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The Humanitarian aspects of organ transplantation*

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Introduction

This being my address on the occasion of receiving the award of the Albert Schweitzer Gold Medal for the year 2000 for myself and other notable physicians and scientists who have been invited from many parts of the world, it is appropriate that I begin with a brief paragraph on who Dr. Albert Schweitzer was and to mention some of his many humanitarian contributions. Albert Schweitzer rightly has been named: “The Greatest Christian and Humanitarian of his time”. His personal philosophy was based on “Reverence for Life” and on deep commitment to serve humanity through thought and action. Dr. Schweitzer devoted his early life to science, music and theology, but at the age of 30 he decided to take up Medicine at the University of Strasbourg and soon became a medical missionary. He established a charitable hospital at Lambar’ene, in French Equatorial Africa, where he spent the rest of his life serving thousands of African patients as a physician, a surgeon, a writer and as an administrator. For his exceptional work he was awarded the Nobel Prize in 1952 and The Order of Merit by Queen Elizabeth II in 1955. The

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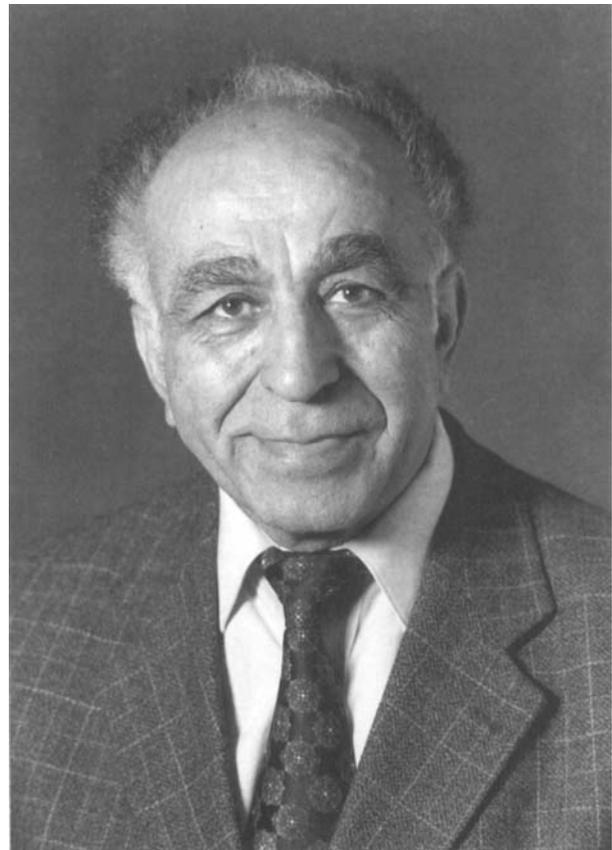


Fig.1 Professor George M. Abouna

transplantation of organs, which I will be talking about, is a most humanitarian act that would have been greatly supported by Albert Schweitzer, for it is really “A Gift of Life”.

I, like Albert Schweitzer, changed my career after graduating in Mechanical and Electrical Engineering

from the University of Durham, England in 1956 and went to Medical school in order to be a Physician and to help and serve fellow humans. In the late 1960's, I decided to devote my efforts to organ transplantation, it being the new therapy that could save patients from certain death due to end-stage organ failure. My field of work comprised the kidney, the pancreas, the liver, bone marrow and others organs. I was fortunate to work with some of the leaders and pioneers in the field, including Dr. Thomas Starzl in Denver, Colorado USA, Dr. David Hume in Richmond, Virginia, USA, Sir Michael Woodruff in Edinburgh, Scotland and Dr. Donnel Thomas in Seattle, Washington State, USA. Later, I was able to help establishing major transplant programs in Georgia, Iowa, Philadelphia, USA; in Calgary, Canada; and more actively in the Middle East, including Kuwait, where, as a founding professor and chairman of Surgery in 1978–1990, I established the first Transplant Center in that area of the world. Over a ten-year period, I carried out some 570 kidney-, liver-, pancreas-, and bone marrow transplantations for patients from all over the Middle East and North Africa. More recently, from 1995–1999, as Dean of Medicine and Chairman of Surgery at the Arabian Gulf University in Bahrain, I also established a transplant center and helped some 56 patients of all ages.

