

Ethical Issues in Organ Transplantation

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Key Words

Organ allocation · Living versus cadaver donor transplantation · Organ sale · Donor compensation · Stem cells · Fetal tissue · Xenotransplantation

Abstract

Clinical organ transplantation has been recognized as one of the most gripping medical advances of the century as it provides a way of giving the gift of life to patients with terminal failure of vital organs, which requires the participation of other fellow human beings and of society by donating organs from deceased or living individuals. The increasing incidence of vital organ failure and the inadequate supply of organs, especially from cadavers, has created a wide gap between organ supply and organ demand, which has resulted in very long waiting times to receive an organ as well as an increasing number of deaths while waiting. These events have raised many ethical, moral and societal issues regarding supply, the methods of organ allocation, the use of living donors as volunteers including minors. It has also led to the practice of organ sale by entrepreneurs for financial gains in some parts the world through exploitation of the poor, for the benefit of the wealthy. The current advances in

immunology and tissue engineering and the use of animal organs, xenotransplantation, while offering very promising solutions to many of these problems, also raise additional ethical and medical issues which must be considered by the medical profession as well as society. This review deals with the ethical and moral issues generated by the current advances in organ transplantation, the problem of organ supply versus organ demand and the appropriate allocation of available organs. It deals with the risks and benefits of organ donation from living donors, the appropriate and acceptable methods to increase organ donation from the deceased through the adoption of the principle of 'presumed consent', the right methods of providing acceptable appreciation and compensation for the family of the deceased as well as volunteer and altruistic donors, and the duties and responsibilities of the medical profession and society to help fellow humans. The review also deals with the appropriate and ethically acceptable ways of utilizing the recent advances of stem cell transplantation from adult versus fetal donors, tissue engineering and the use of organs from animals or xenotransplantation. Data provided in support of the concept that clinical organ and tissue transplantation can be more beneficial and life saving if everyone involved in the process, including physicians and medical institutions, respect and consider the best interests of the patients, as well as honor the ethical, moral and religious values of society and are not tempted to seek personal fame or financial rewards.

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Introduction

Some 50 years ago failure of a vital organ, such as kidney, liver, heart, usually meant immense suffering and certain death. With the advent of clinical organ transplantation and the many advances that have taken place, especially during the past three decades, including surgical techniques, molecular biology, immunology and effective immunosuppression to prevent rejection, came the hope of a second chance of life for many thousands of patients. Indeed, today, with nearly 1,800 transplant centers throughout the world, over 750,000 patients have received one or more vital organ transplants since the beginning of clinical transplantation [1], which was started in the early 1950s by Dr. Joseph Murray and by the late Dr. David Hume. Some of these patients are alive for over 36 years following kidney transplant; 30 years after liver transplant; 28 years after bone marrow transplant; 25 years after heart transplant; 22 years after combined kidney/pancreas transplant, and 14 years after lung transplants [1–5]. As a result of these advances in organ transplantation and the rapidly increasing incidence of vital organ failure, the number of patients who are on the transplant waiting list is increasing very rapidly every year, particularly since the supply of organs, especially from cadaver donors, has remained low and grossly inadequate to meet the growing demand (fig. 1). The situation is considerably worse in some developing countries where access to cadaver organ transplants is very small or even nonexistent.

With this widening gap between organ supply and organ demand, thousands of patients die each year while on the transplant waiting list, and the waiting time to receive an organ transplant has increased enormously. For example, in the United States the number of patients on the transplant waiting list, as of March 2002, has reached almost 80,000 patients, compared to 50,000 patients in 1997 (table 1) or an increase of 60%, while the number of cadaveric organs available for transplant during this period has increased only by 2–3%. At the present time 1 patient is added to the transplant waiting list every 15 min and 16 patients (men, women and children) die

Table 1. The USA national patient waiting list for organ transplants in March 2002 [6]

Type of transplant	Patients waiting for transplant
Kidney	51,215
Liver	17,886
Pancreas	1,245
Pancreas islet cell	270
Kidney-pancreas	2,486
Intestine	178
Heart	4,143
Heart-lung	209
Lung	3,824
Total	79,125

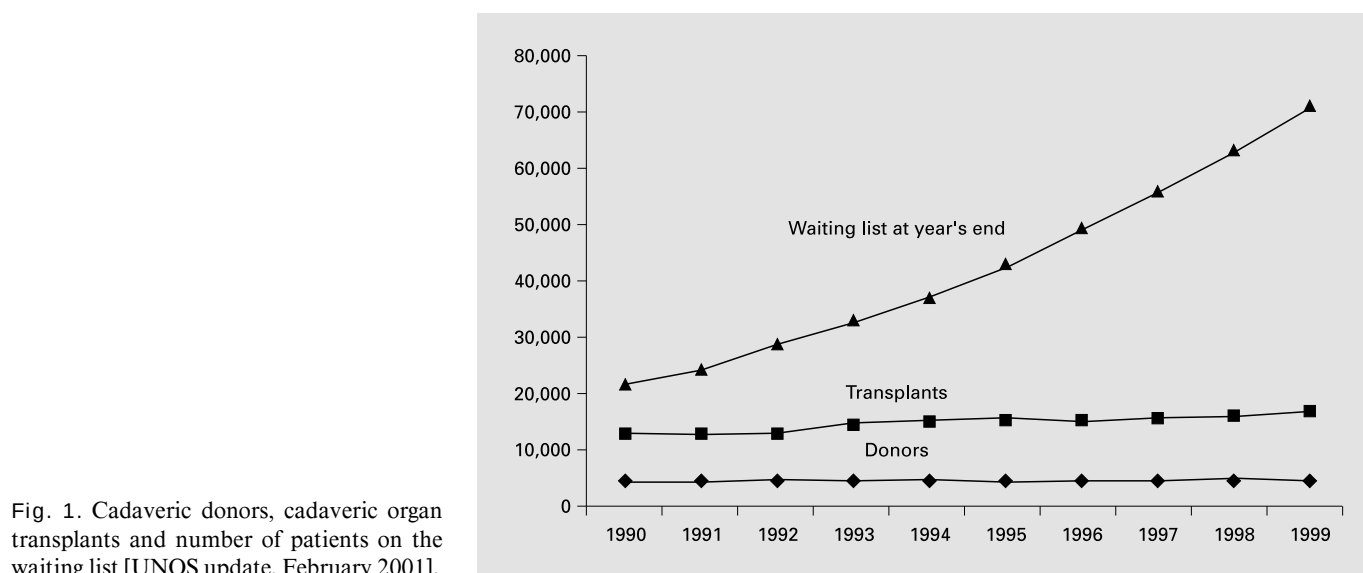


Fig. 1. Cadaveric donors, cadaveric organ transplants and number of patients on the waiting list [UNOS update, February 2001].

