs who arrange for kidney transactions, physicians who perform the surgeries, and, most importantly, spokespersons for society as a whole. These individuals all have ethical dilemmas but of lesser dimensions than the vendors.

Spousal Altruism

Earlier reluctance to accept spouses as altruistic kidney donors largely has evaporated. The reluctance was due to spouses having no more probability of being well matched for HLA than any randomly tested individual or deceased donor source, and these grafts were expected to have a poorer survival than an HLA-matched deceased donor kidney. Wives, as recipients of their husband's kidney, might have degrees of prior sensitization against HLA and other systems because of exposure to the husband's antigens on fetal cells during pregnancy, which might not be detected. In some social settings, wives might be seen as prone to coercion by husbands. With improved immunosuppression, however, poorly matched combinations now give much improved outcomes (see Chapters 10 and 37); also, subtle HLA sensitization is detected more easily, and its potentially deleterious effect is overcome more easily. At present, spousal donors are acceptable ethically when the relationship is stable, and coercive obligations are excluded.

Purely Altruistic Motivation

Friendship and acquaintance are accepted more and more by transplant centers as an altruistic basis for a nonrelated living kidney donation. In our experience, kidney donation to a one-time college roommate was described by a 60-year-old woman, 6 years after giving her kidney, as follows: "I look upon giving one of my kidneys to my friend as being the most satisfying single act of my life."

Although altruism sometimes is expressed toward unknown others—as when individuals agree to participate in research that brings them little or no direct benefit—organ donation on this basis occurs most frequently by means of a postmortem donor card. Kidney donation by anonymous living donors is now being performed in some centers.[64] A well-documented example is that of a German professor of transplantation surgery who donated one of his kidneys to a patient (unknown to him) on the Munich waiting list.[35] Kevorkian[59] claimed that most criminals about to die by capital punishment wish to give their organs, but this request has not been taken up by any state legislature in the United States. This claim is used as the basis for transplantation in China with kidneys from executed prisoners. China has been widely criticized for this practice.[40]

Altruism with Compensation

The ethical debate over "rewarded gifting" has not produced clear consensus.[28] Compensation may be divided into financial profit for organ donation, which is illegal in most countries of the world, and compensation for financial costs associated with organ donation. The latter may be seen as an issue of justice (i.e., that is it is unfair for an organ donor to be financially penalized for incidental expenses incurred in organ donation). Compensation of these costs (e.g., loss of income, costs of transportation and accommodation) is increasingly considered reasonable. Compensation that constitutes financial profit resembles a contract for commercial sale and is considered by most experts to be flawed ethically.

There is ongoing debate about payments related to organ transplantation, mainly with respect to living kidney donors. At a conference in Munich in 2002, the following resolution was passed related to this issue: "The well-established position of transplantation societies against commerce in organs has not been effective in stopping the rapid growth of such transplants around the world. Individual countries will need to study alternative, locally relevant models, considered ethical in their societies, which would increase the number of transplants, protect and respect the donor, and reduce the likelihood of rampant, unregulated commerce."[24]

Kidney Selling

Selling kidneys is illegal in most countries where there is legislation related to organ transplantation. Ethical analyses of kidney sales need to consider contextual features, such as availability of dialysis and alternative opportunities for meeting the necessities of life. Opponents of the practice, such as Kahn and Delmonico,[56] warn of the possibility of societally endorsed exploitation of vulnerable individuals. They argue that governments have a duty to provide for the poor, and that commodification of the body could discourage them from providing less risky sources of income for the destitute.

Caplan[15] raised concerns that the practice may erode public trust in transplant medicine. He noted that kidney sales can have poor outcomes for vendors, and that the creation of a market in organs means changes in the nature of the relationship between physicians and their patients in these situations. Physicians, he argued, have a greater duty to "Do no harm" in this context than to assist patients financially through removing their organs.

Murray[75] approaches the matter from a different angle, urging us to recognize the impact that organ selling might have on social relationships. We live in a "community of needs," both biological and cultural, and needs related to transplants and blood transfusions are best met through "gifts of the body." He claimed we can realize important social values through noncommercial donation, such as fostering a sense of connectedness among people, recognizing the universality of human needs, and protecting the dignity of individuals. Two types of kidney selling are definable and are considered separately.