Organ transplantation today

Some time ago, organ failure meant certain death. With the advent of transplantation came the hope of a second chance of life. Today, tens of thousands of people are alive thanks to the miracle of transplantation. In this new era, many transplant patients are now leading perfectly normal lives, some even taking part in the Transplant Olympics, which are held every year in different parts of the world. In a recent survey among 50,000 people in the United States and Canada by the Good Year Corporation, transplantation was voted to be one of the most gripping events of the 20th century. Organ transplantation was recognized as the third most gripping moment in medical history following Alexander Fleming's discovery of Penicillin in 1928, and the invention of the Polio vaccine by Jonas Salk in 1955 [28].

Today nearly 2000 transplant centers throughout the world perform kidney-, pancreas-, liver-, heart-, lung-, intestine and bone marrow transplantations. More than 700,000 patients have received one organ or another since the beginning of clinical organ transplantation in the 1950s. In 1998 alone, some 45,000 patients received a transplant. The longest surviving patients after undergoing transplantation are; for kidney, 36 years; for liver 29 years; for heart 24 years; for combined kidney-pancreas 20 years; for lung 12 years, and for bone marrow, more than 27 years [16, 27].

An 11-year-old boy on whom I carried out a kidney transplantation at the Medical College of Georgia in Augusta, USA in 1972 is in excellent health, nearly 28 years later. Another patient on whom I carried out transplantation from her sister in 1974, appeared in the Press in Calgary, Canada, in November 1999, she was celebrating her 25th anniversary after a successful kidney transplantation. Also, a patient on whom I carried out a cadaveric kidney transplantation in Philadelphia, USA in 1992 when he was 73 years of age, recently sent me a photograph of himself and his wife celebrating their 50th anniversary. He is now 81 years of age. Finally, a patient on whom I carried out a cadaveric pancreas transplantation in Philadelphia, PA, USA in 1991, is now 9 years later, in excellent health and free from diabetes. Dr. Sutherland and Dr. Nagerian, who are the pioneers in pancreas transplantation and with whom I had the pleasure of working from 1985–86 at the University of Minnesota, have many patients who are alive and well now for nearly 20 years after having received pancreas transplants from cadaveric donors or living relatives [25].

Historical aspects and recent advances

The first successful cadaveric kidney transplantation was carried out by my former Chief, the Late Dr. David Hume, when he was in Boston, Massachusetts in 1952. At that time there was no effective immunosuppression, and of the five patients that underwent transplantation, one, a physician, survived with a functioning kidney for about 150 days. The next milestone in transplantation was a kidney transplantation between identical twin brothers by Dr. Joseph Murray, also in Boston. This was the beginning of successful organ transplantation between family members and live donors. For his pioneering work, Joe Murray was awarded the Nobel Prize in 1990. This prize was shared by a pioneer in bone marrow transplantation, Dr. Donnel Thomas, with whom I also trained in the early '80's. Peter Medawar was the scientist and immunologist who discovered that the rejection of organs by the body is caused by the lymphocytes that are stimulated by the graft. For this important discovery, he also was awarded The Nobel Prize. The discovery by Medawar was put into clinical use by Sir Michael Woodruff of Edinburgh, when he produced an anti-lymphocyte serum to inactivate the lymphocytes of the patient and thus prevent them from rejecting the organ. The first liver transplantation was carried out by Dr. Thomas Starzl in 1964, in Denver, Colorado, USA, with whom I subsequently trained in liver transplantation. Other pioneers in transplantation discovered the histocompatibility antigens, which determines the degree of compatibility between donor and recipient, and thus enable proper selection of a

compatible donor, preventing rejection. They are Dr. Dousset, Dr. Van Rood, Dr. Amos, and Dr. Terasaki.

In the past 20 years, enormous advances, in surgical techniques, organ preservation, and particularly in the discovery of new immunosuppressive agents have taken place. A milestone in the development of immunosuppression was the discovery of Cyclosporine by Dr. Borel. This improved the success rate of transplantation considerably. Many other immunosuppressive agents have since been discovered and tested over the past 10 years, and the use of these agents has further improved the success of transplantation. As a result, the success rate of kidney transplantations has improved enormously from a 1-year graft survival rate of nearly 50% in the 1960s to more than 80–90% in the 1990s. Similarly, the graft survival rate of pancreas transplantation at one-year was less than 40% in the 1960's-1970's, while, in the 1990's, it is now higher than 80%. Similar advances have taken place in liver-, heart-, and lung transplantation [16].