Table 2. Number of transplants performed in the USA in the year 2000 [6]

Type of transplant	Number
Kidney alone (5,293 were living donors)	13,372
Liver	4,954
Pancreas alone	435
Kidney-pancreas	911
Intestine	79
Heart	2,198
Heart-lung	48
Lung	956
Total	22,953

every day while waiting for a transplant. In the year 2000, over 6,250 patients died while waiting for a transplant [2, 5, 6]. These desperate situations have caused many institutions to consider new policies, strategies and reforms in order to increase organ supply from cadavers. Also, many countries throughout the world have been using organs from living donors at an increasing rate, including the United States, where almost 40% of kidneys transplanted in the year 2000 were from living donors (table 2).

It is now widely accepted that through organ transplantation not only is the patient survival markedly prolonged, but the quality and productivity of life is considerably improved for these patients, particularly in children and the senior adults of the population. In addition, transplantation therapy is also associated with markedly decreased cost of health care for the society. For example, the expected survival of a patient with end-stage renal disease treated with kidney transplantation, at 1, 5, 10 years is 20–40% higher than treatment with dialysis. Also, the cost of dialysis is 3 times the cost of kidney transplantation over a 5-year period [7–10]. For these and other reasons the medical profession and society are morally and humanistically required to make more organs available and allocate these organs to patients who are in greater need according to ethically accepted rules and guidelines.

These major problems together with the recent developments and advances in tissue engineering, stem cell biology and xenotransplantation, which offer the promise of a more successful therapeutic modality for the treatment of organ failure in the future, have raised many moral, ethical, and societal questions [10]. Therefore, in order for these important advances in organ and tissue transplantation to be used fairly and effectively for the treatment of patients with failure of vital organs, these

ethical issues must be considered with regard to increasing organ donation by the families of the deceased, the appropriate methods of organ allocation, the use of organs from volunteer living donors, the use of acceptable source of tissues and stem cells, and the utilization of animal organs for transplantation.

Organ Donation from Cadavers

As mentioned earlier, the availability of organs from cadavers in most transplant centers of the world has remained very low and inadequate to meet the need of the population with organ failure. Several methods have been used to enhance organ donation by the families of the deceased in an attempt to improve the organ supply from this very important source. These have included public education about the need and the merit of organ donation as a ‘gift of life’ in order to save fellow human beings, the establishment of potential donor registration consents in driver’s license or other documents, including the internet system. Unfortunately these attempts have resulted in a very small rise in organ donation from cadavers [3, 5–9].

What has proved to be very effective in some parts of the world is the acceptance and implementation of the principle of ‘presumed consent’ where society approves that every adult individual who dies is a potential donor unless he has indicated his objection during his lifetime and regardless of the wishes of his family. Several countries in Europe and in Asia have accepted this principle on moral and legal grounds, such as Spain and Singapore, and have increased organ donation from an average of 20/million population, as it exists in the United States, United Kingdom and Canada, to almost 40/million population [3, 11]. Most major religions including Christianity, Judaism, and Islam do not object to this fundamental principle as was pronounced by Pope John Paul II in 1992, by the Jewish Rabbinical Council of America in 1991 and, particularly, by the Islamic Fatwa Committee of Kuwait, which stated in 1979 that ‘organ transplantation can take place from a dead donor providing that there was a necessity to save a human life and that permission of the family is not required since human organs belong to God and not to the family’ [12]. Many attempts are being made in western countries to implement this principle of presumed consent which will undoubtedly increase organ supply and save many more lives.

However, there is continuing concern regarding the consent laws and regulations of governments and other authorities that are aimed at increasing access to cadaver-

ic organs by accepting the 'presumed consent' law. Some ethicists argue that it is improper to assume consent simply because there is no recorded objection. Some even consider that 'presumed consent' carries a hint of coercion and 'smack' of body-snatching [11]. Other ethicists believe that required or mandated requests are objectionable, when many patients die while waiting and organs are discarded which present a recurring ethical dilemma [13–16]. In some developing countries, in addition to these ethical issues, there are added difficulties because of social, cultural and religious attitudes related to death and to the importance of an intact body for burial. However, the ethical principles that are applied in developed countries are now being promoted in many developing countries by dedicated groups of transplantation clinicians, but the hurdle is still formidable. In some developing countries, particularly in China, there is the practice of taking organs from individuals who are condemned to capital punishment immediately after execution and which are given to selected patients, hospitals, institutions or physicians.

Besides the implementation of the principle of presumed consent, another way which can increase organ donation and is being considered in many countries is that of 'objective appreciation' for the family of the deceased who donate the organs. In the United States attempts are in progress to approve the concept of providing some financial support, which is not payment for organs but to help the family to pay for funeral costs, traveling and other living expenses upon the death of a loved one. Such payment of expenses is different from organ purchase, since the payment will be made not directly to the family, but to the funeral home, hotels and transportation agencies. Indeed, this system for financial support was approved by the State of Pennsylvania in 1994 to a maximum of \$3,000.00, and also in many other states in America, but unfortunately this has not been implemented [17]. This will be discussed later in more detail.

A third method which can increase organ donation from cadavers is a greater use of 'marginal' or 'suboptimal' organs. For many years, some 2,000–3,000 such donors have been discarded in the United States. Marginal organs include kidneys from older donors over 60 years, from small children less than 5 years of age, from donors with diabetes, from kidneys preserved for longer than 40 hours and kidneys obtained from non-heart-beating cadavers. While working in Kuwait in the early 1980s, when access to local cadaveric kidneys was extremely rare, we imported over 100 marginal donor kidneys from the United States and Europe and showed that these

organs with appropriate surgical and medical management eventually function and help save many patients. Indeed, we were among the first to report on the use of such organs, particularly our report on the successful transplantation of kidneys from diabetic donors into non-diabetic recipients [18].

Many centers in the USA and Europe have now begun to use such organs successfully, but unfortunately there is still a large number of these organs that are discarded and not accepted by some centers. This has raised a serious medical and ethical dilemma since refusal to use these organs will deprive many patients from having the benefits of transplantation. Naturally, before using such 'non-ideal' organs it is required that the patient is provided with full information of possible risks and benefits and full consent is obtained prior to transplantation, since the incidence of delayed function or primary nonfunction is definitely greater after the use of marginal donors.

