

Transplantation: developments and ethics

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The second article in our special feature discusses developments in transplantation, focusing on the sources of organs. Comments on some of the ethical issues that arise, with both established procedures and new technologies, are also made

Liver transplant operation: a diseased liver is being removed from the patient (lower frame) while two surgeons prepare the healthy donor liver (top right)

Surgical techniques for transplantation were established as far back as the early 1900s by Alexis Carrel.¹ However, any transplants carried out at this time were invariably unsuccessful because no attention was paid to the phenomenon of “wretched immunology” (a phrase coined by the pioneering British transplant surgeon, Sir Roy Calne), so the graft was rejected. Once the effects of the recipient’s immune response on a “foreign” donor organ were better

appreciated, the way was open for transplants between identical twins. The first successful live transplant, a kidney, was performed on the 24th December 1954 in Boston.² Other renal transplants, all with identical twin donors, followed.

This work was expanded with the establishment of tissue typing techniques, which allowed organs to be transplanted from donors whose tissue was well matched with the recipients, but who were not necessarily their identical twin.³ However it was not until immunosuppressive drugs became available that transplantation could really develop and therefore evolve from a largely

experimental solution to the preferred treatment option for certain diseases.

The development of transplantation has itself introduced further problems. In particular, there is now an increased demand for transplants, which has led to a donor shortage (see Figure 1, p209). This has been further compounded by a reduced supply of donor organs owing to fewer deaths from road accidents and from neurosurgical procedures. There has also been a worrying increase in the proportion of relatives declining consent as a result of adverse publicity. To address the shortage of donor organs a number of initiatives are being

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explored and encouraged by the United Kingdom Transplant group (UKT), with government funding. These principally include the development and expansion of “live” and “non-heart beating” donation. Other more experimental solutions, such as trans-species transplantation and growing organs from stem cells may also be considered in the future.

LIVE DONATION

With the surety of a normal life with one kidney, live donor programmes offered a solution to renal failure within families. Using organs from living people has advantages over using organs from cadavers. In particular, the donor and recipient can be prepared in adjacent theatres, so that the donor organ has minimal cold ischaemia (ie, ischaemia caused by the organ being outside the body).

The minimal period of cold ischaemia means that the organ requires minimal reperfusion, resulting in the best long-term outcomes. It also means that the endothelium of the organ remains intact, and therefore provides a physical barrier to migrating recipient macrophages that would otherwise move freely through the donor organ and recognise it as “foreign”. The presence of this barrier helps facilitate donation between genetically unrelated people, for example, spouses. Live transplants between unrelated people, are particularly valuable where there is a genetic aetiology to renal failure, such as with polycystic kidney disease. They are also necessary if a family has dispersed or become estranged, or if a

potential family donor is medically frail. As a note of caution however it should be mentioned that there are still no data from registries demonstrating that maximally mismatched kidneys have the same outcome as well matched kidneys whether they are from live or cadaveric donors.

New initiatives to encourage more live donors to volunteer include the use of the “laparoscopic donor nephrectomy” procedure. This technique involves the removal of the kidney by “keyhole” surgery — the vessels are clipped or stapled and the kidney removed through a separate 6cm incision usually in the lower abdomen. This approach produces less post-operative pain in the donor and recovery is much faster. In the United States, units which offer this technique have increased their transplant numbers quite significantly, although this increase is made up largely of donors and recipients moving from units that do not have laparoscopic donation. In the United Kingdom this situation is being mirrored in three units offering this service at present. Bone marrow can also be taken from live donors, after tissue matching. A key advantage is that bone marrow can be removed from the same donor on more than one occasion.

In some countries, such as Japan and India, where there are moral constraints on cadaveric donation, live donation is the only acceptable form of transplantation. In these countries, live donors are considered as a source of organs that would normally only be available from cadavers. The best example is in liver transplantation, where live transplantation began as left lobe grafts from

parents to children, then extended to left lobes from adults to adults, and finally to right lobes from adults to adults. In addition, lung transplants are being explored for live donation but, in this situation, more than one donor is usually required, each providing a lobe of a lung. Live donors have also been used to provide portions of a pancreas. Such developments should always be explored with caution due to the not inconsiderable risk to the healthy donor.⁴

NON-HEART BEATING DONATION

If live donation is not possible, organs from young brain dead donors are generally considered to be the next best option. However, with the reduction in the number of young people being killed in road accidents, transplant units now consider using organs from medically more “marginal” donors, such as the very old and the very young. The categories of “marginal” donors have now also extended to include people whose heart has stopped beating. Historically, organs from such donors were commonly used in the days before brain stem death legislation was in place, since there then had to be a full cardiac arrest before the patient could be certified dead.