Unfortunately, because of the rapidly increasing demand for organ transplantation due to the very high incidence of organ failure all over the world, and due to the fact that organ donation and availability of organs for transplantation remains inadequate, there is an enormous gap between organ demand and organ supply. In the United States some 70,000 patients were waiting for transplantation in 1999, but only 20,000 patients were fortunate enough to receive a transplant because of lack of organs [26]. As a consequence, several thousand patients die each year while they are waiting for an organ transplant. This situation is similar throughout the world and even worse in countries of the Middle East, Asia and Africa, where transplantation is either not available or, if it is available, organs from cadavers and other sources are extremely scarce.

In 1978 I left Canada and moved to Kuwait as a Founding Professor and Chairman of Surgery. One of my missions was to start an organ transplantation program for the Arab Middle East. At that time, patients from the Middle East used to go to India and other countries where kidneys were sold on the market, with disastrous consequences not only for the recipients, many of whom were infected with HIV, but also for the poor donors and their families, for the medical profession, and for society in general. My first task was to obtain an Islamic Ruling from the Religious Leaders of Kuwait to allow transplantation. We were very fortunate in that the Islamic Fatwa Committee declared on December 31, 1979, that "transplantation of organs can take place from a dead donor providing that there was a necessity to save a human life, and also from a living donor providing that the taking of one organ, such as a kidney, will not harm the donor in any way, provided permission was given by the donor, since saving a human life overrides all objections,

[4]" This was the first declaration of its kind in the Islamic world.

Following this monumental declaration by the Islamic religious rulers, we were able to assemble an active transplant team and build the largest transplant center in the Middle East, where, in a period of 10 years, we carried out some 561 kidney transplantations, 3 pancreas transplantations, 1 liver- and 6 bone-marrow transplantations. A notable fact of this effort was that only 257 of these patients were Kuwaiti citizens. The remaining 314 came from different parts of the Middle East, Asia, and Africa, since such a treatment was not available in their own countries, and our treatment was free, thanks to the goodwill and support of the Government of Kuwait. We carried out transplantations on 69 patients from Lebanon, 61 from Syria, 56 from Sudan, 30 from Yemen, 28 from Bahrain, 22 from Iraq, and 23 from Palestine/Jordan, together with some 48 other patients from India, Palestine, and Egypt who worked in Kuwait. The transplant center of Kuwait, now called Hamed El-Essa Organ Transplant Center, was built for us by a very generous Kuwaiti family and was named after their brother who died after kidney transplantation in Germany in the early 1970's. It is the biggest center in the Middle East, and in fact one of the largest in the world, being a self-contained hospital with 36 beds devoted entirely to transplantation. We started first with living donor transplantation with a success rate of 80% for 10 years, which was one of the highest in the world. Many of the adult- and pediatric patients, who received kidney transplants from different parts of the Arab World and Asia are alive and well [7, 8, 10]. In 1988 we carried out the first kidney- and pancreas transplantation from a living donor to his diabetic brother (Palestinian family). This was the first successful live donor pancreas transplantation in the world, outside the United States. The patient became free from diabetes and survived for two years until the Gulf War, when he was unable to obtain immunosuppressive drugs. He rejected his kidney and pancreas and died in 1991 [12]. The first successful bone marrow transplantation in the Middle East was carried out in Kuwait for a child with Thalassemia Major. Five of the six children that received such transplants are alive and well today, more than 15 years later [22].

Because of non-availability of local cadaveric organs for quite a number of years, we tried, I believe for the first time in the world, to use kidneys from genetically unrelated but emotionally related donors like husbands and wives. We carried out 51 such transplantations over a period of 8 years in Kuwait, and the results, which have been reported, showed that the functional survival rate of these kidneys was almost as high as that of genetically related donors. For example, a husband gave a kidney to his wife in 1980 (both of Palestinian origin) and over the next four years they produced two lovely

children, and all have been alive and well for over 15 years. Another patient, a woman who received a kidney transplant from her husband who was unrelated, delivered twins two-and-one-half years after transplantation [7].

