[Frontiers in Bioscience 12, 3727-3733, May 1, 2007]

Transplantation: current developments and future directions

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1. ABSTRACT

Organ transplantation has emerged from a few sporadic failed attempts to one of the most successful branches of surgery in the course of 50 years since the first identical twin transplant was performed in Boston. In this article I will attempt to portray the historical background and the recent shift of attitude regarding immunosuppression for solid organ transplants. Previously a culture of increasing immunosuppression and incorporating new and powerful agents into an already effective regimen has resulted in over-immunosuppression and more sepsis without an improvement in long-term graft survival. Over-immunosuppression is probably detrimental in preventing the natural control and "switching off" of the immune response as a vital function of the immune system and as a consequence any attempts to produce immunological tolerance are likely to be impaired by excessive immunosuppressive regimens. I will therefore explain and advocate a minimalistic approach to immunosuppression, a background on tissue typing and a summary of clinical results. Now that the procedure is perceived worldwide as an excellent therapy for previously doomed patients there is an increasing mismatch between the number of donor organs available and patients in need of a graft. This has produced ethical dilemmas previously unknown in the medical profession. These are extremely important considerations as they can undermine the Hippocratic tradition and the high ethical standing previously enjoyed by our profession.

2. HISTORICAL BACKGROUND

Organ transplantation is a success story. In view of the initial difficulties in the 1950s and 1960s, the current therapeutic value of organ transplantation is enormous and surprising. The idea of replacing the damaged vital organ by grafting a new organ is ancient and immersed in religious and folklore legends, but in the early part of the 20th century serious approaches in organ grafting were made, when it was realised that maintaining the organ in good condition during the surgery and providing it with satisfactory arterial inflow, venous drainage and route for its secretions raised technical problems that had not previously been defined and challenged. The source of the donor organ was also a matter of conjecture. Clearly the convenience of obtaining a healthy organ of appropriate size from an animal such as a pig was attractive, but all attempts at cross-species grafting were dismal failures due to incompatibility that was not understood, and even after many years of research the mechanisms of xenograft rejection are not fully defined and nor can they be overcome.

Until the 1950s there were sporadic and universally unsuccessful attempts at both xeno and allografts of kidney using vascular anastomosis of artery and vein to provide a blood supply and drainage. Gradually experimental work showed that an autograft could be performed successfully and that cooling the kidney whilst it was without a blood supply increased the

latitude of time in which to perform the operation. Thus using the simple well-established method of keeping meat by refrigeration, cooling of a kidney externally by immersing it in ice-cold saline and then variations of methods of cooling it with solutions infused into the renal artery led to confidence in performing the operation in animals.

In the 1950s the autograft experiment was in principle repeated in man by Dr. Joseph Murray and his colleagues at the Peter Bent Brigham Hospital in Boston (1). The first patient to receive a successful transplant was referred to the hospital with a note from the patient's doctor saying "by the way the patient is one of identical twins". Thus the stage was set for proving that the surgical technique that was successful in animals could be transferred to the clinic. The identical twin transplants were greeted with optimism by surgeons and nephrologists. However when the donor was not an identical twin, failure usually resulted. The only method known to prolong graft survival had been adopted from bone marrow transplantation using total body x-irradiation of the recipient. This is highly effective in bone marrow transplants between closely matched donor recipient pairs but otherwise failure is to be expected. The same was found in kidney transplants but interest persisted because two recipients of kidneys from non-identical twins, one in Paris and one in Boston both did well. Repeated attempts to use the same recipient treatment in unmatched donor recipient pairs resulted in almost universal failure due to rejection and/or infection (2,3).