INDIRECT ALTRUISM

Indirect altruism, a concept developed by Dossetor, refers to when donor motivation for organ selling is altruistic toward a third party. Indirect altruism is a term coined to describe the following form of altruism: Person *A* wishes to carry out a good deed for a family member, person *B*, whose needs can be met only through using money. *B*'s needs cannot be met by *A* giving her a kidney because renal failure is not *B*'s problem. *A* does not have the money to meet *B*'s need, and society would not or could not provide it. Person *C* is rich and in need of a kidney. If *A* makes a contract to give a kidney to a third party *D* on the understanding that *D* would then sell that kidney to *C* and use the proceeds to help *B*, *A*'s contract with *D* is implicitly altruistic, but *D*'s contract with *C* is purely commercial. The money *D* obtains from *C* enables *A* indirectly to carry out the altruistic intention toward *B*.

Many would find this scenario compelling. Dossetor has defined, at greater length than here, the context in which indirect altruism would have to occur, using an ethically responsible third-party regulator, *D*, who is trustworthy and respected. Other criteria would need to be in place[41] for such arrangements to meet ethical standards. Examples that seem to meet these criteria are described from India.[84] Daar[24,29] and others[82] also have written extensively about this complex subject.

PERSONAL GAIN

Many people find the thought of vending organs for private gain to be repugnant. Some who had taken this position subsequently changed their minds. Others point out that it has been difficult to articulate convincingly the reasons for banning the practice.[12,46,82] The United States has recently looked at financial incentives to increase donation rates. These include partial reimbursement for funeral expenses, reimbursement for travel, and reimbursement for other expenses.[24]

There has been renewed discussion of organ sales in the West because of numerous factors, including great and continuing shortage of kidneys for transplantation, the number of deaths on the waiting list, the knowledge that early transplantation is the preferred treatment for individuals with end-stage renal disease,[63] and the number of Westerners who travel abroad to purchase organs. Veatch[114] argued that the failure to provide adequate income levels for some members of society supports the legalization of kidney sales.

The subject of payments for organs is complex.[27] We previously published a classification of the various types of living kidney donations, with consideration of their ethical acceptability or otherwise, so as to enable discussion to focus on each individual issue, rather than combining all the considerations at once. Living kidney donors can be grouped into the following five categories[36]:

1. Living related donor transplantation: Donation to a blood relative.
2. Emotionally related living donors: Genetically unrelated donors, including spouses and close friends.
3. Altruistic donation: The donor does not know the recipient, with no expectation of material reward.
4. Rewarded gifting: The donor is reimbursed (at least partially) for costs related to the donation, including lodging, travel, loss of income, and hospitalization.
5. Rampant commercialism: Payment for kidneys often to a broker or middleman, of which the donor may receive an amount.

This classification has evolved into the "gray basket concept"[26]—the gray basket being that category in the classification wherein ideas such as indirect altruism[41] or the donor trust,[98] founded on certain ethical principles but nonetheless still controversial, can be discussed sensibly.

Arguments have been made on both sides of this debate, which has many nuances. Radcliffe-Richards and coworkers[82] concluded that "we are not arguing for the positive conclusion that organ sales must always be acceptable, let alone that there should be unfettered market. Our claim is that none of the familiar arguments against organ selling work, and this allows for the possibility that better arguments may be found." Although there is some validity to the various arguments for organ vending for personal gain, our view is that rampant, unregulated commerce in organs for personal gain is against the best interests of society and should remain prohibited throughout the world. The matter deserves ongoing debate, however.

Dossetor, who has given this matter more thought than perhaps most commentators, approves a practice whereby an altruistic good can be achieved by a method that involves obtaining money from wealthy recipients by vending organs through an ethically reliable third party, under conditions in which the donor makes no profit or personal gain except through the spiritual or psychological benefit inherent in acts of altruism. Whether or not such a system can be or needs to be established in a given country depends on many societal factors. These factors are reviewed by considering situations at both ends of the world prosperity spectrum: (1) from the viewpoint of an affluent society and (2) from the viewpoint of a country where the bulk of the population lives in poverty.

