Transplantation – Yesterday, Today and Tomorrow

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The concept of Transplantation started in the mists of time. Even before successful human transplantation became a reality, apocryphal accounts of transplantation were part of mythology. One of the first myths in transplantation has come from the Middle East-Saints Damian and Cosmas, two practising physicians in the 3rd century AD, possibly in the area now called Syria, replaced the gangrenous leg of the Roman deacon Justinian with the leg of a recently deceased Ethiopian. Most accounts have the saints performing the transplant in the fourth century, decades after their deaths; some accounts have them only instructing living surgeons who performed the procedure! Whether the transplant was a live donor or cadaveric is not absolutely clear although let us hope it was cadaveric! In this instance the nature of the transplant was obvious due to the colour difference between the donor and the recipient and has been depicted in paintings. There are other more reliable accounts of an Indian surgeon, Sushruta, using auto-grafted skin transplantation onto the nose for rhinoplasty in the 2nd century B.C. However, the first successful human transplant seems to be of the cornea performed by a surgeon Eduard Zim in Austria in 1905. Around this time Alexis Carrel, a surgeon from Lyon in France, experimented with joining blood vessels together and the apocryphal story is that he learnt the technique of suturing small vessels together from the techniques used by the lace makers of Lyon! Carrel refined the technique of anastomosis by using organ transplantation as the experimental model. He performed kidney auto-transplants and as allografts from animals within the same and different species. Whilst he was able to show that auto-grafts were successful, allografts invariably failed. He was unable to identify the cause of the failures, which we now know as rejected. His view was that this destructive process leading to kidney loss was insurmountable. Carrel received a Nobel Prize for his work in 1912 and could justifiably be considered the father of both vascular surgery and transplant surgery.

Attempts at clinical transplantation took place in the first half of the 20th century. Voronoy, a Russian surgeon, performed the first human kidney transplant in 1933 with a further five later but all failed. It was not until the 1940’s that Sir Peter Medawar, a zoologist by profession, who revealed the immunological basis of transplantation. Medawar was tasked by the Medical Research Council to understand why skin grafts, used to treat skin burn patients in the 2nd World War, invariably failed as allografts although successful as auto-grafts. This work led him to establish theories of transplantation immunity and, therefore, is the basis of subsequent attempts to control the immune response to enable successful clinical transplantation. Medawar duly received his Nobel Prize for medicine in 1960.

Early attempts at clinical renal transplantation took place in the 1950’s on the background of Peter Medawar’s research but the immunosuppression methods used were crude, primarily total body irradiation to suppress the bone marrow and cortisone, and patients often died of sepsis. Nevertheless, there was a huge fillip when the first successful live donor transplant was performed in Boston between identical twins. Clearly, since they were truly
identical twins, no immunosuppression was required. The transplant surgeon, Dr Joe Murray, who was a primarily a plastic surgeon, established the surgical technique which still pertains today. The success of this transplant gave rise to a flurry of transplant activity in worldwide.

Unfortunately, most of these attempts were unsuccessful since they were between individuals who were not identical and overwhelming sepsis led to death in most cases. Roy Calne was a young surgeon from Cambridge who was galvanised by the challenge of transplantation and undertook research in transplantation using drugs to inhibit the immune response. He, amongst others, was able to show that 6 mercaptopurine was able to prevent rejection in kidney transplants in dogs. However, this agent was poorly absorbed and it was the development of azathioprine, a pro-drug developed by Burroughs-Wellcome by Elion and Hitchings, which allowed much better absorption. Azathioprine was broken down in the liver to generate 6 mercaptopurine. Calne was able to show that this drug could prevent rejection in dogs and it was soon used in human transplantation.

Unfortunately, azathioprine was not entirely successful by itself and it was shown by another young surgeon, Dr Thomas Starzl, that steroids together with azathioprine was a much better immunosuppressive combination. This success then led onto a huge growth in renal transplantation particularly worldwide but also in other types of transplants, soon afterwards. Indeed, the first liver and lung transplants were performed in 1963 by Thomas Starzl and James Hardy respectively and in 1966 Richard Lillihei performed the first pancreatic transplantation. However, it was in 1967 that Christiaan Banard performed the first cardiac transplant and captured headlines in the media throughout the world. This development certainly raised the profile of transplantation amongst the general public but results in organs other than kidney were poor and liver and heart transplantation It was clear that acute rejection of the transplanted was continued in only a few centres whilst pancreatic transplantation ceased altogether.