Because the number of patients on the waiting list was increasing rapidly and cadaveric organs were not available in the country in the early 1980's, we decided to accept kidneys from complicated "Marginal Donors". These are the kidneys from non-heart beating donors; from older donors over the age of 60; from young children under 5 years; from diabetic donors and grafts that had been stored for prolonged periods of over 30 h. About 2000 such organs were discarded each year in Europe and the United States because it was assumed that they would not work. We had these kidneys flown to us from the United States and different parts of Europe, and the government of Kuwait agreed to pay for transportation of the kidneys and the accompanying technicians. The results of these efforts showed a graft success rate of almost 70%, which surprised everybody when our results were published in several reports [3, 5, 9]. From this very important experience, many centers in the United States and Europe are not throwing such organs away as they used to do but are transplanting them quite successfully in their own countries. Beside our transplant efforts in Kuwait that helped nearly 570 patients, I returned to the USA after the Gulf War and during 1990–1995 led a transplant team at Hahnemann University, Philadelphia, that carried out similar complicated kidney- and pancreas transplantations for some 240 patients [13]. During the past 3 years I also carried out 56 kidney transplantations for adults and children in the State of Bahrain, when I went there in 1995 as Professor and Chairman of Surgery and the Dean of the College of Medicine. Despite the fact that many of these patients had other major problems including diabetes, cardiac by-pass surgery, and previously failed transplantations, with organs purchased in India, Iran, and Pakistan, the patient survival rate was 98% and graft function rate 95% at one year [6].

In most countries of the world, it is now recognized that kidney transplantation is the preferred treatment for end-stage renal failure, compared to dialysis, because it renders a better quality of life, is less costly, it is 1/3 the cost of dialysis over a period of four years, and the survival rate of transplant patients is much higher than that of patients on dialysis.

Current problems and possible solutions

As already mentioned, the major problem that all transplant centers in the world are facing is the very inadequate organ donation from the living and the dead. How can we therefore enhance this humanitarian act of

making organs available for those patients who need them in order to survive? The incidence of kidney failure in the USA and Europe is well over 150 per million /year, and in the Middle East and Africa it is 120–150 per million /year. Unfortunately, the number of available cadavers is about 20 per million /year in most European countries and America, except Spain, whereas in the Middle East, the Far East, and Africa there are very few cadaveric organs available. Because of this major imbalance between organ demand and organ supply, the transplant waiting list grows by nearly 15% each year. In the United States, for example, a patient is added to the list every 20 min, and the waiting time for transplantation has been increasing enormously varying from 400–1000 days, depending on the organ [16, 26]. Also, many patients die while waiting, especially those needing a liver- or heart transplant. In the USA, for example, 14 patients die each day while waiting, which amounts to 5,000 patients per year [26]. Most patients with organ failure in the Far East and Africa die each year because neither cadaveric organ nor or even dialysis treatment are available.

It is sad that organ donation is declining while organ demand is increasing in spite of the fact that the guiding principles and views of major religions on organ donation and transplantation are very positive and support the belief that "donation of organs for transplantation is an act of charity, benevolence, altruism, and love for mankind. God loves those who try to mitigate the pain and sorrow and relieve the suffering of fellow humans. Human organs are not a commodity and must not be sold; they should be freely donated in response to an altruistic feeling of brotherhood and love for fellow humans" [10]. Indeed, the Roman Catholic position was first expressed to us at the Congress of the Transplantation Society in Rome in 1978 by the late Pope John Paul I. In summary His Holiness said: "We are today glad to express to you (the Transplant Society) our congratulations and our trust for the immense work that you have put in the service of human life in order to prolong it in better condition and we pray to God, the author of life, to inspire and assist you in these magnificent and formidable responsibilities. May he bless you with all your dear ones" [4]. In 1992 Pope John Paul II, who also met with us at the following Transplantation Society Congress in Rome, confirmed these same assurances by the Catholic Church, stating that organ transplantation was a humanitarian act. In 1991, the Jewish Rabbinical Council of America also approved organ donation, it being not only permissible, but even required in order to save life, and they stated that "the saving of life is of utmost importance". As I already mentioned, following the ruling of the Ministry of Islamic Affairs of Kuwait to allow organ donation for transplantation in 1979, most of the other Islamic countries including Saudi Arabia, Egypt, Syria, Iran, Pakistan and Turkey have now

issued similar rulings. Nevertheless, there is a widening gap between organ demand and organ supply, therefore we have to ask what else can we as physicians and scientists do to close this gap? As already mentioned, we have been pleading very hard, both in the Middle East and in the United States, for an increase in transplantation from living genetically related donors; from living emotionally related donors such as husbands and wives; from distant family relatives; and also from living completely unrelated donors provided this is done for humanistic reasons and altruism, but not for financial gain. Finally, many of us transplant surgeons, physicians, and scientists are working hard in Research to make it possible for humans to receive organs from animals (xenotransplantation) successfully and without rejecting them.