For affluent cultures, such as the West, many factors operate to support individuals with special transplant needs, such as state health care programs, unemployment and health insurance, and resources to support existing altruistically based deceased donor programs and new initiatives to increase organ procurement. The benefit/burden calculus for the would-be kidney donor to a third-party vendor who then obtains money for the donor's intended act of indirect altruism is not compelling. The conditions of abject poverty do not exist. Also, in Western cultures, the benefit to society of allowing kidney transplantation through third parties raising funds from kidney vending to carry out acts of indirect altruism do not seem to outweigh the probable harm to the fabric of society that would stem from commercialization of the body, including lessened respect for others, affront to religiously based convictions, decay of primary or direct altruism, and other risks for social corruption. There are many more opportunities to sustain the lives of individuals with chronic renal failure.

Affluent countries offer protection against dire need in many ways, and members of society are largely protected against abject poverty, starvation, and lack of shelter through a tax-financed social security net. Affluent societies provide protection against the need for self-imposed acts of heroism, such as those involved in donating a kidney altruistically, which is then sold to obtain money to benefit others.

Nonaffluent cultures differ in striking ways. Not only is there an absence of the general social security net but also of government-funded health care programs for special needs. People die for lack of adequate housing, nutrition, and simple medical needs, including good sanitation and pure drinking water. People in such conditions already are victimized by abject poverty. The context of their whole lives is different from those of citizens of affluent countries. In such situations, although we still deplore kidney commerce for personal gain, it is impossible for us to condemn kidney donation for prearranged vending through a third party to raise money for an act of indirect altruism to a family member. For the donor in the personal no-gain setting of indirect altruism, the burden may be offset by the benefit to the family member, whereas the welfare of society is not at risk because of the underlying altruistic nature of the act, even though an organ has been obtained for money.

Inherent in this support for indirect altruism in nonaffluent cultures is an insistence that the benefit to *B*, the intended beneficiary of this form of altruism, must be ensured. This ensurance necessitates a socially responsible, noncorruptible panel or tribunal of societal and professional peers to approve individual cases and set up a mechanism to collect money from the recipient purchaser and to effect the intended altruistic good of the donor. In our judgment, if this situation cannot be ensured, an institution would be acting unethically in pretending to meet a standard if it knows it cannot.

Lastly, we consider in this section the ethics issues facing recipients who have bought kidneys from living unrelated individuals—the purchasers of kidneys. Purchasers of kidneys in nonaffluent countries, where kidney transactions could be used to raise money for acts of indirect altruism, are disproportionately rich compared with the donors. Purchasers are buying parts of someone else's body, which many see as a manifestation of victimization of the poor by the rich, akin in some ways to prostitution or enslavement. Wealth is accepted in most cultures as giving special privileges to individuals who possess it, but this does not extend to victimization and partial enslavement of others.

Dossetor[41] suggests, because of the good that might result from indirect altruism to the donor's intended beneficiary of the sale, the purchaser of a kidney might be ethically justified if two conditions were met. In addition to giving a fair price for the organ, (1) the purchaser should be obliged morally to give additional funds to support another distressed person, perhaps from the section in society from which the donor comes, and (2) the purchaser should give additional funds toward the ultimate establishment of a deceased donor renal transplant program. These additional funds, which Dossetor[41] termed mandated philanthropy, should not be paid out at the expense of a fair and generous price to the kidney donor, who uses third-party vendors to effect acts of indirect altruism. The purchaser's responsibility in this regard should be in the hands of a tribunal or panel of peers at the transplant institutions.

So far, the only country that has openly and institutionally created mechanisms for paid organ donation is Iran. Implementing and refining the Iranian model while addressing most of the ethical concerns has made Iran perhaps the only country in the world to reduced the waiting list for kidney transplants.[47] However, the Iran model is not without blemish.[52a]

Daar has noted[30] that despite our condemnation of the practice, the number of commercial transplants has increased in recent years. He argues that serious consideration ought to be given to regulating the practice where such practice is rampant, causing harm to donors and recipients (usually only recipients who can afford to pay), and where countries are unable to stop the practice or provide alternatives.