The next major development and breakthrough came with the discovery of Ciclosporin A, derived from the soil fungus Tolypocladium inflatum by the Sandoz pharmaceutical company based in Switzerland. The company was looking for antibiotic properties of Ciclosporin A but a chemist, Jean Borel, found that, whilst it did not have any antibiotic properties, it did have immunosuppressive effects. Remarkably, it was Sir Roy Calne’s Unit in Cambridge where the first clinical use of the agent took place, substantiating immunosuppressive effects of Ciclosporin A in the clinical setting, leading onto the first international trial in 1980, comparing Ciclosporin A monotherapy with azathioprine and prednisolone. The trial published in 1983 confirmed the benefits of Ciclosporin therapy over the “conventional” immunosuppression, with a reduction in acute rejection episodes and improved graft survival, and a reduction in sepsis due to the fact that less steroid were used to combat acute rejection. These discoveries immediately led to a surge in many types of transplants worldwide. Now of course renal, liver, heart, pancreatic, heart/lung, and lung transplants are common place. Other transplants, such as small intestine and islet cells, are developing although not quite as successful as the other types of transplants. Happily, Elion and Hitchings, who developed azathioprine, received their Nobel Prize in 1988 and Joe Murray received his award in 1990.

Transplant Immunology

An understanding of clinical transplantation does require some knowledge of the immune basis of transplant rejection. The human leukocyte antigens, abbreviated to HLA, are on the surface of cells and help differentiate “self” cells from “non-self” cells which are foreign. The HLA antigens are proteins found on the surface of nucleated cells and are particularly in abundance on the surface of lymphocytes. Their main function is to help the immune system identify the cells of the individual from and defend against foreign invaders—bacteria, viruses and parasites. Clearly the immune system also recognizes the HLA antigens of non-identical cells of the transplant donor organ and, therefore, triggers the immune reaction causing rejection response.

There are several different HLA antigens but the most important ones for transplantation purposes are HLA-A, HLA-B, HLA-DR. These antigens are very “polymorphic” meaning there are many different forms of each of the different antigens due to slight differences in their amino acid structure of the proteins, leading to the heterogeneity which is the mean barrier to successful transplantation. Each person has 2 sets of chromosomes, 1 from each parent and,
therefore, 2 sets of HLA genes. There are thus 6 HLA genes (2 HLA-A, 2HLA-B, and 2 HLA-DR) that are normally matched for transplantation purposes. Results have shown that if the donor and recipient are HLA identical, there is better long term graft survival than if they are completely mismatched. Partial matched transplants survive for an intermediate period of time. Clearly identical twins have identical genetic material and have identical HLA antigens of all types, and hence no acute rejection occurs when transplants are performed in identical twin. However, even twin transplants fail due to non-immune reasons, e.g. recurrent disease as afflicted the first successful renal transplant recipient in 1954. Therefore, tissue typing remains important since it improves graft survival, although constantly efforts are being made to try to overcome the effects of HLA matching with better immunosuppression.

Transplant graft rejection occurs when the host immune cells, primarily T-lymphocytes, recognise mismatched HLA antigens on the cells of the transplanted organ. T-lymphocytes then initiate a cellular immune cascade that results in triggering graft rejection. The mismatched HLA antigens in the organ transplant are processed by cells called antigen presenting cells (APCs). The APCs then "present" the processed antigen on their cell surface with host HLA molecules to helper T-lymphocytes which then interact with the antigen presented through their own T-cell receptors.

The T-helper cell then orchestrates the immune response by proliferating and directing specific precursor cytotoxic T-lymphocytes to become activated and damage the transplant, and with B-lymphocytes to produce antibody. The T-helper cell is critical in orchestrating the immune response and is the cell that is affected and killed by the HIV AIDS virus, making such patients so susceptible to infection. The immunosuppressed state has common features with HIV AIDS in that both conditions lead to increased infection and cancer risk.

The association of HLA matching and graft survival has been shown repeatedly by national and international registries. Although HLA identical transplants survive the longest and complete mismatched transplant survive the least longest, nevertheless, even a 6/6 HLA antigen mismatch gives approximately gives approximately 45% 10 year kidney allograft survival in first cadaveric renal transplants, so is of considerable benefit.

**Immunosuppression**

As stated already, controlling the immune response of transplant recipients is a prerequisite to successful long term transplant survival. The immunosuppressive agents now available help to control the immune response, and there are others being tested in the laboratory of the pharmaceutical industry or in clinical trials. However, the availability of so many immunosuppressive agents creates a problem by itself– how best and in what combination should we use these powerful but dangerous drugs to suppress the immune response and yet avoid the inevitable complications of them?