Using organs from donors whose heart has stopped beating is not ideal, because they are damaged to at least some extent by warm ischaemia (caused by the organ being in the body after the heart has stopped pumping blood). For heart transplantation in particular, only hearts that have been artificially stopped by cardioplegia can be reliably restarted after transplantation, so non-heart

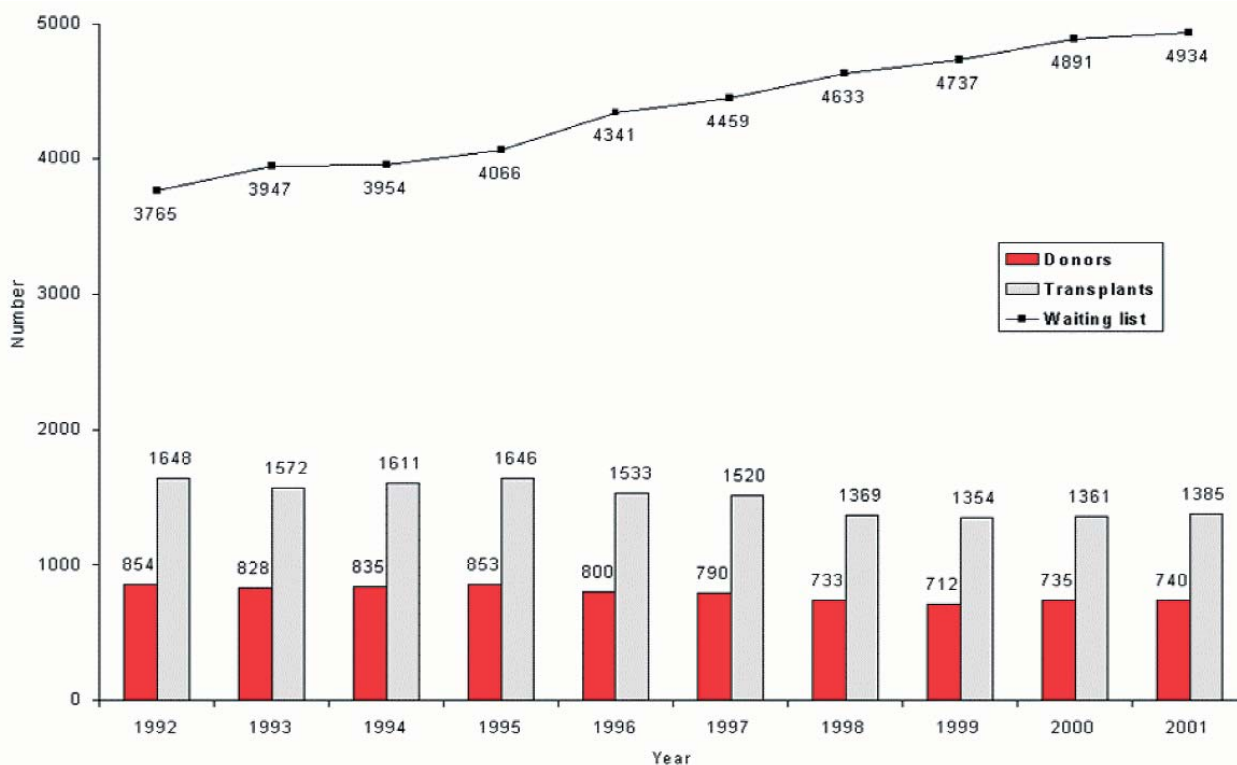


Figure 1: Transplant and donor numbers over time in the UK, by courtesy of UKT

beating donation is not a viable option. In the case of liver transplantation, the graft has to function immediately or the patient will die. Therefore to use a liver from a non heart beating donor which has already been damaged by ischaemia carries a significant risk.⁵

Progress in this area has largely come from a more educated selection of the donor organs involved. Non heart beating donors are divided into “controlled” (categories III and IV) and “uncontrolled” (categories I and II), according to the “Maastricht classification” of donors, with a newer category V sitting somewhere between⁶ (see Table 1). Broadly speaking, organs from those donors in the controlled group have a predictably short period of warm ischaemia, and therefore have a good chance of working immediately without delayed graft function. Hence lungs, pancreases and livers, as well as kidneys, can be used from “controlled” donors.

Organs from “uncontrolled” donors are likely to have sustained a longer period of warm ischaemia, resulting at best in delayed graft function and at worst in the organ never working (“primary non-function”). This means that “uncontrolled” donors can not be used as a source of lungs or livers, but they can potentially be used for kidneys, where a period of delayed graft function can be managed, providing kidneys that will eventually work can be distinguished from those that will never work. Different centres have their own approach to making this distinction, with some being successful with visual inspection and others using machine perfusion and enzyme analysis.⁷ After transplantation, serial biopsies are needed to confirm that resolution of the acute tubular necrosis has occurred and that there is no acute rejection.

Organs that have sustained a period of warm ischaemia will have accumulated lactic acid. Such organs tolerate prolonged

cold ischaemia poorly and have to be transplanted within 24 hours otherwise primary non-function is likely. However, the results of transplants using non-heart beating donors are similar to those from cadaveric donors, provided the kidneys have been carefully selected. If such donors were used in a more widespread fashion, it has been estimated that total transplant numbers could be increased by between 10 and 40

Table 1: Maastricht classification of donors

Category I	Dead on arrival
Category II	Unsuccessful resuscitation
Category III	Awaiting cardiac arrest
Category IV	Cardiac arrest in brain dead donor
Category V	Sudden cardiac arrest in a hospitalised patient

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per cent.⁸ Such an expansion in transplant numbers, if combined with a significant increase in live donation, could go a long way to addressing the current shortage in donor organs.