EMERGING ISSUES IN TRANSPLANTATION

Xenografts

Efforts to obtain organs for direct transplantation into humans have had a positive impact on the xenotransplantation field by factors including (1) advancements in immunosuppression, which have led to improved outcomes in interspecies kidney transplants; (2) ability to manipulate the recipient's immune response; and (3) ways of altering some of the foreignness of pig tissue by inserting into the tissue human genes coding for complement regulatory proteins and other genes. Xenotransplantation already is a highly controversial area. Kantian deontologists may see animals as outside the province of human ethical concern because they are not moral agents. Other traditions believe that animals share ethical status with humans in proportion to their ability to have relationships with humans and a social life among themselves and their capacity to suffer pain and anguish and possibly suffer from frustrated self-awareness and thwarted self-interests.

Although animals may not have rights, many people attribute them with varying degrees of ethical status. People who strongly hold this perspective view xenografting as another form of animal exploitation and another excess of medical hubris, especially if directed at species whose behavior more resembles that of humans (as denoted perhaps by the notion of genomic proximity to humans). Transplant teams should try to understand the motivations of such believers in attempts to avoid extreme polarization of emotional viewpoints. Indifference to these concerns leads to angry confrontations, such as characterizes the abortion issue. Efforts to understand the rational and philosophical basis for people who oppose development of this branch of transplantation science are important. It can be assumed that most people who presently find the prospect of xenotransplantation abhorrent value individual human lives much more highly than individual animals. This assumption should be taken as a given in the debate.

Some ethical issues of xenotransplantation and the possible implications for allotransplantation have been explored.[23,32] These and other ethical issues in xenotransplantation stem from the unique combination of perspectives that constitute the debate (Table 39-1). Some of these are expanded on in this section, although they are in the course of rapid change.

Breeding Animals for Xenograft Purposes

The great British reformer Bentham (1748-1832), regarded as a key figure in the development of utilitarian ethics, also was one of the earliest to advocate the humane treatment of animals. In 1780, he asked two fundamental questions: (1) "The question is not can they reason? Nor can they talk? But can they suffer?" (2) "What insuperable line prevents us from extending moral regard to animals?" A modern utilitarian philosopher, Singer, has taken on the mantle of Bentham where animals are concerned.

Table 39–1 Xenotransplantation Debate

Great scientific research
Significant industry involvement
Much greater public awareness of the *existence of a problem (without a sense of the details)*
Public opposition to the exploitation of animals in this way
Lack of consistency of what the public is told about
State of science
Magnitude of risk
Much greater involvement of scientists with industry in terms of contractual obligations and funding of research
Depletion of traditional sources of university-based funding
Difference in assessment by scientists and policy makers of
Scientific base
Risk of infection
Much more active and organized constituency of ethicists, philosophers, concerned citizens, and animal rights activists with a larger capacity to make their (sometimes confused) views known and not all willing to engage in polite discourse
Much stronger constituency of patients' advocacy groups, who cannot understand why important research is being held back by *theoretical* and *academic* fears and risks

Pain is perceived essentially in the same way by all vertebrates, and it is not controversial that vertebrates used in experiments feel pain. There is a growing consensus, however, that animals can suffer, not just feel pain. Suffering implies self-awareness, and many experimenters are not ready to concede this point because it then implies a degree of intelligence and worth that would allocate rights to animals.[99] Regan[85] and others have argued that animals do have many rights, even if these are of a lesser magnitude than those of humans. Ignoring animal rights (a term popularized by Regan) is a form of speciesism, which is equivalent to racism.

We appreciate the tremendous complexity of animal lives. Animals in captivity can experience fear, boredom, isolation, and separation. They may not be able to use language (that we can understand), but they do communicate. The emotional repertoire of nonhuman primates, according to ethologists Goodall and Fossey, apparently includes love, sorrow, and jealousy.[74] These features also explain partly the increasing concern for animal welfare, culminating in the tendency to pass laws recognizing animals as sentient beings with inherent value. If animals are sentient and have value, it could be argued that they *must* have rights. Are animals members of the moral community? Even if we concede that animals are moral subjects and not just objects, they could never be moral agents as far as humans are concerned. There is an inherent problem in the discourse on animal use in that one of the parties being discussed does not participate in the debate, and we are restricted to evaluating moral sensibilities, principles, and values of *Homo sapiens*.