Once the T-helper cell binds to the foreign HLA antigen peptide presented by the APCs, a series of events take place within the cell which leads to secretion of interleukin 2 (IL-2) which then stimulates growth and differentiation of specific cytotoxic T-cells. It is with this mechanism of either the production of or the effects of IL-2 that most immunosuppressive drugs are associated, since this is a critical step in the initiation of acute rejection. However, because of the multiplicity of drugs it is difficult to know which is the best combination, or whether a combination of drugs should be used or, indeed, only one drug as a single agent. As immunosuppressive drugs have become more powerful, acute rejection rates are certainly reducing and more transplants survive the initial high risk period immediately after the transplant and go onto long-term graft survival.

The critical facet of immunosuppression is that the clinician is trying to balance the risks and side effects of the drugs with their benefits. The benefits are clearly preventing acute graft rejection episodes and maintaining long term graft survival but these have to be counterbalanced by and set against the risks of increased rates of infection, cancer and drugs side effects. Infections of all kinds are increased after transplantation and may be different for different organs. For example chest infection organisms are more prevalent after lung transplantation and urinary tract organisms more common after kidney transplantation. The rate of infection is loosely paralleled with the degree of immunosuppression used. All types of infection- viruses, bacterial, fungal and protozoan infections are increased after transplantation. In Africa, malaria and TB are
additional significant risks. The herpes viruses are a highly successful group of viruses which cause morbidity and occasionally mortality after transplantation. One herpes virus, the cytomegalovirus (CMV) is a particular risk after all forms of transplantation, particularly if the recipient has not had CMV infection him/herself and gets an organ from a donor who has had. With the advent of ganciclovir, specific and effective treatment for CMV is currently available.

A second important risk is cancer and it is thought that patients have at least 3 times greater risk of developing malignancy after transplantation compared to the general population. The commonest cancers are skin cancers – squamous cell carcinoma is the highest risk followed by basal cell carcinoma and melanoma the least. Lymphoma is a serious and often fatal cancer following transplantation. Interestingly, Kaposi’s sarcoma has relatively high instance after transplantation (although still very rare) and this cancer is also common in patients with HIV AIDS. The risk of cancer is cumulative so the longer the transplant is in place the greater the risk.

There are also specific drug side-effects. For example, ciclosporin and tacrolimus, which act in a similar way, are nephrotoxic, a significant hazard after all transplants, i.e. the drugs can effect native kidney function in patients who have heart or liver transplants, and careful monitoring of drug levels is required. Renal transplantation for patients with ciclosporin nephrotoxicity is not uncommon. Azathioprine and mycophenolate mofetil suppress the bone marrow, giving rise to anaemia, leucopenia or thrombocytopenia.

Results of Transplantation

The number of transplants performed down between 1985 and 2005 were reported to the collaborative transplant study run by Gerhard Opelz, based in Heidelberg. Therefore, these are not complete worldwide figure but mainly reflect European and North American practice. The commonest form of transplantation is the kidney with over a quarter of a million transplants performed in the 20 year period, followed by liver, heart, lung, pancreas and heart/lung. Small bowel and islet cell transplantation remain uncommon. Looking at the survival for each of these organs, the same pattern can be discerned, an initial decline in the first 3 months or so followed by a slower rate of decline over the next 10 or 20 years. The initial decline is mainly due to loss from acute rejection, technical factors or acute infection. The long-term decline is due to slow chronic damage to the organ despite the use of immunosuppression. The chronic loss, which in kidney is called “chronic allograft nephropathy”, is almost irreversible. Manipulation of the immunosuppression regime can sometimes alter the slope of this rate of decline but it rarely reverses it. Much of the focus of current research is trying to address this slow chronic loss of solid organ transplants but no answer has yet been found.

What is clear from the figures is that well matched transplants do better than poorly matched transplants for both live donor and cadaveric. However, live donor transplants do in general better, even though poorly matched, even than the best matched cadaveric transplants. The reason for this is unclear but in general live donor kidney usually have better function, have minimal period of storage before being transplanted and are performed electively so there is probably less technical loss, and the recipient can be made medically fit towards a specific date in the future for their transplant. Therefore, there is great emphasis now in the West to push live donor transplantation. Clearly in the East this is the only form of transplantation available but there is comfort in the knowledge that the outcome is better in any event.

Why Transplantation?

Clearly in organ failure such as in liver, cardiac and lung failure, there are no other options available since there is no equivalent of chronic dialysis. However, diabetics can be fully maintained on insulin with transplantation and patient’s can survive long term on dialysis. Therefore, the next section will focus on the benefits of transplantation in the latter two groups.

