Xenotransplantation: Do we have an alternative?

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Recent advances in technology have made the possibility of xenotransplantation becoming a routine procedure a distinct reality in the next couple of years. This news does not bode well with all parties and has reopened the issues and controversies surrounding xenotransplantation which were last hotly debated in the case of Baby Fae over a decade ago. Recent television current affairs programmes in the UK such as Panorama have sought to disentangle the multitude of complex issues. However no clear solution has become apparent. The debates around xenotransplantation have been limited as they have not engaged with those involved with alternative human procurement programmes. These have been structured with the presumption that xenotransplantation is the only viable long-term solution. This may not be so and could be wherein lies the answer to the shortage of organs for transplantation.

Under current procurement arrangements, the use of cadaveric donors and living donors is not going to ensure a large enough supply of organs, especially in cases of kidney and heart disease. In the UK, there are over 6,000 people waiting for a suitable organ for transplantation. While in the US, only a quarter of the estimated 100,000 people awaiting transplant are likely to receive a new organ. The UK and the US currently employ what might broadly be termed an 'opting-in' legal system. Other countries which operate under a similar statute are Germany, the Netherlands, Italy, Canada, Australia and New Zealand. This system relies upon voluntarism and is seen in practice with the use of donor cards and the recently introduced British NHS Organ Donor Register. Other procurement programmes which have been implemented throughout the world with varying success are presumed

1 United Kingdom Transplant Support Service Authority, Human organ information sheet (UKTSSA Publicity Services, Bristol, 1997)
consent (also known as opting-out), elective ventilation, non-heart beating donor, routine enquiry, and required request. These will be explained below. The most recent and radical solution to reduce the scarcity in organs is the development of xenotransplantation - the use of animal organs for transplant.

Xenotransplantation

The early 60s saw the first breakthrough in xenotransplantation when a patient survived nine months with a kidney from a chimpanzee. Five other patients who underwent the same procedure died within days. Liver transplantation was also attempted from chimpanzee to human but was unsuccessful. In the early 80s a baboon heart was transplanted into a baby girl known as ‘Baby Fae’, this unfortunately also failed after 20 days.³

The most recent development has been the use of a pig as a donor. The pig has been identified as being a suitable organ donor on size and anatomical grounds. Research is being carried out in Cambridge, England and New Jersey, US, where it is hoped the strong human immunological response to foreign tissue can be overcome with genetically altered pigs. The idea is to trick the human immunological response into thinking the pig's heart is its own.⁴ The justification for such work is that if it is morally defensible to use animals for food then using them as a potential supply of organs is acceptable.

Clearly, this solution and reasoning is controversial and raises some ethical issues. One of the main questions that needs to be addressed is whether the ethical issues involved in the breeding of animals for food and those involved in the breeding of animals for organs are the same. I would argue that the issues involved are separate and should be considered on their own merits. The acceptability of one practice does not necessarily legitimise the other. The debate about breeding animals for food is a hotly contested area in Britain today and it arouses strong emotions. Surely, neither practice is necessary for human health and survival as alternative options are available.

Others have argued that whilst it is generally believed to be morally acceptable to kill animals for food, this is under circumstances which offer us alternatives. No one has to eat pork to survive - on the contrary, it would often be much cheaper and healthier to rely on other sources of sustenance. With organs for transplantation, however, particularly hearts and livers, there is no alternative for a significant proportion of people who would otherwise die. Under these circumstances, those who wish to deny the use of animal organs for transplantation must provide even more compelling arguments than those who would wish to deny their use for food.5

The UK has a multi-faith population and it is important to recognise the views of different religious groups. For some religions, certain animals are considered sacred, thus organs from these animals would be unacceptable. For example, in Hinduism the cow is sacred whereas for Jews and Muslims the pig is considered unclean.

Medical concerns should also be paramount with the problems of hyperacute rejection and the spread of new diseases in humans still to be overcome. As mentioned previously, the Cambridge research team have made progress in the former area by using genetically altered pigs but are still struggling to come to terms with the latter issue. The research into transfer of diseases from one species to another is well documented. Common examples include influenza viruses which have their origins in pigs, ducks, and chickens which act as reservoirs for the diseases. Most worrying of all, is research in Central Africa which suggests that AIDS resulted from a transfer of the monkey virus into humans.6

The financial gains from xenotransplantation are most considerable and may well impede scientists from taking an objective approach when considering the ethics of such a procedure. Large pharmaceutical companies such as Novartis and Imutran in Europe and Alexion and Nextran in the US, are investing millions of pounds into xenotransplantation research. Projected profits from xenotransplantation could reach as much as US$5 billion in 2010.7 Those who support xenotransplantation need to be clear whether their interests are altruistic or financially motivated.