What is it in humans that bestows on them the moral superiority or higher moral value that would justify the killing of an animal to save a human being? Is it language, tool use, rationality, intentionality, consciousness, conscience or empathy?[14,97] Because philosophers disagree, because premises are different, and because rights theories contain elements of arbitrariness, it seems that, short of a complete change in human consciousness, the issue will remain controversial and divisive.

There are laws to protect research animals in many countries, and there are international guiding principles, such as those of the Council for International Organizations of Medical Sciences. Sensible guidelines include the "3R's" of Russel and Burch,[90] which are to reduce, replace and refine, to which could be added reconsider and respect. There is much effort today directed at looking for alternatives to animal use. Ultimately, it will be public, rather than professional, acceptance, acquiescence, or rejection that determines the issue of using animals in xenotransplantation. Today, a stronger case can be made for the use of pig organs but not organs from nonhuman primates, for human xenotransplantation. At this stage of development, it is perhaps more productive to worry about and attend to animal welfare rather than animal rights.

Within the three major monotheistic religions, Judaism, Christianity, and Islam, humans were made in the *imago dei*, and the rest of creation is there to serve humans. God blew His own breath into the body of man, transfiguring him and making him different from the rest of creation. The pig is ritually unclean in Islam (*najs*) and Judaism (not *kosher*), however. We have looked at this issue[31] and concluded that it would not be a barrier to xenotransplantation, based on the theological argument that need and necessity can allow that which is forbidden, and in any case, the prohibition is to eating only. There is a minority opinion, however, that pigs, partly because they are ritually unclean, cannot be used as source animals. From the religious perspective, it would be important that a xenotransplant should not tamper with the human personality, its freedom and its ability and eligibility to bear responsibility. Humans have stewardship responsibilities accepted noncontroversially by almost everyone, making it necessary to reduce the pain and suffering of animals being used for human purposes.[31,55]

The psychosocial aspects of humans adapting to xenotransplanted organs are unclear. Some recipients may experience emotional difficulties or have problems integrating the transplant in their self-image.[4] Although xenotransplantation eventually may eliminate the wait for an organ, it may give rise to other challenges, such as seeing animals as an infinite resource. One study[102] found adolescents to be very accepting of xenotransplantation in the form of porcine islet cells and raised the question of how recipients would deal with nonadherence to treatment if there were a steady supply of organs through xenotransplantation.

Ethics of Consent When Society Is Also at Unknown Risk

The issue of consent in xenotransplantation has not been addressed adequately, and its implications are underestimated. The major issue in xenotransplantation today is whether we are ready to proceed to systematic clinical trials. Our understanding today is that consent for experimental procedures should be informed, unhurried, and voluntary. Informed consent exists for the purpose of protecting the subject from the risks of the experiment. Normally, taking into account societal considerations might prejudice the interests of the individual subject. Generally, consent has nothing to do with protection of contacts or of society. It requires that the subject be made aware of the risks involved, the potential benefits to the subject, and all the alternatives available.

For xenotransplantation, there is a risk (especially from new xenozoonoses) to the public at large. Zoonotic infections such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), parvoviruses, and the SARS coronavirus have spread around the world, prompting calls for global international surveillance of xenotransplantation-associated diseases.[33] Trials cannot proceed ethically until there is agreement from society as a whole that it is willing to accept this risk. There are no easy and reliable ways of obtaining such a societal consent. It is a major ethical problem that initially can be addressed only by making every effort to inform and involve all segments of society, using every media outlet. Public policy decisions based on a risk-benefit analysis would likely favor individual patients, rather than the public at large. The "precautionary principle" may place priority on society as a whole.[22] This principle, as formulated in the Wingspread Declaration, states: "When an activity raises threats to human health or the environment, precautionary measures should be taken, even if some cause-and-effect relationships are not established scientifically."[33]

In xenotransplantation clinical trials, particularly for the early patients, many of the normal elements of individual consent would need to be compromised. Subjects would probably be very sick, and voluntariness would be questionable because, especially in the case of liver and heart subjects,

the alternative may be death. The risks of rejection and the potential benefit can be estimated vaguely, but the risk from xenozoonoses cannot, because clinicians do not know which viruses would be more pathogenic in humans or would mutate or recombine in the host. Clinicians would not know if the source animal has any viruses about which nothing is known. The incubation period and latency of some retroviral infections (e.g., HIV) could be several years. There is considerable evidence that HIV jumped species from nonhuman primates to humans.