Let us briefly deal with organ donation by non-family living donors who donate for humanistic and altruistic motives. In one of his writings Albert Schweitzer once said: "Constant kindness can accomplish much; as the sun makes ice melt, kindness causes misunderstandings, mistrust, and hostility to evaporate." He also said: "There is no higher religion than human service, for to work for the common good is the greatest creed." Indeed, in recent years many strangers have come to the rescue of patients in need of organ transplantation. We witnessed this in Kuwait in 1982 and in 1984 when two non-family donors, Fereda Ali and Mohamed Khawli, came forward and asked me to allow them to donate one of their kidneys for transplantation to two of their friends. One of them was Magida Abdulla and the other one was a physician on dialysis, Abdullah Alcaserty. They were suffering from kidney failure, and had no family donors. Both of these patients have been alive and well for 16 to 18 years, after having received kidney transplants from their friends, and the donors have expressed great happiness and pride following their humanitarian donation [7]. In July 1996, Professor Hoyer, a transplant surgeon in Lübeck, Germany, feeling sympathetic to the plight of many transplant patients waiting for cadaveric organs, decided to donate one of his kidneys to a patient quite unknown to him at the University of Munich Transplant Center. The operation was carried out with great success by Dr. Walter Land, and the recipient of the kidney has been enjoying normal life ever since. Meanwhile, Professor Hoyer, feeling proud of his humanitarian deed, has tried to encourage other people to do the same [19].

In 1999, Joyce Roush, a mother of five and a nurse, approached the doctors at Johns Hopkins University and offered to donate a kidney to a 13-year-old Christopher Bienick, whom she did not know. After the transplantation, Ms. Roush was thrilled by the successful procedure which gave Christopher a new start in life. She remarked: "I think God tapped me on the shoulder and asked me to do this." There was also an outpouring of

public response that followed the news of her gift. In 1999, Mr. Robert Johnson, aged 48, an English building maintenance worker from North Hampshire, after reading a story about Lisa Ostrovsky, a 10-year-old Russian Jew living in Israel who was awaiting a lung transplant at St. Louis Children's Hospital, USA, quit his job, got on an airplane, and went to donate one lobe of his lung for Lisa. He was found to be physically and psychologically suitable, and the child is doing well after transplantation. Mr. Johnson was quoted: "I see this as an opportunity to do my bit." In January 2000, Mr. Kyle McNamera, aged 32, donated a part of his liver to Randy Roberts, aged 38, who had been a friend for 10 years. He had contracted Hepatitis C and subsequently went into liver failure and had been placed on the waiting list for a cadaveric organ at the Lahey Clinic. The doctors at the Lahey Clinic remarked: "There is a great feeling of relief when, after such a difficult procedure, the patients are on their way back to a healthy, normal life, and there is a sense of being thankful that this was made possible through the donation of a liver by a healthy individual for humanitarian reasons" [15]. Indeed, such individuals might be called saints on religious grounds, and on social and scientific grounds might be regarded as heroes. Such humanistic acts of saving lives or improving the quality of life of others have become possible through the art and science of transplantation.

Finally, I would like to mention xenotransplantation. Many transplant scientists working in this area hope that "xeno" which today means, "foreign" will be "familiar" tomorrow, and we feel that this can be the ultimate solution for organ shortage [17]. The first kidney transplantations were carried out from chimpanzee to man by Remeetsma in 1963 and by Starzl in 1964. One kidney functioned for 5 months. The first liver transplantation from chimpanzee to man was also carried out by Starzl in 1970 when I was working with him in Denver, Colorado, USA. A further one was carried out more recently in Pittsburgh, USA in 1992, from a baboon to a patient with HIV who lived for about 70 days. The first extracorporeal perfusions of a pig liver, used outside the body for temporary support of patients in hepatic failure, were carried out by Eiseman in mid 1960's and by myself in the late 1960's and early 1970's. We treated ten patients with baboon- and pig liver perfusions for fulminant hepatic failure, with a high degree of success [11]. The first heart transplantation from a baboon to a child (Baby Fae), was carried out by Dr. Bailey in 1983 and functioned for about 20 days.