7 Ibid.
In 1996, the UK's Department of Health set up an Advisory Group on the Ethics of Xenotransplantation. Their recent findings have indicated that xenotransplantation is permissible on ethical grounds but there are still some medical concerns that need to be researched further.\(^8\) The Nuffield Council on Bioethics has also considered the issue and raised no objection.\(^9\) However, careful scrutiny of the membership of these advisory groups is required as was highlighted in the case of Bovine Spongiform Encephalopathy (BSE) investigation. Some governmental advisers had a vested stake in the treatment and eradication of BSE thus it was unclear whose interests were really being met by their recommendations.\(^10\) Those with connections with pharmaceutical companies and surgical teams involved in xenotransplantation may also find it difficult to offer an impartial opinion.

With the risk of a variety of diseases spreading into humans coupled with the ethics of xenotransplantation, further consideration should be given to the alternative procurement programmes.

**Alternative procurement arrangements**

*Opting-in* - The opting-in system operates with the use of donor cards and more recently the British NHS Organ Donor Register. For this system to have a direct impact, either a donor card must be found on the body of the deceased at or shortly after the time of death, or, the deceased person's name should be on the Organ Donor Register. The Register is accessible to each of the Transplant Co-ordinators who are able to check the Register first, each time they have a potential donor to consider. This register is aimed at providing a more efficient method of discovering whether a deceased person wanted to donate their organs.

In March 1996, the British Department of Health launched a national publicity campaign encouraging people to sign up for the Organ Donor Register. Full page advertisements were placed in national newspapers and prime-time television advertising was used. These measures,

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however, are going to have little impact unless the issue of disseminating information is addressed more closely.\textsuperscript{11}

These efforts made are most commendable but have done little to overcome the problem of targeting those individuals who are against donation. Increased card carrying or joining the Donor Register among those who already support donation is likely to have little impact on the donation rate as their families are more likely to consent to donation. The underlying problem which really needs to be addressed, is to achieve card carrying or signing on the Donor Register by those members of the public whose families would otherwise have refused consent.\textsuperscript{12}

\textit{Presumed Consent} - A presumed consent law presumes that an individual has consented to organ donation at the time of death unless there is contrary documentary evidence or, in some countries, objections by the family.\textsuperscript{13} Assuming that the commitment of society is strong toward donation and that the public trusts the concept and application of brain death, this system should theoretically reduce the donor shortage drastically. It would also require involved professionals to identify those who could be donors, and an efficient organ procurement and distribution network.

Presumed consent schemes have been introduced into many countries (Austria, Belgium, Finland, France, Italy, Norway, Spain, and Sweden) and also Singapore, although attempts to enact such legislation in the UK have always failed. 'Opting-out' was debated in Parliament in February 1984, and it was proposed that people would be considered to be prospective donors unless an objection was recorded - a wish to 'opt-out'. There would be no need to consult the next of kin. The proposal was criticised as an infringement of personal liberty, people became concerned as to the inaccuracy of records, and this opposition, not least in the form of letters to Members of Parliament, led to the shelving of the plan.\textsuperscript{14} The latest attempt to legalise 'opting-out', the Transplantation of Human Organs Bill in 1993, also failed for similar reasons.

\textsuperscript{12} New et al, ‘A question of give and take’.
\textsuperscript{13} Ibid.
In practice, it is the case that in most countries with presumed consent, transplant teams will not proceed until the family is contacted and agrees, even though it is not required by law.\textsuperscript{15}

In the UK at present, public policy relies upon voluntarism, and is seen in practice with the use of donor cards and the NHS Organ Donor Register. The rights of the next of kin to make decisions on behalf of the deceased are still recognised. This reliance upon voluntarism is exemplified by the practice of blood donation in the UK which is frequently cited as an example of public generosity.\textsuperscript{16}

\textit{Elective ventilation} - Over half of the organ donors in the UK are as a result of intracranial deaths which have occurred in the Intensive Care Unit (ICU).\textsuperscript{17} However, not all intracranial deaths occur in the ICU; some occur in general wards. These patients could also be potential organ donors if transferred to the ICU. Patients would then be artificially ventilated to preserve the organs until brain-stem death can be established.