Clinicians have become aware only more recently that porcine endogenous retroviruses can infect human cells in vitro.[81] The demonstration that 160 patients exposed to live pig tissue[79] did not become infected by porcine endogenous retroviruses is partly reassuring but should not be seen as definitive evidence justifying large-scale clinical trials.[116] Oldmixon and colleagues[78] discovered a unique herd of pigs that do not transmit porcine endogenous retroviruses to humans. Studies suggest it may be possible to produce pigs for xenotransplantation that pose a greatly reduced risk of infection.[7,96,117]

The main foreseeable problem with clinical trials in xenotransplantation is with the question of postoperative monitoring. The recipient would have to agree to the requirement for strict monitoring, which may be intrusive and may result in quarantine, containment, or other physical restrictions if the recipient develops infections likely to endanger contacts, health care workers, or the public. Privacy and confidentiality almost certainly would have to be signed away in this consent procedure, especially because the contacts also would require monitoring. The recipient may be restricted from having sexual relations for perhaps 1 year or more. Contacts themselves would have to consent to postoperative monitoring, which may be intrusive in the case of a major infection difficult to diagnose or treat. There is an implicit need for community consent—not an easy thing to obtain because it normally would require public hearings, advisory bodies, and legislative and executive branch processes.[54]

The fact that the patient is going to be required to comply with postoperative monitoring alters the nature of consent to something more aggressively binding and contractual. There is another normal feature of consent—the subject has the right to withdraw at any time from the experiment. This right would have to be transgressed because the recipient could not opt to withdraw later from the experimental procedure, which must conform to standards such as the Declaration of Helsinki. It would be extremely difficult, for example, for the recipient of a pig heart to withdraw from a study and have the organ removed[20]; another example is when the participant harbors an infection that might jeopardize public health. The consent would need to be enforceable in a direction different from that in the past—this time against the best interests of the subject and in favor of the public. This situation would be a travesty of the concept of consent as it is known today. A type of "Ulysses Contract" could be used to compel the investigation, treatment, or confinement of a xenotransplant recipient, even in the event of rejection of the graft.[22]

Avoidance of Regulation by Xenotourism

Almost all of the influential discussions about the dangers of xenotransplantation and development of guidelines and control frameworks are taking place in Europe and North America (see later). Xenotransplantation may start elsewhere, however, in environments where the regulations are lax, and the scientific base and facilities are inadequate. An example was the case of Baruah,[73] a physician who was arrested in Assam, India, early in 1997 for violation of the Organ Transplantation Act. He had claimed to have transplanted successfully the heart, lungs, and kidneys of a pig into a human recipient at his own hospital, assisted by local colleagues and apparently by a colleague from Hong Kong. The patient died a week later, and the family, feeling suspicious, lodged a complaint with the police. This kind of activity might pose dangers because in the near future clinicians from scientifically advanced countries may start collaborating with colleagues in countries where the regulations may be more permissive. It would be better to consider seriously an international effort to draw up universal guidelines, while hastening to lay the groundwork for national regulatory mechanisms for clinical trials.

Cost and Other Economic Considerations

Xenotransplantation will be expensive for at least a number of years. The biotechnology companies are likely to control the cost of the organs and in the absence of real competition would want to keep this cost as high as the market would tolerate. The cost of rearing source animals under special conditions, monitoring them, developing laboratory tests, training staff, taking extra precautions, monitoring recipients and contacts, and installing infection control measures all would add to the cost. There also is the question of who would pay for expensive new immunosuppression.[69] It is unknown if, in the long run, the cost would decrease sufficiently for this to be one of the justifications for xenotransplantation. When the results achieve sufficient success to be seen as established treatment and not clinical research, countries with ethical commitment to equity in access to established therapies would need to assess carefully how to maintain the principle of distributive justice.

National and International Efforts to Develop Guidelines

One must approve the efforts that have been made to consider the challenging issues of xenotransplantation and be prepared to regulate its development along ethically acceptable lines. Table 39-2 lists some of these efforts. There is great concern about ethics issues, regulatory frameworks, relationship with industry production of source animals, and the risk of xenozoonoses and their detection. In addition to those listed, there are initiatives by other international bodies and by national bodies in France, the Netherlands, Spain, and Switzerland.