Allocation of Cadaver Organs

Another area which has raised serious ethical issues is the method of allocation of cadaveric organs. As already mentioned, with the rapid increase in the number of patients waiting for transplantation and the limited organ supply, it has become necessary to develop an organ allocation system which is medically appropriate and ethically fair and acceptable [14, 19–21]. In the United States, for example, the method of allocation has been developed by the national organization, the United Network for Organ Sharing (UNOS), which considers the following criteria according to the type of organ. The first criterion is the geographic area of the donor compared to that of the recipient. Local organs are first given to local recipients. If there is no suitable local recipient, they are distributed to recipients within the state or the region and finally they are offered to the entire nation.

The second criterion is the blood group compatibility and histocompatibility matching.

The third criterion is that of the point system which each patient on the waiting list accumulates on the following variables: (a) the time of waiting, (b) immunological matching, (c) medical urgency, (d) the age of the patient, where pediatric patients less than 11 years of age are given higher points.

In the case of a liver graft allocation, besides the geographical location of the donor and the ABO compatibility, the medical urgency has been taken into consideration in most centers of the world, where each patient is

assigned a status. The highest urgency is that of status 1, the next is 2A, then status 2B and then finally status 3. The grafts are first allocated to the patients with status 1, then to the other three less urgent status patients. The status of urgency is given points as measured by the internationally accepted Child-Turcotte-Pugh Criteria. Also, pediatric donor liver must be given to a pediatric recipient. Next is the time on the waiting list. However, this system of liver allocation was recently changed in the USA as outlined below. Allocation of thoracic organs, again, depends on the location of the patient, the waiting time, the medical urgency, and the organ size.

The problem with this system of allocation as has been practiced in the United States and other countries, is that the kidney or other organ has to be transported to the location of the recipient and this may take many hours and thus cause considerable damage to the organ as a result of the ischemic reperfusion injury, which is known to take place following long preservation of the organ. Also, when this organ does reach the designated center where the patients is, the surgeon in that institution may decide not to use the organ if it is from a marginal donor, since some centers have no experience in the use of such organs. As a consequence, the organ becomes damaged even further as a result of transportation and long preservation and eventually many organs are wasted in this way. We and other colleagues who have much experience in the use of marginal organs believe that it is more ethically and medically appropriate if these organs are transplanted as soon as possible where they are located or sent to centers where marginal donors are accepted and in so doing, fewer organs will be discarded. This proposal was confirmed by Matas and Delmonico [21]. According to this proposal all transplant centers and potential recipients who will accept a marginal donor organ are placed on a special list in every organ procurement area. Also, any transplant center that does not wish to use marginal organs should be identified and placed on a special registry so that no organ will be sent to that center. In response to these serious concerns, the United Network of Organ Sharing, as recently as March 2002, adopted newer organ allocation criteria [6]. In the case of kidney grafts marginal organs will only be sent to a center where the patient and the surgeon have given prior consent to using such organs. With regard to liver grafts, the allocation criteria are changed and are now based on a scale of urgency and the expectation of the patient dying within 30 days while waiting. In the USA, the new system of allocation for adult patients is now called 'model for end-stage liver disease' (MELD), and for pediatric patients it is the pediatric end-stage liver disease

(PELD). Within this new system it is expected that organ allocation will be based entirely on the need to save the life of the patient and thus will be more ethically appropriate.

Also, it is very important that organ allocation should be used only on the medical criteria and on the need of the patient rather than on the social, financial or political status. Indeed, in February 2002, a patient who was in urgent need for a heart transplant but was serving a criminal sentence for robbery in the United States was chosen to receive a heart transplant in spite of his legal and social status. This event raised much objection by fellow patients who were on the waiting list, but the local transplant center, quite rightly, felt that this patient was in the greatest need and was given the heart transplant on humanitarian grounds. This case illustrates the sound ethical principle that organs should be allocated on the basis of humanitarian need rather than on social, financial or political status of the individual.

Other ethically based suggestions and criteria that have been used by some transplant organizations are: to give preference to a patient who has, himself, donated or is willing to donate a tissue or organ; to give older organs to the older donors; a child's donor organ to a child recipient, and to give the organs from donors with viral infections to similarly infected recipients. Finally, patients with positive HIV serology, who until recently were refused to receive a kidney transplant, are now being accepted as candidates for transplantation like other patients since anti-HIV therapy is currently available [22]. It is also ethically and morally reasonable that patients who are on the waiting list for end-stage liver disease caused by alcohol consumption must not be given a liver transplant until they had abstained from alcohol for a minimum period of 6 months.

Finally, another moral criterion for the organ distribution and allocation is that the urgency for a life-saving organ and the other criteria already mentioned should be the fundamental criteria regardless of the race, religion or ethnic origin of the recipient. The allocation of organs to noncitizens of the country of the donor has been a very important issue in the United States and also in Europe. Because of severe organ shortage both in Europe and the United States, only 5–10% of organs can be given to non-citizens of the country and that is done only for humanitarian reasons, although, by so doing less organs will be available to the nationals of the country, but this has helped assuage those concerned about profiting from wealthy foreign patients.

Certifying Death

Before organs are removed from any donor and before any request is made to the family, the medically accepted brain death criteria must be applied. In the early days of transplantation only donors whose hearts had completely stopped and whose respiration had ceased (cardiac death) were used for organ transplant. Subsequently and in the late 60s, it was realized and medically confirmed that when the patient's brain had completely ceased to function, but his heart was beating while he was maintained with artificial ventilation, then the donor as a human individual was dead. It was in 1967 when Dr. Christiaan Barnard of South Africa removed the heart of a donor who had brain death even though the heart was beating and carried out the first heart transplant in the world into a man with terminal heart failure. This procedure and its potential implications stunned the world. However, a report from Harvard University, which was published in 1970, did show that the development of irreversible coma was, in fact, the new criterion for death [23]. Currently, in most centers of the world, the newly established concept of deaths is that of 'brain death'; however, this has to be adequately supported and diagnosed by physicians who have nothing to do with the process of transplantation. Today most societies and major religions accept 'brain death' as the death of the individual [24]. The Islamic countries in the Middle East were among the first to accept this concept at the conference of the Council on Islamic Jurisprudence, which was held in Amman, Jordan in 1987 [3, 12]. Currently, most countries of the world accept the concept of 'brain death' as the death of the individual.

