Clinical transplantation: current problems, possible solutions

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I have attempted to summarize the progress that has been made in organ transplantation in the past 50 years since the first identical twin transplant. For those who have worked long in this area its success has been remarkable. We currently expect patients to survive the operation and more than 90% of the graft to be functioning at a year with the half-life of the graft beyond 10 years, with some patients surviving into the fifth decade after kidney transplantation with grafts from unrelated donors and the fourth decade for liver transplants. Now the main stumbling block is shortage of organ donors and this is unlikely to be solved easily. There has been a considerable increase in donations from living volunteers and also the worry of immoral and illegal practices.

In the future, we can expect considerable advances in immunosuppression with more effective, less toxic drugs and in some patients induction therapy that may approach tolerance so that no maintenance therapy will eventually be needed. Cell transplantation is likely to be developed as treatment for the clinic in the next 5–10 years, but developments of transplantation from animal to man still remains unsolved and unlikely to be successful in the clinic in the near future.

Keywords: current basis of transplantation; future prospects; historical review

1. INTRODUCTION

Now more than 50 years since the first identical twin transplant, we can look on organ transplantation as an extremely successful form of treatment for hundreds of thousands of patients who would otherwise have been doomed to death from failure of a vital organ. The results have been far more encouraging than many of us working in the field would have expected in the early days. However, there are still many problems to be solved to optimize this form of treatment.

The successful kidney transplant between identical twins performed at the Peter Bent Brigham Hospital by Dr Joseph Murray and his colleagues (Murray *et al.* 1955) was the herald of clinical organ transplantation, and now the shortage of donor organs is the chief stumbling block to further development. Unfortunately with this shortage a number of unexpected ethical worries have arisen like a 'can of worms'.

At the time of the historic operation in Boston there were two major problems confronting the would-be transplant surgeon. First, could the operation be done successfully surgically and, second, what kind of a rejection process would be an obstacle between individuals who are not identical twins?

2. THE SURGERY

The careful experiments on auto transplants of kidneys in Boston and elsewhere paved the way for the first successful clinical identical twin transplantation. The auto transplants provided the medical and surgical team with optimism that success should result, because

identical twins were biologically the same individual and accepted skin grafts without trouble, provided the skin graft was performed correctly surgically. The twin transplant confirmed the expectation that a young, healthy donor could survive with one kidney with no disability, provided the single kidney was not damaged, and in fact the donor of the first twin transplant is still alive more than 50 years later. The human kidney could be removed with preservation of its blood vessels and ureter, cooled to minimize the biological damage to be expected when a highly metabolic organ is deprived of its blood supply and then successfully transplanted into the iliac fossa of the recipient, rejoining the artery, vein and ureter to permit normal blood flow and drainage of urine. This achievement, which was quickly repeated in a number of other twin transplants, confirmed the surgical side of this operation.

Two other important observations were made. First, 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', Second, 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

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One contribution of 16 to a Theme Issue 'Immunoregulation: harnessing T cell biology for therapeutic benefit'.

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 (Gibson & Medawar 1943). 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* (Anderson *et al.* 1951). The definitive experiment, injecting cells from one inbred strain of mice into the foetus of another strain, resulted in graft acceptance in survivors of this procedure and raised the concept of a state of immunological plasticity in the embryo before the immune system is fully developed (Billingham *et al.* 1953). 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.

Elsewhere in this volume are two comprehensive reviews of current ideas on how to induce transplantation tolerance. First by Hale *et al.* (2005) in non-human primate preclinical models and then by Stuart Knechtle (2005) on clinical approaches.

The story of immunosuppression during the succeeding 50 years has had and still has this aim in view. Clinical immunological tolerance does occur when the recipient's immune system is destroyed and replaced by bone marrow from the donor, who must be a close match of tissue type, usually a human leucocyte antigen (HLA) identical sibling. Another interesting phenomenon has been the demonstration experimentally that a liver graft could induce tolerance, without any immunosuppressive therapy, the liver undergoing rejection which spontaneously recovered (Calne *et al.* 1969). In man this happy state is not achievable, but recipients of liver transplants after years of immunosuppression can sometimes stop the immunosuppression without penalty and have, therefore, developed 'operational immunological tolerance'. Other recipients of liver transplants are not so lucky and this phenomenon only seldom occurs in grafts of other organs.

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 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 calcineurin inhibitor instead of full dose of three drugs, which had been in common practice previously. There are likely to be many advances,

fine-tuning this approach, which we have called *prope* or almost tolerance (Calne *et al.* 1998). Perhaps in some patients eventually maintenance immunosuppression could be stopped, but we badly need a test of which patients can be safely managed in this way.

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 of all kinds and tumours, particularly lymphomas. A strategy of using different agents together to maximize immunosuppression and minimize 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, azathioprine 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.

3. CLINICAL OBSERVATIONS

The first organ to be transplanted successfully in the 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 10 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 transplantation has become very popular in North America, but less so elsewhere due to the serious complications that can occur following the operation from leakage of pancreatic juice. Recent immunosuppressive regimen avoiding corticosteroids have reduced complications, for example using Campath induction and FK506 maintenance.

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 (Shapiro *et al.* 2000). 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 the patients did not require insulin injections. This had fallen to about 75% at 2 years but deteriorated more quickly after that, being perhaps 50% at 5 years. The Edmonton programme was an important proof of principle 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 β 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 long periods in the liver in the absence of immunosuppression and autoimmune Type I diabetes (Farney *et al.* 1991).

In the future, hopefully, cells that do not 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 Reemtsma transplanted a kidney from a chimpanzee to a patient and the graft functioned for nearly 10 months (Reemtsma *et al.* 1964). The chimpanzee is now regarded 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. 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. 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 do not 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 (Wijkstrom *et al.* 2004).

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 utilized 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.

4. 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 provided 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 organize cadaveric organ donation, Spain, there is still considerable shortfall of donors compared with the 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 fully to understand 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 do not 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 heartbeating 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 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 h 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 among the most important challenges in organ transplantation for the future. A consequence of the success of the procedure!

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