— XENOTRANSPLANTATION

Inert and sterile tissue grafts from animals, such as heart valves and vessel conduits, are now routinely used in surgical procedures. Using solid organ grafts from animals in humans (xenotransplantation) is slowly becoming possible.

The problems associated with the immune system of the recipient recognising the donor organ as foreign are compounded in trans-species transplantation by the potential involvement of the complement system. Activation of complement can result in hyperacute rejection (the loss of the graft within minutes due to intravascular thrombosis).

Where there is a close genetic relationship (ie, a concordant relationship) between the two species involved, such as between chimpanzee and man, the complement system in the recipient is only activated if the recipient has antibodies to the donor. Since the recipient does not usually have such antibodies, the graft is not normally lost by hyperacute rejection. Where there is a more distant genetic relationship (ie, a “discordant” relationship) between the two species involved, such as between pig and man⁹ complement is activated by the phylogenetically older alternate pathway (which does not require the formation of an antigen-antibody complex), resulting in hyperacute rejection.

Although transplantation of a chimpanzee kidney into a human was carried out by Reemstma as far back as 1964,² it is now generally considered morally repugnant to use chimpanzees as donors, and so animals with discordant relationships to humans have had to be considered, particularly the

pig. The problem of complement activation was rectified initially by inserting human complement control molecules on the pig cell surface.¹⁰ This allowed transplantation of organs from pigs to baboons. The organs did not undergo hyperacute rejection, but they failed later due to acute rejection.

It is believed that porcine cells have now been developed at the Roslin Institute, Edinburgh, which are deficient in the major target of complement namely a glycoprotein called aGAL. Work is also thought to be under way to create a strain of pigs with this deficiency, and then replicate them by clonal expansion. In effect, this work is essentially converting a discordant relationship into a concordant one, thereby potentially avoiding the problems of hyperacute rejection.

— OTHER SOURCES

In future, it might be possible to “make” organs, for example, in a laboratory. Joints

modelled from “man-made” material have been manufactured and implanted into man for some time now. Implants of biosynthetic structures, for example, an ear with a cartilaginous core, or a phalanx with a bony metaphysis, cartilagenous diaphyses and a tendon insertion, are still experimental. The structures generally consist of a polyglycan mesh which is seeded with chondroblasts or osteoblasts. The chondroblasts and osteoblasts ultimately replace the polyglycan mesh with cartilage or bone.

It is unlikely that such technology could be used to develop solid organs, due to the difficult nature of developing a suitable blood supply to allow transplantation. For such structures, the use of organ progenitor cells (stem cells) to allow a normal organ to be grown might be possible. The organ would probably need to be grown in another host species and then harvested for use. This raises two further issues: how to transplant across species and how to replicate the valuable donor source reliably.

ETHICAL ISSUES

During each phase of transplantation development different ethical dilemmas have arisen. Some issues were present at the first successful transplant and are still relevant now. Other issues are the result of much more recent advances in technology.

The ethics involved in using healthy living donors as a source of organs have been around since the beginning of transplantation, and are still not resolved.

Giving financial reward to donors is generally considered unethical in western societies, due to the possibility of the potential donor being exploited by middle men. However, in countries which have the death penalty, such as China, it may be reasonable to offset the funeral expenses of the condemned by allowing the body to be used as a donor after death. But this raises further issues if the organs are to be exported to a country where the death penalty is not used.

There are concerns about putting a healthy donor at risk by carrying out a surgical procedure that is unnecessary for their own health. This raises an issue of whether the donor should be recompensed if they are damaged by the operation, whether they should be eligible for sick leave, and who should bear the cost of any insurance cover.

Withdrawing ventilatory or ionotropic support from category III non heart beating donors is also controversial. If the decision to withdraw support is made independently of donation, then there are few ethical implications, but if the donor is kept supported until the donor team can attend, then the situation becomes more morally complex.

Regarding the new technologies, there are animal rights issues associated with trans-species transplantation. There are also safety

concerns about bringing animal retroviruses into humans.

Stem cells can potentially be harvested from adults, from umbilical cord blood, or from embryos. Harvesting stem cells from embryos is particularly controversial, especially if cloning is used to create the embryos. The recent case concerning the screening of embryos to assess them for their likely suitability as donors of umbilical cord blood to a sibling has also sparked concern among some.¹¹

CONCLUSION

The shortage of donor organs is being addressed by increasing the number of live donations, mainly by changing surgical practice in favour of laparoscopic techniques. Cadaveric donation rates are being increased by using non-heart beating donors. Grafts from genetically modified xenodonors, potentially propagated by cloning, still have some way to go in development. Using stem cells to grow human organs is still very much in its infancy.

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