Use of Organs from Fetuses

The ethics of using tissues and organs from fetuses have been a matter of enormous discussion. Indeed, fetal tissue such as pancreas, brain, liver, thymus, bone marrow and adrenal gland have all been used sporadically in clinical transplantation despite widespread concern over the legality and ethical appropriateness of the procedure. Also the collection and sale of fetal tissue by corporations is known to occur. Legal regulation concerning the use and disposal of fetal tissues are lacking in many countries. There are codes of practice that have been laid down in many western societies. The use of fetal tissue, including transplantation, remains largely under the supervision of Institutional Ethics Committees. Further, there is ethical

debate concerning the possible use of organs of anencephalic babies for transplant. Some have argued that because of the absence of neocortex these are 'nonpersons' and are 'brain-dead' and thus, such infants should be available for organ donation if this is the wish of the parents [25]. However, as brain stem function is present in these infants, the 'whole of the brain' or 'brain stem' requirement for certification of brain death precludes removal of organs until cardiorespiratory death occurs. Therefore, the use of organs from such infants is rarely possible. The first such case of using an organ from an anencephalic infant was that of Baby Gabrielle born in 1987 with prenatal anencephalopathy, who was brought to Children's Hospital in London, Ontario. She was placed on a respirator and declared brain-dead. The baby was then flown to Loma Linda University Medical Center in California, her heart was taken and transplanted into baby Paul Holc, who had been delivered by cesarian section to receive the transplant. However, this led to much ethical debate and Dr. Leonard Bailey, a well-known transplant surgeon at Loma Linda, suspended all such transplants and there continues much debate afterwards, on whether such donors should be used [20, 25].

Organ Transplantation from Living Donors

Because of the rapidly increasing demand for organs and the widening gap between organ demand and organ supply, many institutions have resorted to using organs from volunteer living donors. These have included kidney, liver and bone marrow transplants for children and adults with congenital and acquired bone marrow diseases and deficiencies; partial pancreas transplantation for the treatment of diabetes; single or double lung transplantation (from 1 or 2 donors) for pulmonary fibrosis, and small bowel transplantation for children or adults with congenital or acquired diseases. In the Middle East, the Kuwait Transplant Program was the first to carry out successful bone marrow transplants in 6 children from family members in the early 1980s. Living donor pancreas transplantation, which was pioneered in Minnesota in the 1970s, has now been carried out in some 150 patients in several centers in the United States. Again, Kuwait was the first center in the world, outside the United States, to carry out a successful living donor pancreas transplant for a diabetic patient, who had previously received a kidney transplant from his brother. The same brother came forward and volunteered to donate a part of his pancreas for the same patient. Both donor and recipi-

ent enjoyed a normal life for some 3 years, but following the Gulf War in 1990 the recipient developed complications which, unfortunately, could not be treated and he lost his kidney and pancreas. Living donor small bowel and single or double lung transplants are being carried out in several centers in the United States and Europe with good results. The ethical issues with all such transplants are similar and since kidney and currently liver transplantation from live donors are the most commonly used, these issues will be reviewed in some detail.

Kidney Transplantation

Historically, the first successful kidney transplant was carried out by Dr. Joseph Murray in 1954, in Boston, between living identical twin brothers [4]. Living genetically related donor transplantation of kidneys was later adopted by many transplantation centers in the world, until the early 1980s, when cyclosporin became available which made kidney transplantation from cadavers more successful, and consequently living kidney donor transplantation was considerably reduced, although the use of living donors continued in the developing countries because of lack of legal and societal regulations to use organs from cadaver donors. However, due to the rapidly increasing number of patients on the transplant waiting list and the insufficient cadaver donor availability many centers in Europe and USA have recently resorted to the use of more living genetically related donors. In the USA, for example, while the number of kidneys from cadaver donors increased from only 7,000 to 8,079 between 1996 and 2000, the number of live-donor transplants escalated from 3,000 to 5,294. Currently the number of live donor transplants in the USA represents nearly 40% of all transplants (table 2) [5, 6]. Similar trends are taking place in Europe and Canada.

While working in Kuwait in the early 1980s, where local cadaveric organs were not available and the number of genetically related living donors was insufficient, we were among the first in the world to use kidneys from living donors who were not genetically related to the recipient, but were emotionally related, such as husbands, wives and friends. Some 50 such donors were in fact used and it was shown that the survival outcome of these transplants was almost as good as that of genetically related donors [26, 27]. Indeed, the first 3 of these donors were friends of the recipients and they came forward to offer their kidneys, for altruistic and humanistic reasons, to the needy recipients. Currently living unrelated donors, including

emotionally related and friends and also donors who want to give their kidneys for altruistic reasons, have been increasing within Europe, United States and Canada. Indeed, one such altruistic donor is the well-known transplant surgeon Prof. Hoyer in Lübeck, Germany who, feeling sympathetic to the plight of many patients waiting for a cadaveric donor, decided to donate one of his kidneys to a patient quite unknown to him at the University of Munich Transplant Center in 1996. In 1999, Joyce Roush, a mother of 5 and a nurse, donated one of her kidneys at Johns Hopkins University Hospital to a 13-year-old patient whom she did not know. Another humanistic individual, Robert Johnson, in 1999 traveled all the way from England after reading a story about a 10-year-old Russian Jew who was awaiting a lung transplant at St. Louis Children's Hospital in the USA. Mr. Johnson donated one of his lungs to this patient. In the year 2000, Mr. Kyle McNamera donated a part of his liver to Randy Roberts, who had been a friend for 10 years, and a successful liver transplant was carried out at the Lahey Clinic. These individuals and many others who have donated their organs to another person whom they did not even know, purely for humanistic reasons, might be called heroes [3].

Directed versus Anonymous Donation

Currently there is some debate whether altruistic donation should be anonymous or the donor should choose the recipient that he wishes to donate the organ to. Donation could be criticized ethically that it unfairly favors some potential recipients by allowing them to jump to the top of the waiting list; however, many transplant surgeons and ethicists believe that this is a very special kind of advantage when a good Samaritan donates one of his organs to a friend or colleague who is on the waiting list. For this not only helps the recipient, but actually also those who are on the waiting list who will move up the ladder and will have a better chance of having a cadaver organ. A recent survey of 1,000 randomly selected adults living in the USA by Spital, of the University of Rochester in New York, showed that over 90% of the respondents believe that kidney donation by friends is acceptable and about 80% feel the same way about kidney donation by altruistic and anonymous donation by strangers [28]. A similar survey by Transplant Centers in the USA showed that 93% of the centers would accept a friend as kidney donor (direct donation) and 38% indicated that they would also accept an altruistic (anonymous) stranger. Similar findings were reported from a similar survey by Landolt et al. [29] in Vancouver, Canada.