In January 1999, the Parliamentary Committee of the Council of Europe decided to call for a moratorium on xenografts. This moratorium has been criticized as inhibiting research funding and investment, but it has been praised by others.

The government of the United Kingdom developed the Advisory Group on the Ethics of Xenotransplantation, which published a report entitled "Animal Tissues into Humans (the Kennedy Report)"[1] in August 1996. It advocated an effective embargo against clinical trials in the United Kingdom until a National Standing Committee could be established to supervise and coordinate the many aspects of accumulation of knowledge and set up mechanisms to

Table 39–2 **National and International Reports in Xenotransplantation and National Regulatory Efforts**

National and International Reports on Xenotransplantation
World Health Organization (WHO) Consultation in Xenotransplantation
Institute of Medicine (U.S.)—Xenotransplantation Science, Ethics, and Public Policy
United Kingdom Advisory Group on Ethics of Xenotransplantation—The Kennedy Report
Nuffield Council on Bioethics—Animal-to-Human Transplants: Ethics of Xenotransplantation
Organization for Economic Cooperation and Development (OECD)—Policy on International Issues in Transplantation Biotechnology
Health Canada—National Forum on Xenotransplantation: Clinical Ethics and Regulatory Issues, November 1997
National Regulatory Efforts
United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA)
Canada: Standards for Xenotransplantation—Canadian Standards Association (CSA)
German Medical Council on Xenotransplantation
Council of Europe Steering Committee on Transplantation—responsible for the moratorium on xenotransplantation of January 1999
Èstablissement Français des Grèffes

protect the public and patients, look after the welfare of animals, and decide when clinical trials could start. It concluded also that it would be ethically acceptable to use pigs and to modify them genetically for xenotransplantation.

The British government responded to the Kennedy Report in January 1997 and announced establishment of the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA), to be chaired by Lord Habgood of Calverton. The response agreed broadly with the Kennedy Report's conclusions, but it called for more input in regard to (1) the unacceptability of using nonhuman primates for therapy and (2) the conclusion that not enough was known about the immune response, physiology,[72] and risk of xenozoonoses to proceed to clinical human trials.

The Ethics Committee of the International Xenotransplantation Association[103] published a Position Paper in 2003. It stressed the need to minimize the risk of infectious disease transmission and suggested standards for clinical trials. Einsiedel[42] argued that the Position Paper needed to examine the issue of public education more closely. This sentiment was shared by others,[6] who suggested that town hall meetings, referenda, and possibly virtual meetings over the Internet ought to occur when considering public policy that may pose risks.

One attempt was made by the Canadian Public Health Association,[13] which conducted six citizen forums across Canada that featured 107 panelists. The project also sought public opinion by telephone, mail, and website surveys. Although Canadians did not think xenotransplantation should proceed at this time, they wanted to explore alternatives, such as stem cell research, widening the human donor pool, and disease prevention. A similar project led by the Australian National Health and Medical Research Council was initiated, which involved public meetings in several cities.[104] Although attendance was low, the meetings revealed strong support for animal rights. Obtaining such informed societal opinion and agreement is difficult and costly.

Physiological Issues

Less discussed are the hazards inherent in an animal organ, such as the liver synthesizing animal proteins that might (1) be unphysiological for humans, having a dysfunctional effect; (2) induce an immunological response; or (3) interact with human protein homologues in some unforeseen way. There are other physiological incompatibilities for other organs.

Regenerative Medicine

According to Daar and Greenwood[34] and Greenwood and colleagues,[49] regenerative medicine is an interdisciplinary field of research and clinical applications focused on the repair, replacement, or regeneration of cells, tissues, or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma, and aging. It uses a combination of several existing and newly emerging converging technological approaches that moves it beyond traditional transplantation and replacement therapies. The approaches often stimulate and support the body's own self-healing capacity. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering, and the reprogramming of cell and tissue types.