The problem with xeno-graft is that of hyperacute rejection, since we all have preformed natural xeno-antibodies against animal organs. This was first described by Dr. John Najarian and others and is now more clearly identified by Dr. David Cooper and Dr. David Sachs of Harvard University [17]. There is also activation of

complement which leads to vascular thrombosis in the graft, as clearly outlined by Dr. White, Cambridge University, England, and by Dr. Jeffrey Platt at Johns Hopkins University, Baltimore, MD, USA [17]. The other problem is the genetic discordance of histo-compatibility antigens between man and animals. In our early experience in using animal organs in a specially designed apparatus of extracorporeal liver perfusion for the treatment of patients in hepatic coma which have been reported previously, we removed some of the xeno-antibody by plasma exchange. Of ten patients that we treated using pig-, baboon-, human-, and calf livers, 65% woke up and recovered from deep coma while they were awaiting transplantation or had acute hepatitis [11]. One patient whom I treated in the early 1970's, when I was with Dr. David Hume, was in coma from viral hepatitis, and after 20 h of perfusion with baboon- and pig livers, she woke up and could be discharged from the hospital. Two other patients who were also suffering from acute hepatitis and were in deep hepatic coma, fully recovered after treatment with baboon liver perfusions in 1972. They have been alive and well for more than 28 years [2]. Another patient with acute on chronic hepatic failure was brought out of deep coma nine times and kept alive for 76 days while awaiting liver transplantation, which unfortunately did not materialize [1]. Recently, we have redesigned our Extracorporeal Liver Perfusion System which was very successfully applied in a pre-clinical trial in dogs with acute liver failure. The results were published in June 1999 [14]. In this experiment we used dogs with a surgically induced liver failure. We first removed the preformed antibody by doing a temporary kidney transplant from a calf and allowing the kidney to reject, and, in so doing, removed the preformed xeno-antibody. Then we brought the calf liver, placed it in the specially designed perfusion apparatus and connected it to the dog in an almost antibody free environment. The liver worked for many hours, performing all the functions of the animal's failing liver. All the animals woke up from coma, and in 70% their liver regenerated and they became long term survivors. We are now in the process of starting a clinical trial using this new apparatus. We strongly believe that this new apparatus for Ex-vivo Xenogeneic Liver Perfusion will be a highly successful means of supporting patients with liver failure pending regeneration of their own liver or acting as a bridge to transplantation of a human cadaveric liver. Indeed, this support system is badly needed, since in the USA alone some 30,000 patients die from hepatic failure each year. Another way of preventing acute rejection of the extracorporeal liver perfusion is to apply transgenic technology, where the complement of the animal is genetically replaced a human complement. Some centers have used transgeneic pigs for liver perfusion [20], and will hopefully do so for future organ transplantations.

Scientists are now exploring other methods of preventing xenograft rejection, such as using cloning technology. Their aim is to knock out the animal gene that produces the antigen which is targeted by the xenoantibody that all of us have as humans. If that antigen no longer existed, the antibodies would not react against the animal organ, and the organ would survive. Several notable scientists anticipate that with these developments, by using transgenic and cloning technology, successful xenotransplantation will become a clinical reality by the year 2010.

It is, of course, very important that the donor animals used for xenotransplantation be bred in special farms and regularly tested for infective organisms [24] including bacterial cultures as well as undergoing serological PCR tests for viral infections including HIV, HBV, HCV, SIV and PERV. Only animals the culture and sera of which are negative for micro organisms must be used. Although there is some fear that retroviral infections may be transmitted from pig to man, for example, all recent studies have shown that there is neither evidence of porcine DNA retroviral infection in patients who underwent short term extracorporeal transplantation of pig kidneys [23], nor in patients transplanted with porcine pancreatic islet cells nor in baboons implanted with porcine endothelial cells [21].

In closing, I would like to deal with the feeling and reaction of the general public towards using animal organs for transplantation. In a recent survey by the National Kidney Foundation of the United States, on the attitude of 1,700 individuals towards xenotransplantation as a possible solution to organ shortage, transplant candidates, recipients, surgeons, physicians, primary care doctors, and clergy confirmed the view that "xenotransplantation is one of the most viable options to increase organ availability and should be supported by increased government funding for more research" [27].

In the meantime, until the problem of xenotransplantation is successfully resolved, we all hope that, more and more people willing to donate their organs to save the lives of fellow human beings will come forward and get the feeling of pride and the privilege of doing such a humanitarian deed. I think it is appropriate to conclude with another profound adage by Dr. Albert Schweitzer who said: "Even if it is a little thing, do something for those who are in need of help, something for which you get no pay but the privilege of doing it."

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