A protocol for electively ventilating patients has been developed in Exeter. This has proved to be most successful, initial predictions showing an increase in donors of 50\%.\textsuperscript{18}

There are drawbacks to this procedure, the main being that there is a risk of patients falling into a persistent vegetative state. Also at present, the law relating to consent is a hindrance to this procedure. Elective ventilation benefits the organ recipient not the patient. For such practice, patient consent would be required but this is not possible as the donor would be comatose before ventilation was even considered.\textsuperscript{19} Such obstacles need to be resolved soon if this procedure is to produce a regular supply of organs. A recent report by the British Transplant Society has recommended legislation to overcome these concerns.\textsuperscript{20} Large-scale clinical trials are planned in order to effectively

\textsuperscript{15} New et al, ‘A question of give and take’.
\textsuperscript{16} Ibid.
\textsuperscript{17} Ibid.
evaluate the potential of elective ventilation. A rigorous ethical protocol will need to be in place before such an initiative could commence.

**Non-heart beating donor** - This procedure has proved to be very successful in the Netherlands.\(^{21}\) The number of transplanted kidneys rose by 21% over a 9-year period. In the UK (Leicester) also, over a one year period 38% of all transplanted kidneys resulted from non-heart beating donors.\(^{22}\) The non-heart beating donor involves donors who have not reached brain-stem death. The kidneys are cooled before explantation by means of the insertion of an irrigation tube into the cadaver so that the kidneys can be protected by cold perfusion until the relatives can be found and donation requested. This procedure allows those who suffer a fatal cardiac arrest, for example, to nevertheless donate their kidneys.\(^{23}\)

Success in Holland and Leicester has been attributed to transplant surgeons, co-ordinators, and Intensive Care Unit staff all being located on one site.\(^{24}\) This will not be the case in all large hospitals and thus the success of non-heart beating donors may be limited.

The overriding concern with such a procedure is that in order to cool the kidneys a tube is inserted into the cadaver before permission for organ donation is obtained. This constitutes invasive surgery solely for the purpose of obtaining organs. Such a concern is also pertinent in the case of presumed consent.

**Routine Enquiry** - It has been alleged that the differences between the public's inclination to donate and the number of donated organs is explained by the reluctance of involved professionals to donate.\(^{25}\) Routine enquiry seeks to redress this and is used extensively in the US. The Uniform Anatomical Gift Act 1987, which forms the model for many state statutes, makes provision for routine enquiry. This initiative

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aims to take advantage of the inclination of the public to donate as demonstrated in the polls. It requires the involved professionals to enquire of family members regarding the donor status of those who have achieved, or are about to achieve, the definition of brain death.

Routine enquiry has become legislation in eighteen states. Indeed, the US Congress has made the implementation of routine enquiry policies a condition of payment under their health insurance schemes (Medicare and Medicaid), and the Joint Commission on the Accreditation of Healthcare Organisations requires this as a condition of certification. Routine enquiry has become legislation in eighteen states. Indeed, the US Congress has made the implementation of routine enquiry policies a condition of payment under their health insurance schemes (Medicare and Medicaid), and the Joint Commission on the Accreditation of Healthcare Organisations requires this as a condition of certification. Thus, if routine enquiry policy is not followed, the health insurance schemes become invalid.

Required Request - Required request involves hospitals asking each person they admit about their donor status. The procedure of required request is very active in the US. The development of required request policies by hospitals was encouraged by the Omnibus (Budget) Reconciliation Act 1986. This Act provides that failure on the part of hospitals to adopt required request policies will lead to the denial of Medicare and Medicaid reimbursements from the Health Care Finance Authority, as is the case for routine enquiry. Twenty six US states have this type of policy. It has even been suggested that the institutions make this request in outpatients clinics, emergency rooms, etc., and that doctors make the request in their offices.

In the UK required request was considered in the late eighties by the Department of Health and Social Security, but was rejected in favour of a policy involving better information concerning donation and an extension of the donor card system. Nevertheless, it could be argued that required request might be one way of closing the gap between voluntary donors and patients requiring organs. One estimate in the US suggests that whilst 200,000 persons are declared brain dead each year, organs are only harvested from 2,000, whilst the combined need for hearts, lungs, and kidneys, is estimated at 50,000 or more. In the UK there are an estimated 2,300 cases where brainstem criteria determine death, which could alleviate some of the pressure from the waiting transplant lists.