Also in the 1950s two other important observations were made. First that if the patient suffered from an autoimmune nephritis this could recur in the transplant and also there was a likelihood of the disease appearing in the donor's remaining kidney because of the susceptibility of identical twins to similar diseases. Thus it later became practice in these cases to give the recipient immunosuppression. Important ethical and legal matters were raised, since the operation disobeyed Hippocrates' advice that "first one should do no harm to a patient", then, having accepted that an emotionally involved adult donor, such as an identical twin, could make a rational judgement to donate a kidney, what would the situation be if the donor was a minor and was not yet legally empowered to make such a commitment? This question was considered by the Massachusetts Supreme Court, whose judgement permitted a minor to give a kidney to an identical twin with the interesting argument that if the potential donor did not provide a kidney for the twin, later in life the potential donor would feel serious misgivings and distress that he or she had not been permitted to donate a kidney as a life-saving measure for the twin.

The immunological obstacle, however, proved to be stubborn. Medawar and his colleagues had shown that skin grafts were destroyed by a mechanism that had immune characteristics; having reacted against one skin graft the recipient of a second skin graft from the same donor would react more violently, demonstrating an acquired immunity and a memory of the first tissue (4). A few years later Medawar and his colleagues demonstrated a natural way of overcoming graft rejection, which occurs in non-identical cattle twins that share a blood circulation *in utero* (5). The definitive experiment, injecting cells from one in-bred strain of mouse into the foetus of another strain, resulted in graft acceptance in survivors of this procedure and led to the concept of a state of immunological plasticity in the embryo before the immune system is fully developed (6). Although this had no obvious clinical application, it raised the question as to whether by any means this state of immunological plasticity could be temporarily induced in a potential recipient of an organ graft so that the graft would be accepted but the immune defences would be rapidly restored.

In 1959 6-Mercaptopurine used in the treatment of leukaemia was shown by Schwarz and Dameschek in Boston to prevent antibody formation in rabbits challenged with foreign protein. They called this observation "drug induced immunological tolerance" (7). Studies in kidney grafted animals treated with 6-Mercaptopurine in the UK and the US produced a moderate prolongation of graft survival (8,9) and led to a practical clinical regimen of treatment using Aziothioprine, an analogue of 6-Mercaptopurine (10,11,12), and corticosteroids.

The one-year graft function was around 50% and kidney transplantation remained confined to about 10 centres worldwide and the procedure was viewed with suspicion because of the poor overall results. Then in the late 1970s Borel and colleagues of Sandoz discovered the immunosuppressive properties of the fungal cyclic peptide cyclosporine, which prolonged skin grafts survival in mice (13). Further studies of cyclosporine in the UK showed prolonged survival of cardiac allografts in rats (14) and pigs, and renal transplants in dogs (15). When we first used cyclosporin in man, based on the dosage given to animals, severe nephrotoxicity resulted. After a worrying learning curve of dose adjustments cyclosporin was shown to improve the 1-year survival of kidney grafts to around 80%, and for the first time surgeons became confident in transplanting the liver and heart based on cyclosporin immunosuppression (16).

The compound was a watershed in the development of transplantation and instead of a handful of centres worldwide, transplantation became a much-valued form of therapy and it wasn't long before there were more than a thousand centres, the kidney being the chief organ transplanted, but increasingly good results were obtained with heart and liver and eventually, with lungs and pancreas (Figure 1). One method of minimising the nephrotoxicity of cyclosporine was to combine the immunosuppressive effects of cyclosporine, azathioprine and corticosteroids so that the total immunosuppressive activity would be additive, but the individual side effects of the different agents would be minimised. Gradually the "half-life" of organ transplants improved.

There has been a succession of new immunosuppressive agents investigated experimentally,