Treatment Options for Patients with Renal Failure

The two options for patients with established renal failure are dialysis, peritoneal or haemodialysis, and transplantation, cadaveric or live donor. The reason why renal transplantation is the better treatment for patients compared to dialysis is that a kidney transplant replaces fully the organ which is
diseased and therefore it is a more physiological treatment for renal failure. There quality of life after a transplant is better because the patient is not tied to performing dialysis and there is reasonable evidence that patient survival is better with transplantation compared to dialysis. Lastly, certainly transplantation is much more cost-effective. A renal transplant provides an organ that works throughout the day and night, with better blood pressure control and constant homeostasis with a better acid-base balance, there is no or relatively limited fluid restriction the organ secretes erythropoietin and generally no exogenous erythropoietin is needed to be prescribed and finally the kidney hydroxylates Vitamin D. In terms of quality of life there is no fluid or dietary restriction other than that encouraged to provide general good health, there is no restriction in movement in terms of holidaying. In terms of patient survival the key element is that cardiovascular mortality remains high in all patients with renal failure. However, once the transplant is successful the mortality rate at all ages for renal transplant is less than that on dialysis. Finally, transplant costs for the first year are equivalent or slightly more than the cost of dialysis taken into account comprehensive costs in the first year. After the first year, however, transplantation costs essentially are the costs of immunosuppression only and the cost of visits to doctors as outpatients. Therefore, any country which wishes to provide the best form of renal replacement therapy at the best economic cost, must choose renal transplantation.

Clearly, for diabetics in renal failure renal transplantation is the answer for the reasons alluded to above. However, why pancreatic transplantation in addition to kidney transplant? The available evidence suggests that those diabetic patients in renal failure who get a combined transplant live longer with a better quality of life than those who have a renal transplant only. There is greater morbidity and mortality associated with a combined kidney and pancreas transplant within the first 6 to 12 months compared to kidney transplant alone, but thereafter, the mortality risk is lower.

Live Donor or Cadaveric Renal Transplantation?

As alluded to above, live donor renal transplantation has many benefits—the quality of the kidney is usually better (especially now that many of our cadaveric donors are elderly in the West), the operation can be scheduled for optimum time for the recipient's health, technical problems (such as multiple renal arteries) can be anticipated and dealt with appropriately and usually the age of the live donors is younger. In addition, live donor transplantation can be performed with a minimal infrastructure whereas cadaveric transplantation has a requirement for the government and the people to accept “brain stem death” criteria. This acceptance will depend on the cultural views of the general population. Also, there are considerable infrastructural-development of intensive care/neurosurgical units to provide the donors, transplant coordinators to help secure donation, and surgical team to retrieve the organs. Despite great efforts using publicity and education over the past 30 to 40 years, cadaveric donation rates have decreased in the West. Therefore, cadaveric transplantation is something that may be possible in the future in sub-Saharan Africa but not at present. For Africa, live donation will be able to be achieved more quickly, it is a more cost-effective method of developing transplantation, it secures the best outcome for patients and it requires minimal support in terms of dialysis compared to a cadaveric programme.

The surgical operation

Transplant operations are vascular operations. All solid organs require an arterial and a venous anastomosis. Clearly renal transplants require plumbing of the ureter into the bladder but this is a relatively straightforward procedure which can be performed by trained surgeons and not necessarily require the skills of a urological surgeon. Therefore, training in vascular surgery is very helpful, particularly in the West where many of our recipients have heavily calcified and diseased iliac arteries onto which the donor vessels need to be anastomosed. Worldwide, urological surgeons probably perform more renal transplants than vascular or general surgeons but any surgeon who is trained appropriately can develop the skills to perform renal transplantation.

For cadaveric programmes a patch of aorta is taken with the renal artery and aortic patches are anastomosed to the iliac vessels. In live donation, this is not possible and the renal artery(s) are thus anastomosed to the external iliac artery. In general the external iliac arteries are used as the inflow vessels and the external iliac vein as the outflow vessels for the kidneys. Because the iliac vessels are very close to the bladder, only a short segment of ureter need be
anastomosed to the bladder, thereby avoiding the risks of ischemia with a long segment of ureter.

The Challenges in Setting up Renal Failure Surfaces in East Africa

One of the major questions regarding renal failure sub-Saharan Africa is how prevalent is renal failure? There has been no substantial epidemiological work performed thus far although some work has been done in Ghana by Dwomoa Adu, consultant nephrologist in Birmingham, and co-workers have shown that 42.8% of cases presenting to a government run polyclinic had renal dysfunction. Also, it is known that African Americans have 3 to 4 times the prevalence of renal failure compared to the indigenous white population. Clearly there are major differences between East Africans and African Americans, certainly the diets are very different, nevertheless, it is likely that there will be a high prevalence of renal failure in East Africa. The cause of renal failure in Africans is thought to be hypertension primarily followed by glomerulonephritis, diabetes and obstructive uropathy. Thus, there is a need for renal services. Nevertheless, more work needs to be done to define the extent of the need.