Kidney Donation by Minors and Children

Minors have been successfully used by many centers as donors of kidney and bone marrow for their family members with safety and successful outcome. In order for minors, children aged 16–18 years of age, to be accepted as organ donors, extensive medical and psychological evaluation is mandatory with full and informed consent and without any pressure from other members of the family. In a recent consensus statement organized by the American Medical Association with participants from many Medical and Transplant Societies, it was recommended that minors who wish to give consent for donation should be accepted when the following criteria are met: (1) when the potential donor and recipient are highly likely to benefit (as in the case of identical twins); (2) when the surgical risk to the donor is extremely low; (3) when all other opportunities for transplantation have been exhausted, no potential adult living donor is available and timely and/or effective transplantation from a cadaver donor is unlikely, and (4) when the minor freely agrees to donate without coercion (as established by an independent donor advocate). The participants of the conference were all unanimous that unless all these criteria are available it will not be ethically recommended that a minor should be used as a live organ donor [30].

Justification of Transplantation from Living Donors

Living related donation, emotional related or altruistic is very justifiable on humanistic grounds and it is ethically and medically acceptable, providing that donor evaluation both medical and psychological is carried out in accordance with accepted protocols and that a fully informed consent is given by the donor. Also, the rate of donor complications after kidney donation is extremely small. The reported mortality rate after kidney donation is 1 in 10,000. Our own experience, in the United States, Middle East and Canada of over 800 living donor transplants, genetically, emotionally and altruistically related showed there were no deaths and no serious complications. On the side of the donor, there are many psychological and spiritual benefits, and most donors express an increased sense of pride and satisfaction and the joy of giving a gift of life to a relative, a friend or to another fellow human being.

Another justification is that the success rate of living donor kidney transplantation is considerably higher than that of cadavers. The expected patient survival rate and graft function at 5 years is 95 and 80%, respectively, with living donors and 75 and 55% with cadaver donors, although this difference is expected to be reduced with the

recent introduction of more effective immunosuppression medications [2, 7, 9]. The Consensus Committee of the American Medical Association, already referred to, has stressed that in living donor transplantation it must be shown that the benefits to both donor and recipient outweigh the risks associated with donation and transplantation and that donation should be for altruistic and humanitarian reasons but not for financial payment. However, some of the participants of the Consensus Committee recommended that the donor should be compensated for financial expenses associated with donation and that guidelines be established which are similar to those being used for short-term disability to defray lost wages, etc. In fact, the National Kidney Foundation in the United States is now planning another consensus conference to produce a working protocol that identifies the many issues that surround living donation [30].

The Canadian Standards Association has recently discussed the ethical matters covering living donation of whole or renewable parts of a vital internal organ, single kidney or part of a liver, and arrived at the following recommendations [31]: *Ethically acceptable*: (a) when there is a rescue of a seriously ill or dying patient; (b) maximize the medical outcome among potential recipients, and (c) time spent on the waiting list has been very prolonged. *Ethically flawed procedures will be*: (a) ability of recipient to pay; (b) inappropriate lobbying, e.g., by influential person on behalf of a possible recipient; (c) deviation from nationally approved protocols and agreement for recipient selection, and (d) nondeclared conflict of interest in recipient selection, such as selection for promoting the particular program. *Other questionable ethical issues are*: (a) maximize the outcome for society; (b) favoring those who have lived a preferred lifestyle, and (c) social merit and position in society.

Liver Transplantation

Liver transplantation is accepted as the best modality for the treatment of patients with end-stage liver disease. The current status of severe cadaver organ shortage has led to the death of a large number of patients waiting for liver transplantation (approximately 13% each year) and the waiting time for patients needing a liver transplant has continued to rise to approximately 400 days [1, 5, 6].

Experience in the successful use of reduced size liver or a split liver transplantation (from cadavers) in children in the late 1980s did allow the introduction of segmental liver transplantation from living donors to children with liv-

er failure. The lateral segment of the liver is used. The first successful such transplant was carried out by Dr. Strong in Australia in 1989, and later pioneered by Dr. Broelsh at the University of Chicago in 1990 [32]. Since then some 1,500 such procedures have been carried out, with only 2 reported deaths among the donors. Following this successful experience in children, several centers have now extended this technique to transplanting a part of the liver from adult donor to adult recipient using a large segment, usually the right lobe, which is about 60–70% of the liver volume. Since 1996, some 400 such transplants have been carried out in 30 centers in the United States with excellent graft outcome and similar numbers in European and Asian countries. Because of the magnitude of the donor hepatectomy and the associated problems and complications, there is certainly much concern for the donor's safety and health. The ethical issues of concern include: (a) informed consent, (b) lack of coercion, (c) risk/benefit analysis, (d) involvement of the recipient in the consent process, and (5) future physical and financial risks [32–36]. While most centers, medical organizations and ethical committees approve the use of the left lateral segment of an adult parent to a child as a life-saving procedure with low risks to the donor and many advantages to the recipient, many have expressed reservation in the use of adult-to-adult liver transplantation, in view of high risks to the donor: (1) there is lack of agreement on the technique with regard to safety and effectiveness; (2) the indications for surgery have not been clearly defined or standardized; (3) the procedure has been developed with variable standards or approval by Institutional Review Boards, and (4) many centers in the USA and elsewhere in the world have performed fewer than 10 procedures each, which is alarming for an innovative operation that places 2 people, 1 of whom is healthy, at great risk. Also, there have been 7 known deaths among some 1,500 procedures or 1 death per 250 donors compared to 1 per 10,000 donors following live donor kidney transplantation [37]. It has also been reported that there is a 25–30% incidence of morbidity after removal of the right segment of the donor liver [34, 35]. These have included wound infection, nerve injuries, bile leak, portal vein thrombosis, hepatic insufficiency, and bleeding. Also, the procedure should only be carried out in recognized centers when more than 20 procedures have been done, so that there is sufficient institutional or 'field strength' where the transplant surgeon has sufficient experience in cadaver split liver transplantation and in liver transplantation in children [33–36]. Another factor to consider before allowing adult liver donor transplantation is the 'institutional climate', such as the moti-

vation of the surgeon or the institution to increase their payment, prestige, scholarly publications, and status within the medical community. Many feel that live donor liver transplantation from adult to adult should not be done as an emergency procedure for a patient dying with fulminant hepatic coma, since the donor is placed under a very compromising situation and the required time for appropriate donor evaluation and obtaining at least three consecutive consents, which normally must take 1 to 2 weeks in only a few hours [37]. The situation has been likened to asking a healthy man to take the risk of jumping into the ocean to rescue a drowning man [38]. In a recent position paper by the American Society of Transplant Surgeons (ASTS), some of these issues were discussed with guidelines and criteria which suggested that all adult-to-adult liver transplants be registered with the Society. It is hoped that this will be implemented soon. Finally the two major ethical issues that are of considerable concern are the autonomy of the donor and recipient and the utility of the procedure. The transplant team must inform the donor of all the risks. The recipient must also accept that the donor is placing himself at great risk. Indeed, when the risks are explained to the recipient, he may refuse to accept donation, as it happens with kidney transplantation on occasions.