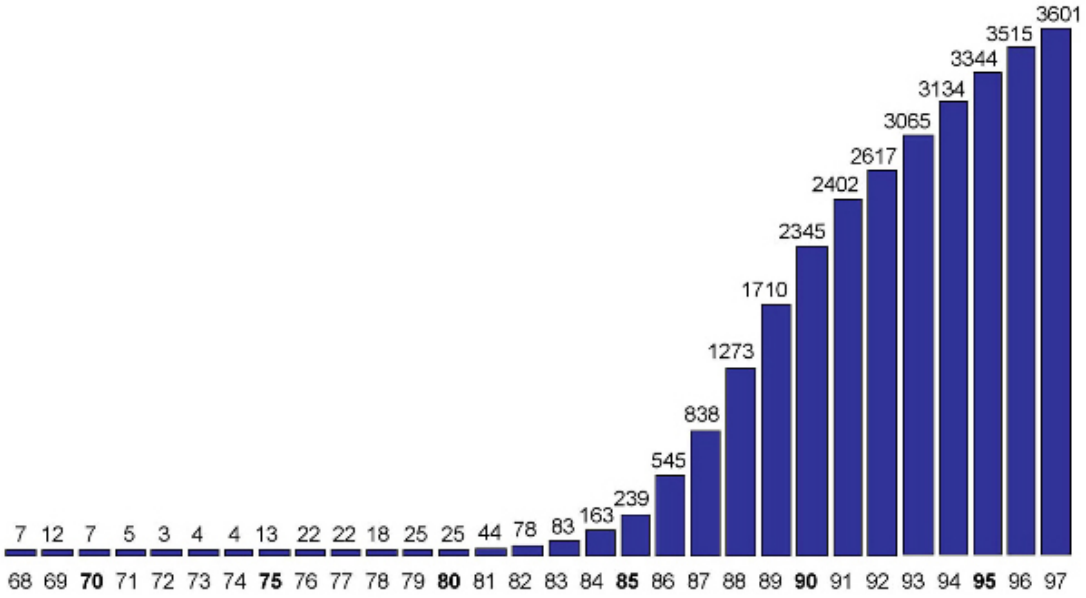

Figure 1. Yearly European Liver Transplant Activity shows marked increase coincident with the introduction of cyclosporine immunosuppression.

and a number have been introduced into the clinic including polyclonal and monoclonal antilymphocyte antibodies. There has been an unfortunate tendency to add more and more potent immunosuppressive agents to the patient's therapy with concomitant over-immunosuppression. Bone marrow transplantation has also advanced with new regimens of non-ablative transplantation with mixed chimaerism (17), initially planned to retain the graft against leukaemia effect but also utilised in a very important series of clinical experiments at the Massachusetts General Hospital in patients subsequently given kidney transplants, where tolerance has occurred despite the disappearance of the donor chimaeric state in the blood (18).

Besides being expensive, the conventional drug regimen can cause great hardship to patients and non-compliance is common. Some patients with liver transplants stopped taking their drugs and performed a clinical experiment demonstrating immunological tolerance, surviving many years with good liver function despite the absence of any maintenance immunosuppression (19). Other patients were not so lucky and this weaning of maintenance immunosuppression is far more likely to be successful with liver transplants than with kidney transplants, which is consistent with experimental demonstration of liver tolerance without any drugs after orthotopic liver transplantation in pigs and rodents.

The story of immunosuppression during the succeeding 50 years has had and still has the aim to provide tolerance. Clinical immunological tolerance does occur when the recipients immune system is destroyed and replaced by bone marrow from the donor, who must be a close match of tissue type, usually an HLA identical sibling (20, 21, 22).

Over the years there have been many refinements of immunosuppression, which for organ grafting has moved away from total body lethal x-irradiation to drug and antibody treatment. There has been a tendency for clinicians to add more and more of potent immunosuppressive agents to the patient's therapy, but more recently attempts to achieve graft acceptance with minimal immunosuppression are beginning to meet with some success. One example is the use of the lympholytic monoclonal antibody, Campath 1H, as an inducing agent and then subsequently maintaining the patient on a half dose of one calcinurin inhibitor instead of full dose of three drugs, which had been common practice previously. There are likely to be many advances, fine-tuning this approach, which we have called *prope* or almost tolerance (23, 24). Perhaps in some patients eventually maintenance immunosuppression could be stopped, but we badly need a test by which patients can be safely managed in this way.