Previous discussions have explained why a transplant service would be the better medium through which renal failure services could be provided, although some degree of dialysis to support such a programme would be necessary. To start a transplant programme, a “team” of surgeon(s), nephrologist(s), anaesthetist(s) and good nursing support are necessary. As mentioned, surgical techniques are standard and well within the capacity of general or urological surgeons to undertake. Surgeons could spend a time abroad or a surgeon from abroad could be attracted to spend time in East Africa training other surgeons. There are already physicians with an interest in nephrology although again some additional training may be necessary. Anaesthetic techniques are now very standard for managing patients who require transplantation and so should not be a great challenge for anaesthetists in Africa. Nurses will need training in dialysis and the requirements of supporting transplant patients and allowing nurses sometime in a Western dialysis/transplant unit might be useful.

There are other requirements for a fully fledged transplant programme—good radiology to detect pre- and post-transplant problems, particularly using colour flow duplex ultrasound. CT and peripheral angiography are already available in many centres. Since infection is such a major problem after transplantation, a good microbiological service is essential. Urinary tract infection is very common, CMV infection, the problems associated with Hepatitis B and Hepatitis C are more common in Africa. Indeed, the donor and recipient have to be screened for these conditions. Again TB and malaria will be significant risk following transplantation.

Drug costs will inevitably be a major issue for patients in East Africa since patients have to pay for drug costs themselves. Modern immunosuppressive drugs costs are significant but it may be that Western drug companies may provide some subsidy to reduce costs. One important aspect, however, is essential—the monitoring of drug levels of the calcineurin inhibitors Ciclosporin or tacrolimus to avoid nephrotoxicity. There are ways of keeping drug levels down using multiple drug therapy and that may be one way around the problem. Generic drugs are available from India and these may be cheaper than from the major pharmaceutical companies in the West. There are also cheap drugs that could be prescribed, azathioprine and prednisolone. Using one of the calcineurin inhibitors for the first 3 to 6 months in combination with azathioprine and prednisolone and then weaning them off the calcineurin inhibitor slowly over a 3 month period may be a simple way of addressing drugs costs.

Good support from pathology in order that diagnosis of acute rejection can be made, is advisable. Facilities to detect chronic allograft nephropathy, recurrent disease or drug nephrotoxicity are also required. Finally, whilst ABO blood group compatibility is all that is required for live donation programme, long-term tissue typing laboratory facility will be necessary.

Currently the only country to provide renal transplantation is Kenya although in only relatively small numbers. East African countries require other surgical developments and prioritization needs to be balanced for the need. There remain manpower and training issues and provision of long term care which is necessary after transplantation, economic challenges in terms of drugs costs. However, patients from East Africa do go abroad for renal transplantation, which involves a loss of foreign
exchange, and sometimes the results are indifferent. Therefore, a case can be made for renal transplantation to be developed in East Africa despite the costs. One possibility is to centralize development to one COSECSA country thus avoiding multiple developments all at once. Once this single centre was up and running and adequate numbers of transplants were being performed (at least 100 per year) then surgeons, nephrologists and other professionals from other countries could be gradually trained thus keeping costs down and yet disseminating experience. The other countries could then develop their own programme as and when conditions and the economy allow in each country.

Cleary there are huge challenges within East Africa – HIV AIDS, malaria, TB, adequate provision for basic healthcare. There will be some who feel that the latter require addressing before high-tech procedures such as renal transplantation should be started. However, this is narrow view of progress. Developments in all aspects of healthcare need to be made whilst at the same addressing the basic needs.

The future of transplantation

The future development in transplantation will be just as remarkable as the first 50 years. The past 50 years has been a gradual but progressive improvement in outcome for patients with renal failure and for those with other organ diseases. In the future greater success is likely with developments in drug therapy and even the development possibly of “tolerance”, abrogating the need for immunosuppressant, the holy grail of transplantation. However, the long term goal will be to prevent renal disease or to repair damaged kidneys with possibly stem cell transplantation thereby avoiding the need for transplantation at all.

Conclusion

Live donor kidney transplantation is a viable option for East Africa. However, government support is mandatory if this to be made available on a large scale. Economic development is the key to improving prospects for healthcare for the countries as a whole and is the key to progress in East Africa.

Thank you.