

# Ethical Issues in Organ and Tissue Transplantation

George M Abouna

Clinical organ transplantation 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. It is emphasized 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.

**Keywords:** *Organ allocation, Living versus cadaver donor, Organ sale, Donor compensation, Stem cells, Xenotransplantation*

Some fifty 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, including surgical techniques, molecular immunology and effective immunosuppression to prevent rejection, came the hope of a second chance of life for many thousands of patients. Indeed, today, over 800,000 patients have received one or more vital organ transplants since the beginning of clinical transplantation, which was started in the early 1950s by the late Dr. Joseph Murray and by Dr. David Hume. Many of these patients are alive for over 40 years following kidney transplant; 34 years after liver transplant; 32 years after bone marrow transplant, 28 years after heart transplant; 24 years after combined kidney/pancreas transplant; and 16 years after lung

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*Clinical Professor of Surgery, Drexel University, Philadelphia, USA  
Address reprint requests to: Prof. G. M. Abouna, 734 Woodcrest Road,  
Radnor, PA 19087, USA, Fax: 610-964-857 E-mail: abouna@earthlink.net*

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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.

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 in 1997, 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 one patient is added to the transplant waiting list every 15 minutes and 16 patients, die 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 have been using organs from living donors at an increasing rate, including the United States, where almost 50% of kidneys transplanted in the year 2002 were from living donors. It is now widely accepted that through organ transplantation not only is the patient survival markedly prolonged, but the quality of life is considerably improved. In addition, transplantation therapy is also associated with markedly decreased cost of health care for the society.

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. 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 sources

of tissues and stem cells, and the utilization of animal organs for transplantation.

### 1. Organ Donation from Cadavers

As mentioned earlier, the availability of organs from cadavers in most parts 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. 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 very small rise in organ donation from cadavers [3,5-10].

There are newer methods to increase organ donation:

a) 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 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].

However, there is continuing concern regarding the acceptance of "presumed consent". 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 totally objectionable, when many patients die while waiting and organs are discarded which present

a recurring ethical dilemma [13-17]. 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.

b) 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. Indeed, this system for financial support was approved by the State of Pennsylvania to a maximum of \$3,000.00, and also in many other States in America, but unfortunately this has not been fully implemented.

c) The use of "Marginal" or "Suboptimal" organs. For many years, over 2000 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 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 [18].

Many centers in the USA and Europe have now begun to use such organs successfully, but unfortunately there are 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.

## 2. Allocation of Cadaver Organs

Another area, which has raised serious ethical issues is the method of allocation of cadaveric organs. The

rapid increase in the number of patients waiting for transplantation and the limited organ supply, have made it necessary to develop an organ allocation system which is medically appropriate, 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 consider 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. 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 10 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 is taken into consideration, 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 3 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. Allocation of thoracic organs, again, depends on the location of the patient, the waiting time and the medical urgency, and the organ size.

The problem with this system of allocation, 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 patient is, the surgeon may decide not to use the organ if it is from a marginal donor. 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 others, who have much experi-

ence 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 recently 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. 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 thirty days while waiting. The new system for adult patient is now called "Model for End Stage Liver Disease" (MELD), and for pediatric patients is the Pediatric End Stage Liver Disease (PELD). Using this new system has resulted in significant decrease in the number of patients on the waiting list.

Also, it is very important that organ allocation should be based on the sound ethical principle that organs should be allocated on the basis of humanistic 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].

Another moral criterion for the organ distribution and allocation is that the urgency for a life-saving organ regardless of the race, religion or ethnic origin of the recipient. The allocation of organs to non-citizens of the country has been a very important issue in

the United States and also in Europe, where only 5% to 10% of organs can be given to non-citizens of the country and that is done only for humanitarian reasons.

### 3. 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 heart had completely stopped and whose respiration had ceased (cardiac death) were used for organ transplant. It was in 1967 when Dr. Christian Bernard 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 criteria for death [23]. Currently, in most centers of the world, the newly established concept of death 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.

### 4. 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 in clinical transplantation despite widespread concern over the legality and ethical appropriateness of the procedure. Legal regulations concerning the use of fetal tissues are lacking in many countries, but there are codes of practice that have been laid down in many western societies. Further, there is ethical debate concerning the possible use of organs of anencephalic babies for transplants. Some have argued that because of the absence of neocortex these are

"non-persons" 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 cardio-respiratory death occurs. Therefore, the use of organs from such infants is not possible. The first such a case of using an organ from an anencephalic infant was that of Baby Gabrielle born in 1987 with prenatal anencephalopathy and was declared brain-dead at Loma Linda University Medical Center, where her heart taken and transplanted into baby Paul Holc, who had been delivered by caesarian 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, whether such donors should be used [19,23].

### 5. Organ Transplantation from Living Donors

Because of the rapidly widening gap between organ demand and organ supply, many institutions have resorted to using organs from volunteer living donors. These have included kidney, liver, partial pancreas transplantation for the treatment of diabetes, single or double lung transplantation (from one or two donors) for pulmonary fibrosis: and small bowel transplantation for children or adults with congenital or acquired diseases. 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. In 1988, Kuwait was the first center in the world, outside the United States to carry out successful living donor transplants for a diabetic patient, who had previously received a kidney transplant from his brother. Both donor and recipient enjoyed a normal life for some three 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 transplantations from live donors are the most commonly used, these issues will be reviewed in some detail.