Another issue is that of utility. It must be demonstrated that the risk-to-benefit ratio is acceptable and that the recipient outcome is at least as good as with cadaveric liver transplantation. A recent report from Broering et al. [34] has, in fact, shown that the outcome of split liver transplantation of cadaver donors was similar to that of using segmental liver transplantation from living donors and they recommended that in order to avoid the risks to the living donor, split liver transplantation from cadaver donors should be more widely practiced. There are situations in which live donor transplantation cannot be ethically justified, such as patients who have hepatitis C or hepatitis B liver disease, since these diseases can recur in the recipient. Thus the life span can be short. Also, in patients with acute liver failure who require an emergency transplant, it does not give enough time to allow the potential donor to be fully informed and give consent, which is required on at least two or three occasions, and also to consider financial and social issues. Also with the current technology of ex vivo liver support devices, which can help the patients live for several days pending regeneration of their own liver or the availability of a cadaver liver for transplantation, patients with acute liver failure should first be treated with these devices instead of carrying out emergency live donor transplantation [38].

One advantage of using live donors is that it will enable other potential recipients on the waiting list to have more access to cadaveric livers and thus reduce the mortality amongst those on the waiting list. As for the living donor, there is certainly a feeling of pride and spiritual satisfaction and even of heroism, which must be taken into consideration.

Organ Sale for Transplants

Recent advances in organ transplantation have resulted in a rapidly increasing demand for this highly successful new therapy creating an ever-widening gap between organ demand and organ supply. This situation has, unfortunately, led to a flourishing international trade in human organs, particularly in the developing countries of the world where cadaveric organs are not easily available and where there is marked disparity in wealth, such as the Middle East on the one hand and the Far East on the other. As a consequence, a deplorable type of medical practice has emerged, where human kidneys are bought from the poor for transplantation into the wealthy clientele with soaring profits for brokers, private hospitals and physicians. It is estimated that since 1980, over 2,000 kidneys are sold annually in India to wealthy recipients from the Middle East, the Far East and Europe and it is estimated currently that several thousand patients from the Arabian Gulf countries have received kidneys sold in India, Iraq, Philippines, Iran and elsewhere. It is not surprising, therefore, that this practice of trading in human organs has alarmed the medical profession, the public and many governments and it has rightly been condemned by all major religions, by most transplant societies including the International, European, American and even the Middle Eastern Society for Organ Transplantation [39–42]. In our report of 1993, which was based on our experience with many patients from Kuwait and the Arabian Gulf region who had obtained purchased kidney transplants in India, we pointed out that organ sale has serious negative impact on all aspects and on everyone involved in the process of transplantation, including the donor, the recipient, the local transplant program, the medical profession and the moral and ethical values of society [42]. Most ethicists believe that organ sale is an affront not only to altruism, but also to basic human dignity as opposed to a utilitarian approach to the important issue of transplantation for the following main reasons: (a) Organ sale promotes coercion and exploitation of the poor. (b) It promotes poor quality of care to the donor and particularly to the recipient as a

result of poor standards of donor selection and inadequate screening for transmissible disease. (c) It benefits ruthless entrepreneurs, greedy doctors who care for their egos and financial gain. It is also against the patient's right for autonomy. It is contrary to accepted moral and ethical beliefs of most societies, including the major religions of Christianity, Judaism and Islam. It diminishes the current benefit of altruistic donation by living donors and the families of cadaveric donors. It makes human organs a commodity for profit and sale, thus inviting corruption and an unjust and unfair system of organ access and distribution and it predisposes to criminal tendencies of killing children and women for organ sale, which has been reported. For these and other reasons organ sale has been forbidden in all Western societies, by all major religions and by many countries in the world [43].

Some proponents of organ sale claim that well-controlled organ purchase does have several major advantages: by making more organs available it can reduce the waiting time for organs, reduce the number of deaths among waiting list patients as well as reduce the overall cost of treatment of patients with end-stage kidney disease. Some professionals in the transplant community believe that it will be much more productive as well as protective from sale of organs by vendors, at least in the developing countries where cadaver organs are not available, if the practice of organ sale is regulated by an independent organization [44, 45]. They argue that the feeling of repugnance of organ sale for the rich and the healthy should not justify removing the only hope for the destitute and dying. Cameron and Hoffenberg [45] have recently recommended that organs be paid for through nationally established organ sharing networks to ensure the quality of care received by donors and to promote the equity of distribution which will involve the ethical and medical problems that exist with organ sale. Radcliffe-Richards et al. [44] in a recent article in *The Lancet* have emphasized that current exploitation of donors and lack of informed consent through organ purchase are due to poverty and lack of education, which do not justify banning organ sale. They suggest that a national organization be established to regulate the sale of organs to provide educational and appropriate consultation to patients to enable them to have informed consent and even a 'guardian' for the donor. Also this organization will regulate and control organ vending, proper selection, payment of fees and provision of necessary care which will prevent the current exploitation, the risk of removing organs, both for the donor and the recipient, and provide screening and counseling, together with reliable payment and financial ad-

vice. They believe that this will not affect cadaveric donation, since payment can also be made to the family of the deceased [44].

The Use of Executed Prisoners as Donors

Several authors and ethicists have recently commented on the current practice in some countries of the use of organs from executed prisoners. While all Western societies strongly condemn the arbitrary use of taking organs from executed prisoners, which is a common practice in China, where organs are taken and given to various institutions for transplantation or even sold to other countries [39, 45]. It is suggested that it will be ethically permissible to allow a prisoner on death row to donate an organ to a relative or a friend. Another solution would be if all societies accepted the principle of 'presumed consent' for all its members upon their death. However, it is strongly recommended that the treatment for prisoners should follow the guidelines of the United Nations Universal Declaration of Human Rights. All transplantation societies in Europe and USA have condemned the practice and have recommended that it be abandoned [41, 45].

Acceptable Financial Incentives for Organ Donations

The current status of rapidly increasing demand for organ transplantation and the high death rate of patients waiting for an organ have prompted many transplant professions, ethicists and government organizations to reconsider a number of alternatives which might be morally and ethically acceptable that will promote organ donation and save the lives of many patients.

It is recommended that the families of dying patients who donate their organs for transplantation should receive appropriate compensation by the state and the government that will cover the funeral expenses, the cost of travel, and to provide some financial compensation for a deceased 'bread winner's' family. A sum of \$3,000.00 has been suggested by the organ procurement organizations in most of the regions in the United States and also by United Network for Organ Sharing and by members of the Health and Human Services Organization (HHS) and by many members of the Congress. Although such compensation was approved by the state of Pennsylvania in 1994, it could not be implemented since the US Department of Health did not approve it [17]. The American

Society of Transplant Surgeons has already endorsed the larger payment and the American Medical Association Council on Ethics and Judicial Affairs will be meeting to discuss this matter and make a decision regarding appropriate compensation. It is generally felt that such compensation will help the family of the donors to pay for the burial expenses of a loved one and may encourage more organ donation that will help many of the 80,000 patients waiting for organ transplantation.