Developing Countries

Low-income and middle-income nations tend to have high rates of communicable diseases and are experiencing an alarming increase in noncommunicable diseases, such as cancer, diabetes, and cardiovascular diseases (Table 39-3).[49] Many of these countries have developed initiatives related to regenerative medicine. The Nacional University of Cordoba in Argentina has conducted gene therapy experiments in mice to treat rheumatoid arthritis with promising results. The Chaoyung Hospital in Beijing, China, has begun using cells derived from fetal tissue to treat many neurological diseases, such as amyotrophic lateral sclerosis, Parkinson's disease, and spinal cord injuries.[50] Physicians in India have used adult stem cell therapy to repair the eyes of 125 patients who have experienced infections, burns, and trauma.[92]

Regenerative medicine could reduce the financial burden created by many diseases.[49] Bone marrow stem cell transplantation or microencapsulated islet cells could reduce the amount of spending on insulin treatments for diabetics and could lower the incidence of related complications, such as blindness, heart disease, and diabetic ulcers. Autologous cells could be injected into heart muscle to repair tissue damaged by myocardial infarction and cardiomyopathies, saving lives and reducing the cost of treating heart failure. Specially engineered immune cells could help reduce the devastation caused by diseases such as HIV/AIDS, tuberculosis, hepatitis, and malaria.

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Table 39–3 **Top Ten Regenerative Medicine Applications for Improving Health in Developing Countries**

Ranking	Applications of Regenerative Medicine	Examples Identified by Panelists
1	Novel methods of insulin replacement and pancreatic islet regeneration for diabetes	Bone marrow stem cell transplantation for pancreatic regeneration Microencapsulation (e.g., poly-lactide-co-glycolide) for immunoisolation of transplanted islets Cultured insulin-producing cells from embryonic stem cells, pancreatic progenitor cells, or hepatic stem cells Genetically engineered cells to express insulin stably and contain a glucose-sensing mechanism
2	Autologous cells for regeneration of heart muscle	Myocardial patch for cardiac regeneration Direct injection of autologous bone marrow mononuclear cells for cardiac repair Stromal cell injection for myocardial regeneration Localized angiogenic factor therapy through controlled-release systems or gene therapy
3	Immune system enhancement by engineered immune cells and novel vaccination strategies for infectious disease	Genetically engineered immune cells to enhance or repair immune function Single-injection DNA vaccines
4	Tissue-engineered skin substitutes, autologous stem cell progenitor cells, intelligent dressings, and other technologies for skin loss owing to burns, wounds, and diabetic ulcers	Bilayered living skin constructs (e.g., Apligraf) Engineered growth factors (e.g., rhbFGF, rhEGF) applied in conjunction with topical treatments (e.g., SD-Ag-Zn cream) Intelligent dressings composed of a slow-releasing growth hormone polymer Epithelial cell sprays
5	Biocompatible blood substitutes for transfusion requirements	Polyhemoglobin blood substitutes for overcoming blood shortages and contamination issues
6	Umbilical cord blood banking for future cell replacement therapies and other applications	Preserved umbilical cord blood stem cells to provide future cell replacement therapies for diseases such as diabetes, stroke, myocardial ischemia, and Parkinson's disease Pooled cord blood for the treatment of leukemia
7	Tissue-engineered cartilage, modified chondrocytes, and other tissue-engineering technologies for traumatic and degenerative joint disease	Matrix-induced autologous chondrocyte implantation for cartilage repair Tissue-engineered cartilage production
8	Gene therapy and stem cell transplants for inherited blood disorders	Genetically engineered hematopoietic stem cells to restore normal blood production in patients with β-thalassemia
9	Nerve regeneration technologies using growth factors, stem cells, and synthetic nerve guides for spinal cord and peripheral nerve injuries	Synthetic nerve guides to protect regenerating nerves Embryonic stem cell therapy for spinal cord regeneration Growth factor–seeded scaffolds to enhance and direct nerve regeneration
10	Hepatocyte transplants for chronic liver diseases or liver failure	Microencapsulation of hepatocytes to prevent immunological reaction Derivation of hepatocytes for transplantation from bone marrow cells Transdifferentiation of hepatocytes for transplantation from bone marrow cells

From Greenwood HL, Singer PA, Downey GP, et al: Regenerative medicine and the developing world. PLoS Med 3:9, 2006.

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