2.2. Minimalist Approach

From the patient's point of view minimal immunosuppression without obvious side effects is an attractive proposal compared with conventional immunosuppression. *Prope* tolerance was first used with the powerful lympholytic monoclonal antibody Campath 1H. The five-year follow-up of the first renal transplant patients treated with Campath induction and maintenance low-dose cyclosporine has been satisfactory (25).

There is now a considerable experience of the use of induction followed by steroid-free minimal maintenance immunosuppression and it seems likely that this will become a favoured method of recipient management in the next few years for all organ grafts except patients with active viral infections, which may be exacerbated by Campath.

2.3. Tissue Typing

The interest in organ transplantation greatly stimulated the science of immunology. Mechanisms of graft rejection are partially understood and the fate of a graft depends not only on excellent surgery with avoidance of damage to the organ in the process but, as indicated above, the degree of HLA matching of donor and recipient is crucial in any approach to tolerance. The HLA system of antigenic determinants arises from genes on the sixth human chromosome. The ABO red blood group system is also of importance in graft outcome.

Of the drugs used to suppress the immune system, each has some side effects specific to the agent in question and others common to all immunosuppressive agents, namely increased susceptibility to infections and to tumours, particularly lymphomas. A strategy of using different agents together to maximise immunosuppression and minimise side effects has been partially successful and the new approach of minimal immunosuppression should be of additional benefit. The agents vary from small molecules, for example, aziothioprine and corticosteroids to complicated peptides and macrolides, cyclosporine, tacrolimus and sirolimus, and large molecular protein antibodies, polyclonal and monoclonal.

In the past decades much interest has been focussed on blocking the second signal of antigen recognition, which is essential for the immune response to proceed. In animal models second signal blockade can result in long-term graft acceptance without other potentially toxic immunosuppressive agents. These and other immunosuppressive agents are in the process of early clinical trials and no doubt will have an impact on immunosuppression in the future. (26).

2.4. Clinical Observations

The first organ to be transplanted successfully in man was the kidney and even when the donor is not an identical twin, patients can do extremely well with grafts from live donors and from unrelated and often totally unmatched cadaveric donors. In the latter category in several centres patients are surviving after more than 40 years with good function in the original kidney graft.

The half-life of kidney transplants has been increasing and is currently more than ten years. Failures are mainly due to rejection, nephrotoxicity of the calcineurin inhibitor agents and recurrent disease. Liver and heart transplantation have also provided excellent treatment for many patients. Unfortunately the commonest indication for liver transplantation is now Hepatitis C, which almost invariably recurs in the graft and can lead to liver failure irrespective of rejection and other causes of graft loss. The chief complication of heart allografts is chronic rejection, which involves the coronary arteries and with appearances similar to accelerated atherosclerosis. So far adequate treatment for this has not been discovered. There have now been many cases of bilateral lung transplantation with or without the heart. The lungs seem to be a special target for chronic rejection, the alveoli being particularly affected and again, good treatment for this complication is not available. Pancreas transplantion has become very popular in North America, but less so elsewhere due to the serious complications that can occur following the operation due to leakage of pancreatic juice. Recent immunosuppressive regimens avoiding corticosteroids have reduced complications, for example using Campath induction and FK506 maintenance (27).

A major conceptual advance in the treatment of diabetes was the successful transplantation of islets of Langerhans by the group in Edmonton led by James Shapiro (28). The early results were excellent using an immunosuppressive protocol with no steroids and treating patients suffering from hypoglycaemic unawareness before they had severe secondary complications. Most patients required the islets from two donors. At one year around 80% of patients did not require insulin injections. This had fallen to about 75% at 2 years but deteriorated more quickly after that, being around 50% at 3 years (29). The Edmonton programme was an important proof of principal that islet transplantation can get good results but fall-off over the years may be due to a combination of chronic rejection, exhaustion of the islets and immunosuppressive drugs preventing progenitors from replacing lost beta cells. Also the autoimmune disease of Type I diabetes may affect the graft. There are a few reports of autotransplants of islets from patients with chronic pancreatitis who have been free from the need of exogenous insulin for many years, which would suggest that the islets themselves can persist and function well for a long periods in the liver in the absence of immunosuppression and autoimmune Type I diabetes (30).