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26 New et al, ‘A question of give and take’.
27 Ibid.
28 Schwartz, ‘Bioethical and legal considerations in increasing the supply of transplantable organs’.
While there was an initial increase over time in the number of procured organs, neither routine enquiry nor required request appear to have had a major impact.30 One reason for this, it is suggested, is the lack of institutional commitment to ensuring that the required request procedures are followed.31 The US experience illustrates that simply to enact required request legislation is not enough. It is vital to have adequately trained and qualified personnel.32

Routine enquiry and required request may not be working because the real problem in organ procurement is not legal but psychological.33 Medical professionals worry about their legal liability in the organ procurement process; they also find organ procurement time consuming and emotionally demanding.34 Some commentators advocate better professional education to help implement the policy.35 Others suggest a policy of 'routine referral' that would require hospitals to report potential donors at the time of admission to the ICU.36

Upon review, it seems that all of the systems of organ procurement are at present unsatisfactory. Xenotransplantation is a contentious issue which raises serious ethical and moral concerns. The British Advisory Group on the ethics of xenotransplantation has made recommendations for a National Working Party on Xenotransplantation.37 There is no doubt that if appropriate measures were taken the supply of organs through the existing programme could be markedly increased. Routine salvaging, with presumed consent, might risk overriding an individual's deeply felt objection to post-mortem donation, whilst the operation of a veto by relatives may frustrate a genuine desire to become a donor. In fact none of the systems in practice today can guarantee that an individual's wishes will be respected. The wishes of the donor card holder may be frustrated because no one looked for the card, or the family concealed the fact that one was held. A system of presumed

30 New et al, ‘A question of give and take’.
31 McDonald, ‘Organ donation, new issues, new controversies’.
32 Randhawa, ‘Improving the supply of organ donors in the UK’.
consent might go into operation before it is known that the individual did not wish to donate. Elective ventilation and the use of non-heart beating donors are fraught with ethical dilemmas. Additionally, any major shift in policy would require new laws and regulations to be enacted and accepted by politicians and the general public. This, of course, would involve implementing an effective information campaign which would come across major difficulties as with the previous donor card campaigns.

If the voluntary system is to be maintained, measures need to be taken to attract more voluntary donors. Proposals now in force in the UK include provisions for individuals to express consent to organ donation on their driving licence, or to register as a donor when they apply for a new licence. There is also a need for better information about the mechanics of brainstem death in nursing and medical courses.

There is a need too for further investigation into reasons why potential organ sources are not adequately used. Intensive care units are potential sources but many patients who might be donors do not get into the units. Some doctors prefer to care for some dying on the wards and do not want them started on positive pressure ventilation. This is legitimate, and therapy should not be directed with extrinsic interests in mind; however, it gives rise to the problem that patients not on ventilators cannot be suitable donors.

It is argued that the most important factor is the difficulty some doctors feel in approaching relatives whose only interest (as is theirs) is in the survival of the potential donor. There is no doubt that the most important determinant of the frequency of organ donation is the willingness of medical and nursing staff caring for potential donors to initiate this process and to undertake the considerable extra work that this entails.

Conclusion

At present, public policy relies upon voluntarism with any attempt to shift from this being rebuffed in previous years. The British NHS Organ

Donor Register has been set up consisting of names of donors who have given express consent. Every Transplant Co-ordinator has instant access to this register. To avoid incorrect readings on the register and to allow opportunity to revoke a decision, individuals should be regularly contacted, by letter, to reaffirm (or reconsider) their status.

If the donor register proves to be successful, one would see a marked reduction of transplant waiting lists. For those patients requiring a kidney transplant, a reduction in the number of patients on dialysis would also occur. This in the long run would be very cost-effective saving millions of pounds each year as the cost of a transplant is cheaper than maintaining a patient on a dialysis machine. As a general rule the cost of a successful transplant plus one year of post-operative therapy amounts to less than the cost of one year of the cheapest form of chronic dialysis. After the first year of post-operative therapy, the costs are negligible.\(^{40}\)

Xenotransplantation in Britain should not go ahead until the existing organ procurement programme is reviewed and the possibility of introducing other human organ procurement programmes which are used currently in some other countries explored. Has our society not reached a point of sophistication where we should be aiming to cease using animals altogether? There should be increased liaison between transplant communities throughout the world to discuss the experiences of various procurement programmes. Previous attempts to change legislation may have failed but with the prospect of xenotransplantation, there may well be a 'change of heart'.

**Biography**

_Gurch Randhawa is an active researcher and writer of policy analysis in the area of organ donation and transplantation. He was Project Director of a study (supported with a grant from the King's Fund) exploring the knowledge of and attitudes towards organ donation and transplantation among the Asian communities which has recently been completed._

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\(^{40}\) **Conference of European Health Ministers, Ethical and socio-cultural problems raised by organ transplantation** (Council of Europe, Paris, 1987).