Currently it has been agreed that a living donor may be compensated for a maximum of \$300 to cover the cost of travel and other living expenses, which is implemented in all states of the USA. It has also been agreed by a number of organizations including the United Network for Organ Sharing as well as the Federal Government that their employees who wish to donate an organ can do so without suffering any financial loss. These employees can now receive up to 30 days of paid leave when they donate a major organ and up to 7 days when they donate bone marrow [46].

In a recent article by Emerling [47], several other suggestions have been made to help organ donation by living donors: (a) the Federal Government should provide a lifetime tax exemption for every American citizen willing to donate an organ, (b) some form of life insurance be paid for and offered for the organ donor, and (c) any foreign national who volunteers for donating an organ should be awarded American citizenship. It is expected that these suggestions will be accepted by the United States Congress since their effect will not only save many lives but will also save vast sums of money to the government as a result of supplementing the very expensive need for dialysis.

The Use of Stem Cells and Cloning in Transplantation

Some of the very recent developments in transplantation over the past decade have been the use of stem cells from bone marrow, cord blood, and from fetal and adult tissue, including somatic cells and neural cells. These cells have the great potential for differentiation and proliferation into other types of body cells including neuronal, hepatic, hemopoietic and muscular and thus help many patients with organ failure after their transplantation into the patients [48–52]. These stem cells have also been shown to induce immunological tolerance and chimerism when they are transplanted into recipients of vital organ grafts and their rejection of a transplanted organ such as bone marrow, kidney, heart, liver, is prevented [52, 53].

Many classes of these stem cells, obtained from both fetal and adult tissue, have been identified and are being cultured and stored in many research laboratories in the United States and Europe [50, 53, 54]. While the use of such cells has the future potential of treating many patients with diseases beside vital organ failure, including diabetes, Parkinson's disease, multiple sclerosis, systemic lupus erythematosus, Alzheimer's disease, etc., there is considerable moral and ethical debate in many countries with regard to using stem cells taken from embryos as compared to cells taken from adults [49, 50–53]. More recently it has been shown that stem cells can be procured from adult cord blood and from cadaveric donors that have been heparinized following the diagnosis of brain death [55]. Indeed, in a recent report it was shown that the cells taken from the peripheral blood of a cadaver when used after an appropriate conditioning regimen, produced immunologic tolerance in a highly sensitized patient who was unable to receive a successful transplant for sickle cell disease [56]. The transplanted stem cells resulted in immune reconstruction of the recipient lymphocytes and eliminated the source of the antibody which had prevented her from having a transplant. Stem cell biology holds enormous potential, therefore, both in transplantation and in development of artificial organs as they can replace the function of failing organs and tissue and also produce immunologic tolerance and chimerism to minimize or dispense with the current use of immunosuppression drugs, which often cause organ toxicity and life-threatening infections.

However, considerable debate still continues on ethical grounds regarding the use of stem cells from fetal tissue for biomedical research and transplantation. Historically, in the 1950s some fetal tissue was effectively used in the development of the polio vaccine and the rubella vaccine, while in the 1960s fetal thymus cells were successfully transplanted into patients with DiGeorge syndrome. Indeed, the Center for Biomedical Ethics, at the University of Minnesota, has reported that 1,000 patients have received transplanted fetal tissue cells worldwide [48, 51].

In the USA, however, questions about using fetal tissue cells have been raised since the 1970s, when it was considered that the use of such cells was an 'assault and mutilation' of an immature human being. Various commissions were then established in the USA as well as in other countries to study the ethical question of using fetal tissue cells for transplantation and research. Most of these commissions concluded that some types of research on the use of some fetal cells and tissues were ethical providing that

certain safeguards were put into place. For example, in the United States, the National Commission for the Protection of Human Subjects, which was established within the Department of Health in the 1970s, concluded that 'living fetuses in utero or ex utero' were not to be used for research unless it was intended to benefit that fetus or its mother and it posed no added risks to the fetus. The commission also recommended that an Institutional Review Board must be established to review any proposed research. In 1988, US Congress amended the National Organ Transplant Act to include fetal organs and tissues, and they listed body parts and tissues that may not be bought or sold. Also, in 1988, the National Institute of Health (NIH) convened a panel of experts, ethicists, lawyers, theologians, physicians and biomedical researchers on the use of fetal tissue from aborted fetuses. The Commission recommended that 'fetal tissue transplantation research is acceptable providing there be anonymity between the donor and recipient and that separate consent procedures be used to separate the decision to abort from the decision to donate tissue'. In 1992, the President of the United States issued an Executive Order that fetal tissue banks may collect and distribute fetal tissue resulting only from spontaneous abortion and ectopic pregnancies [48].

Many opponents of fetal tissue research have argued that using fetal tissue from elective abortion is a way of legitimizing abortion and this will then encourage institutions to increase the number of abortions. As a result of this major concern, the current regulations in the USA do not allow the use of stem cells from aborted fetuses or from embryos created by in vitro fertilization. The recent directive by the President of the United States, in April 2001, stated that only stem cell lines that are already in existence in research laboratories, some 64 cell types, can be used for research and transplantation and the House of Representatives voted to outlaw all cloning regardless of whether it is for reproduction or stem cells.

In Canada, on the other hand, in March 2002, new guidelines were issued by the government which bar human embryo cloning but permit government-funded scientists to use embryos left over from fertility treatments or abortions, thus permitting Canadian researchers more available sources of human cells and tissues than their counterparts in the USA.

In the United Kingdom, the use of embryo stem cells for research and transplantation was formally permitted and recently passed into law in March 2002. According to this law, two licensed scientific research laboratories, one in Scotland and one in London, England are permitted to

extract the cells from donated in vitro fertilized embryos and use them for research. Britain is also the only country so far that has legalized the cloning of stem cells for research and it is setting a national stem cell bank to store and culture such cells.