In the future, hopefully, cells that don't normally produce insulin and other vital proteins will be persuaded to do so either by cultural techniques and/or genetic engineering. The success of bone marrow transplantation and islet transplantation would suggest that further advances in cell transplantation are likely. Whenever cells are separated from their normal environment there is a worry that they may not react physiologically and may not produce enough of the vital protein at the right time or too much at the wrong time, a particularly important consideration in diabetes. If cells assume a different metabolic role with the expression of genes that they would normally suppress, or the addition of genetic material by engineering, it is quite likely that the process will not continue indefinitely and if the therapy is short-lived it may not be worthwhile. These are important questions that are being looked into currently and the results will have an impact on the potential for cell transplantation or direct genetic engineering of tissues *in situ* in the future.

There have, over the years, been fluctuations of enthusiasm for the prospect of transplanting organs and tissues from animals to man but to date there have been no long term successes. The best result was in the 1960s when Reemstma transplanted a kidney from a chimpanzee to a patient and the graft functioned for nearly 10 months (31). The chimpanzee is now regarded as unsuitable as a donor to man for ethical reasons and other non-human primates as donors have also caused great controversy. The pig seems

a more acceptable potential donor, but the pig and man have been separated in evolutionary terms for many millions of years and almost every protein produced by a pig cell differs from that produced by human cells, although as we know insulin itself has only one amino acid difference and can function perfectly well in man. In addition, there are many difficulties with the prospect of xenografting in addition to hyperacute rejection, accelerated rejection and other immunological factors there are physiological considerations as to whether pig proteins will function satisfactorily in man and the rapid growth of a pig could also be a disadvantage. For instance, the heart could continue to grow in the patient and might not be accommodated within the chest. The natural lifespan of a pig is probably around 15 years and this might put a limit on the longevity of a xenograft if rejection could be overcome. On top of all this, there is the unknown but potential hazard of pig retroviruses, which can live and reproduce in human tissues although there is as yet no evidence of them causing disease.

Considerable efforts have been made to make the pig more compatible with humans. The first important advance was the development of transgenic pigs producing the decay accelerating factor inhibiting complement activation. This greatly reduced the initial explosive antibody induced haemorrhagic rejection (32, 33). The next stage was to remove the principle natural antigen responsible for the violent rejection, namely Gal. Organs from the Gal "knockout" pigs tended to survive longer when transplanted into monkeys but despite these formidable achievements it has still been very difficult to obtain long-term pig to primate xenograft organ survival (34,35).

It would seem that solving the problems of xenografting is rather like running a relay race in which the hurdles are high and opaque and until you have got over one you don't know what lies ahead or how long the race is. Despite the fact that I have sympathy with Norman Shumway's comment "that xenografting is the future of organ transplantation and always will be", there has been a recent report of adult pig islets functioning for long periods in immunosuppressed monkeys by Bernard Hering and colleagues in Minneapolis (36).

It would seem that for most organ transplants the surgical difficulties have been overcome, but there are still controversies over the best way to transplant half a liver from an adult donor to an adult recipient and now surgeons are looking to the possibility of transplanting other non-vital organs besides the pancreas, such as face transplants. Already there has been some success with transplanting hands, particularly in the severely handicapped patient with bilateral loss of hands. We can expect steady improvement in results and new immunosuppressive agents utilised in a manner of minimal immunosuppression required to keep the graft functioning well in the hope that in some cases at least, maintenance immunosuppression may be stopped so that "operational tolerance" will occur.