### A. 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 1980, when cyclosporin became available which made kidney transplantation from cadavers more successful, and consequently living kidney donor transplantation was considerably reduced. However, due to the rapidly increasing number of patients on the transplant waiting list and the insufficient of cadaver donor availability many centers in Europe and USA have recently resorted to the use of 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 50% of all transplants [5,6]. Similar trends are taking place in Europe and Canada.

While working in Kuwait in the early 1980's, where local cadaveric organs were not available, we were among the first in the world, to use kidneys from living donors who were emotionally related, such as husbands, wives and friends. Some 50 such donors were used and it was shown that the survival outcome of these transplants were almost as good as genetically related donors [26,27]. Currently living unrelated donors, including emotionally related and friends and also donors who want to give their kidneys for altruistic reasons has been increasing within Europe, United States and Canada. Indeed, one of such altruistic donor is well-known transplant surgeon Professor Hoyer in Lubeck, 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 donat-

ed 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 individual and many others have donated their organs to another person whom they did not even know, purely for humanistic reasons, might be called "Heros" [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. Direct 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 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 Spittall, 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]. Similar findings were reported from a survey by Landolt et al. [29] in Vancouver, Canada [27].

### **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 14-18 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 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 kidney donation 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 to the donor. Also, the rate of donor complications after kidney donation is extremely small. The reported mortality rate after kidney donation is 1 in 5,000. 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 of graft function at five 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 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 in 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:** when (a) there is a rescue of a seriously ill or dying patient; (b) maximize the medical outcome between 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 an influential person on behalf of a possible recipient; (c) deviation from nationally approved protocols and agreement for recipient selection, and (d) non-declared 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.

## B. 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 1980's did allow the introduction of segmental liver transplantation from living donors to children with liver failure. The lateral segment of the liver is used. This technique was developed 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 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% to 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 (e) future physical and financial risks [32-36]. While most centers, medical organizations and ethical committees approve the use of left lateral segment of 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 two people, one of whom is healthy, at great risk. Also, there have been some 7 known deaths among some 1,500 procedures or 1 death per 250 donors [37]. It has also been reported that there is some 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 motivation 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. 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.

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 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, which does not give the donor 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 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.

## 6. Organ Sale for Transplants

Recent advances in organ transplantation which have resulted in a rapidly increasing demand for this high-

ly successful have, 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 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, kidneys are sold annually to wealthy recipients from the Middle East, Far East, Europe, 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, we showed 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 utilitarian approach to the important issue of transplantation for the following main reasons: (a) organs 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. Makes human organs a commodity for profit and sale and 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 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]. 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. Ratcliff-Richards et al. [44] have emphasized that current exploitation of donors and lack of informed consent through organ purchase is 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 for patients to enable them to have informed consent and even a "Guardian" for the donor. Also this organization will regulate and control organ purchase, 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 advice. They recommend that this payment can also be made to the family of the deceased.

#### **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 has 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.

In the USA, 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 largest 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.

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 and this is currently implemented in all the 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 to support living organ donation by their employees who wish to donate an organ without suffering any financial loss. Now these employees can 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, (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.

#### **7. 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 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].

### **8. 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 and their rejection of a transplanted organ such as bone marrow, kidney, heart, liver, is prevented [52-53].

Many classes of these stem cells have been 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 utilized effectively when taken 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 mutility" 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 was 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 it's mother and it posed no added risks to the fetus. 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. 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 regulation in the USA do not allow the use of stem cells from aborted fetuses. The recent directive by the President of the United States, in April 2001, directed 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 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 bars human embryo cloning but permits government funded scientists to use embryos left over from fertility treatments or abortions, thus permitting Canadian researchers with more available source 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 to extract the cells from donated in-vitro fertilized embryos and use them for research. Britain is also the only county 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.

### 9. The Use of Animal Organs and Xenotransplantation

Even if the current rate of organ donation from humans doubles there will still be insufficient organs to meet the need. Xenotransplantation, the transplantation of organ from animals, does indeed offer a potential solution to this major problem all over the world. During the last two decades there has been increased advances in the identification and control of the immunological barrier to xenotransplantation. Recent scientific and technological advances including the identification and removal of the pre-formed antibodies which all humans have against animals, the advances in genetic engineering and transgenic technology which can replace the animal tissue which activates the human complement and cause vascular thrombosis of the graft and 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 effective in the treatment for Parkinson's disease. Also, Phase II clinical trials are underway using Pig Islets for treatment of patients with insulin-dependent diabetes. Pigs 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, we were among the first to use extra-corporeal liver perfusion using baboon and pig livers in a specially-designed apparatus connected to the circulation of patients in deep hepatic coma for 12-24 hours. It was shown that these animal livers carry out all the function of the patient's failing liver by removing the accumulated toxic compounds and synthesizing essential compounds. Of the 10 patients treated, almost 70% recovered from coma and lived for long periods, while 3 of them recovered completely, regenerated their liver and were discharged from hospital. Two of these patients are alive today for more than 28 years, and are in excellent health and without any problems [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, also from a baboon, to a newborn infant with heart failure, Baby Fae, by Dr. Bailey who survived for 20 days.

The use of animal organs raises important moral, medical, ethical and social issues. First is 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 is 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 the waiting lists for transplantation [68, 69]. Among such patients who can benefit from xenotransplant are those patient's who are denied human organ transplants because they are too well or have other risk factors. Also, many patients who due to 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 events of the 20<sup>th</sup> 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 medically and ethically accepted solutions including the provision of better care and counseling with informed consent to the bereaved family, by showing greater respect to the body of the deceased and by 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 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 organs 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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