The Use of Animal Organs and Xenotransplantations

As mentioned earlier, the high success of organ transplants and the high incidence of organ failure have caused an increased demand for organs for transplantation. As a result there has been an ever-increasing waiting list, with many deaths of patients awaiting transplantation and the rising cost of treatment. Even if the current rate of organ donation from human beings doubles, there will still be insufficient organs to meet the need. Xenotransplantation, the transplantation of organs from animals, does indeed offer a potential solution to this major problem all over the world. During the last two decades there have been increased advances in the identification and control of the immunological barrier to xenotransplantation. Recent scientific and technological advances include the identification and removal of the preformed antibodies which all humans have against animals, advances in genetic engineering and transgenic technology which can replace the animal tissue which activates human complement and causes vascular thrombosis of the graft, and the cloning of such transgenic animals. Many transplant scientists working in this area are optimistic that what is 'xeno' today, which means foreign, will become 'familiar' tomorrow [3, 57, 58].

Animals can be used to help save many human patients in one of three ways:

(a) Using tissues: Neuroendocrine cells, especially from pigs, have been shown in several studies to be quite promising in the treatment of Parkinson's disease. Also, phase II clinical trials are underway using pig islets for treatment of patients with insulin-dependent diabetes. Pig and human insulin have similar structure and indeed, porcine insulin has been used for many years to treat diabetic patients [54].

(b) Using animal organs such as the liver, extracorporeally, for the treatment and support of patients with vital organ failure. In 1970, the author was among the first to employ extracorporeal liver perfusion using baboon and pig livers in a specially designed apparatus which was connected to the circulation of patients in deep hepatic coma for 12–24 h. It was shown that these animal livers carried

out all the functions of the patient's failing liver by removing the accumulated toxic compounds and synthesizing essential products. Of the 10 patients treated, some 70% recovered from coma and lived for 6–76 days while waiting for a liver transplant and 3 of them recovered, regenerated their liver and were discharged from hospital. Two of these patients are alive today for more than 28 years later, and are in excellent health [59–61]. Other investigators have used similar apparatus using the livers from transgenic pigs to keep these patients alive until a human liver becomes available for transplantation [62].

(c) Whole organ transplant: Several attempts have been made of transplanting organs from other primates into humans. The first was a kidney transplant by Reemetsma in the 1960s, and a liver transplant by Starzl in the 1970s. These survived for a short period [63]. However, in 1992, a patient with liver failure and HIV was given a baboon liver transplant by Dr. Starzl in Pittsburgh and with modern immunosuppression, the patient survived for 70 days. This, however, caused a public outcry because of using a baboon [64]. In 1983, the first heart transplant was carried out by Bailey, also from a baboon, to a newborn infant with heart failure, Baby Fae, who survived for 20 days.

The use of animal organs raises important moral, medical, ethical and social issues. First, the type of animal species used. Most societies and the animal right organizations will not allow the transplantation of organs from primates. However, the use of organs from domestically used animals, such as pigs, sheep and calves, raises no objection. Second, the transmission of infection. It is very important that animals be bred in a special environment and be tested for infectious organisms. Although there is some fear that retroviral infection may be transmitted from pig to man, several recent studies have observed that there is neither evidence of porcine DNA nor of retroviral infection in patients who underwent short-term transplantation of pig kidneys, livers and transplantation of islet cells or endothelial cells [65–67]. Third, it is also important that any experiments or trials of using animal organs for transplantation must be reviewed and supervised by the Ethics Committee of an institution.

With these guidelines, it is expected that the use of organs from animals such as pigs will help many thousands of patients who are on waiting lists for transplantation [68, 69]. Among such patients who can benefit from xenotransplant are those patients who are denied human organ transplants because they do not meet the allocation criteria for human organs. Also, many patients who die of organ failure, such as liver failure of whom 30,000 die

each year in the USA alone, may be saved by using animal organs in an extracorporeal device as a bridge to regeneration of their liver or to transplantation of a human liver. Before carrying out xenotransplantation, informed consent is very important with regard to the medical and psychological aspects of living with an animal organ. Naturally, before clinical trials are carried out with xenotransplantation, it is important that the scientific, medical community, the general public and society must carefully consider these potentially important newer methods that can save the lives of thousands of patients [70]. Indeed, in a recent survey by the National Kidney Foundation in the United States, the attitude of 1,700 individuals towards xenotransplantation as a possible solution to organ shortage was sought. These individuals included transplant candidates, recipients of transplants, physicians, surgeons, primary care doctors, and clergy. It was confirmed that the view of the majority of these individuals was that xenotransplantation is one of the most viable options to increase organ availability and should be supported by increased government funding for more research and clinical trials [71].

Conclusion

Clinical organ transplantation has been recognized worldwide as one of the most gripping medical events of the 20th century following only two other events in medical history: the discovery of penicillin by Alexander Fleming in 1928 and of the polio vaccine by Jonas Salk in 1955. However, the poor availability of adequate organ supply from human cadavers has caused an ever-widening gap between organ demand and organ supply, which has led to very long waiting times and many deaths among potential transplant recipients. This situation has led to difficulties in organ allocation, to the use of more organs from living donors, and to the abhorrent practice of trading in human organs which have created many ethical dilemmas.

Many physicians and ethicists believe that these problems can be minimized by medically and ethically accepted solutions including the provision of better care and counseling with informed consent to the bereaved family, by showing greater respect for the body of the deceased and by the acceptance of the principle of 'presumed consent' and finally by compensating the family of the potential cadaver donor for funeral, travel and other expenses. The use of volunteer living donors, which has many medical advantages, can also be enhanced by appropriate public education with the emphasis of providing a 'gift of life'

to a fellow human being purely on humanitarian grounds, but not for financial gain. It is, however, ethically acceptable to also provide compensation for the living donor, as it is for the family of the deceased donor, to cover the loss of work, traveling and other expenses resulting from the serious surgical procedure of organ donation.

The current advances in stem cell biology and tissue engineering can bring many benefits for the treatment of common diseases including diabetes, Parkinson's disease, systemic lupus erythematosus, etc. and also help in providing immunologic tolerance when given to a potential recipient of a solid organ transplant. However, ethical concerns do arise with regard to the source of such cells and tissues. Most societies, ethicists and clergy will object to taking these cells from aborted embryos unless the abortion is done purely for the benefit of mother and fetus and has no relation to willingness to donate. However, stem cells taken from the cord blood after birth and also from cadaver donors after full consent are acceptable.

The use of animal organs does have a definite potential to save the lives of many patients on the transplant waiting list. Indeed, with current advances in transgenic and cloning technology many notable scientists believe that successful xenotransplantation will become a clinical reality by the year 2010. Naturally, before using suitable domestic type animals, the moral and ethical guidelines of society must be respected as well as that there will be minimal risk to the recipient, including transmission of infection.

Finally, for clinical organ and tissue transplantation to be fully beneficial and life-saving, everyone involved in the process, including physicians and medical institutions, must only respect and consider the best interest of the patient and honor the ethical, moral and religious values of society and not be tempted to seek personal fame or financial reward.

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