2.5. Ethical and legal matters "the can of worms"

When I first started working on research in organ transplantation in 1959 I had no idea that ethical and legal considerations would assume great importance. I had imagined that overcoming rejection and learning how to do the surgery would permit good results eventually in organ grafts taken from cadaver donors where there was little to worry about in terms of traditional medical ethics providing the diagnosis of death was irrefutable and adequate permission had been given. Now, however, matters have changed largely because of the success of transplantation increasing the demand for organs. Whenever there is something much wanted and in short supply there will be pressure to obtain the commodity by payment and eventually even by criminal activity. There are enormous pressures on a patient who requires an organ graft and would expect a good result if there was a donor available. Even in the most successful nation to organise cadaveric organ donation, Spain, there is still a considerable shortfall of donors compared with the number of patients needing grafts and this shortfall tends to get more disparate in all countries as the years go by. There has been much discussion concerning the payment of donors for organs, whether the donor or the donor family should be paid directly or through a government agency or whether payment should be forbidden, in which case there is the danger of payment through the back door or bribery by other means. Certainly there is very little precedent for organ donation from the rich to the poor, it is nearly always in the other direction and there would appear to have been serious abuse in some developing countries, where many donor families have been rescued from extreme poverty by one of the family members selling a kidney or even half a liver. In China and other countries where capital punishment is practised, organ donation from prisoners has been widespread, the details are seldom published, but many patients from countries where this is not permitted, travel as organ transplant recipients on "package deals" to receive organ grafts. This practice has been outlawed by the Transplantation Society but has not stopped.

In Western countries there is an increasing tendency to perform living donor organ transplantation. As was mentioned at the beginning of this article, the argument for transplantation between identical twins seems to be generally acceptable and sanctioned by law. Similar feelings are usually expressed for transplantation between adult siblings and parents to child. Now, however, there are many cases of transplantation between people who are not blood relatives, between spouses and even totally unrelated friends. In some centres the onus of finding a donor is put onto the patient who is expected to find either a family donor, perhaps even their own child, or a generous benefactor. It is difficult for the doctor to explain and for the potential donor to understand fully the dangers of organ donation and the fact that the result may be a failure, either surgical or immunological. There is always a danger to the donor and morbidity is quite common even in kidney donation, but mortality is probably in the region of 1 or 2 per 1000. For liver donation the morbidity to the donor of an adult half liver to an adult recipient can be as high as 40% with a risk of death of between 1 and 2%. Many of us feel that this is an unacceptable risk to confront a perfectly

healthy person, who may not even be an emotionally related blood relative. The potential donors may feel an obligation or if they refuse, or the family is against it, they may feel guilty if the recipient dies. I don't believe these worries and anxieties have received sufficient prominence in discussion as they deserve. The transplant centres and the recipients and their family are usually strongly motivated to proceed and the centre usually wishes to do as many transplants as possible. In some countries, for example Japan, and many developing nations, permission for organ donation from brain-dead donors is difficult to obtain. In the UK only between 50 and 60% of the population will give permission for organ donation after death. The concept of "brain death" is hard to explain to medical students so it is not surprising that this is even more of a difficult concept for non-medical members of the population. Removal of organs after cessation of the heartbeat means that the organ donated will have suffered some damage and be inferior to that taken from a heart-beating donor.

On top of all this the actual practice of organ transplantation is viewed differently according to whether the transplant team are paid individually for each operation, as is often the case for both the donor and recipient team in the United States, but does not apply in many European countries. To be part of the donor team means being always available often for long journeys, frequently in the middle of the night, to a centre where one's presence is not exactly welcomed, and the removal of organs from somebody who has died tragically is always a sad business. The recipient team also has to be continuously available, although there may be some latitude in organ preservation time, depending on the organ in question. There is very little permissive preservation time for the heart but 24 hours or so for the kidney. There is therefore a shortage of transplant surgeons in some countries, especially now that the operations are routine with most of the excitement and glamour evaporated, and there is not a lot of room for surgical improvement. I would suspect that the matters alluded to in this section may be amongst the most important challenges in organ transplantation for the future. A consequence of the success of the procedure!

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Key Words: Organ Transplantation; Immunosuppression; Ethical Considerations, Review

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