ORGAN TRANSPLANTATION

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GLOSSARY

Allotransplant (allograft) – organ from one person donated to another person.

Anastomosis – a natural connection between two tubular structures, such as blood vessels. Also the surgical union of two hollow organs or parts that are normally separate.

Autotransplant – tissue or organ from oneself (e.g. skin graft).

Asystole – arrest of the action of the heart.

CAPD – Continuous Ambulatory Peritoneal Dialysis.

Collins' solution – preservation fluid originally devised for kidneys, now used for other organs. Comprised of glucose and phosphates.

Cystic fibrosis – a disorder of the mucus-secreting glands of the lungs, pancreas, mouth, gastro-intestinal tract and the sweat glands of the skin.

Dilated cardiomyopathy – enlargement of the heart resulting from stretching of the muscular walls due to weakening of the myocardium.

Dialysis – the process of separating the soluble crystalloid substances from the colloids in a mixture by means of dialyser, the principle upon which the artificial kidney works.

EDTA – European Dialysis and Transplant Association.

Epidemiology – the prevalence and incidence of the condition under study.

EPO – erythropoietin.

Haemodialysis – dialysis when the patient's blood is used, as in kidney dialysis, is known as haemodialysis.

Haemostasis – arrest of bleeding.

HLA – Human Leucocyte Antigens.

Heterotopic transplantation – organ transplanted to an artificial site.

Hyperglycaemia – excess of glucose in the blood, the condition accompanying diabetes mellitus.

Hypertension – high blood pressure.

Hypotension – low blood pressure.

Immunosuppression – drugs used to suppress the immune system in order to discourage rejection of a transplanted organ.

Infarction – the changes which take place in an organ when an artery is suddenly blocked, leading to the formation of a dense mass in the part of the organ supplied by the artery.

Ischaemia – bloodlessness of a part of the body due to contraction, spasm, constriction or blocking of the arteries.

Ischaemia time – time an organ is kept in a state of ischaemia.

Ischaemic heart disease – ischaemia resulting from disease of the coronary arteries, thus also known as coronary artery disease.

Nephrotoxicity – toxicity adversely affecting the kidneys.

Normoglycaemia (euglycaemia) – normal blood glucose levels.

Orthotopic transplantation – organ transplanted to its natural site.

QALY – Quality adjusted life year.

'UW' solution – preservation fluid developed at Wisconsin University. Its formulation includes lactobionic acid, raffinose and various electrolytes.

Xenotransplant (xenograft) – organ donated by one species and transplanted into another (e.g. primate to human).

INTRODUCTION

Organ transplantation is one of the most spectacular medical achievements of this century. The first successful human transplant operation took place in Boston, in 1954, when a single kidney was transplanted between identical twins (Murray *et al*, 1955). Subsequent improvements in surgical techniques, organ preservation, immunosuppressive therapy and life-support technology have made transplantation one of the most rapidly growing areas of modern surgical practice.

Operations that only a decade ago were regarded as high-risk, high-cost, experimental procedures are now accepted as a valuable part of the surgeons' repertoire. Organ rejection has been reduced dramatically with the introduction of new immunosuppressive drugs, notably cyclosporin, so that longevity and quality of life after transplantation are constantly improving.

Cyclosporin has been credited with huge improvements in kidney transplantation and the transition of heart and liver transplants from experimental to effective therapy. As a result organ transplantation is becoming the favoured procedure in many circumstances, leading to a situation where demand for donor organs exceeds their supply. Attempts to overcome this problem have involved efforts to develop an artificial heart and the possibility of transplantation of organs from animals to humans.

Transplantation challenges ethical precepts, but traditionally such reservations have taken a back seat to the temptations and incentives to perform innovative operations. Now, however, the ethical issues are being widely discussed. Quite apart from the well publicised scandals involving the sale of donor organs, problems have arisen in the conceptual foundations of the 'brain death' criterion.

This paper aims to deal exclusively with solid organ transplantation, namely, heart, lung, liver, kidney and pancreas, while recognizing the omission of the important area of tissue transplants, concerning bone, bone marrow, cornea, skin and heart valves. The OHE believe that the area of solid organ transplantation deserves detailed examination in the context of important resource allocation since it already absorbs a large amount from NHS funds.

DONOR ORGANS: THE BALANCE OF SUPPLY AND DEMAND

Sources

Organs for transplantation can come from several sources. Kidneys, and segments from the liver and pancreas can be procured from live donors and all organs can emanate from ventilated cadavers, that is 'brain dead' donors (see Box 1). Kidneys can also come from non-breathing cadavers. Artificial or mechanical alternatives are available for kidneys in the form of dialysis and an artificial permanently implantable heart may be viable by the end of this decade. Organs from animals are another possible alternative, which may, in the future, lessen the need for human donors.

As a result of increasingly successful transplants demand for donor organs continues to rise. The highest growth in demand is for heart and heart-lung transplantation. The waiting time is now up to seven months for a heart-lung transplant, with about a quarter of those on the waiting list dying before the operation can take place.

Since the 1950s voluntarism and informed consent have served as moral guidelines governing the procurement of organs. However, with the emergence of transplant operations as a viable procedure, voluntary organ donation became insufficient to ensure the necessary supply. Countries such as France, Denmark, Sweden, Austria, Switzerland, and Israel consequently adopted presumed consent policies, whereby physicians can take required tissues and organs unless either the deceased carries a card to prohibit this, or the next of kin object. Other countries, such as Britain, have viewed such policies as too coercive with the potential to violate individual rights, and hence have adopted a 'softer' approach to organ procurement.

Supply

The donor supply shortage with respect to the UK is illustrated by the figures in Table 1. These show the number of transplants for 1989 reported to the United Kingdom Transplant Service and the waiting list for transplants at 13 January 1991.

It should be noted that these figures refer exclusively to operations carried out within the NHS and are reliant on the transplant centres providing accurate and reliable data.

It is often difficult to predict the size of the pool of potential organ donors because it can vary with time and place. The most common source of donor organs is from individuals dying from cerebral trauma, often as a result of a road traffic accident. (Other causes include intracranial haemorrhage, respiratory arrest and primary

BOX 1 Brain Death

Cadaver organ donors are almost always 'brain dead', being maintained on ventilators. During the past decade irreversible loss of all brain function has become accepted as a definition of death. Acceptance of this criterion has been influenced by the following factors:

1. Diagnosis of irreversible loss of all brain function is clinically practical and should be completely reliable.

2. These patients never regain consciousness – they suffer cardiovascular collapse and asystole within hours, days or rarely weeks.

3. Brain dead patients are the only source of hearts, lungs, and whole livers and the main source of kidneys.

The results of various surveys, however, suggest that health professionals involved in organ retrieval are not always able to distinguish between brain death and other states where the patient is not dead by any accepted definition of death (e.g. a persistent vegetative state). There is, thus, a need for greater consensus on a concept of death, otherwise there may only be further confusion and perhaps resistance to organ donation.

Wikler and Weisband (1989) argue that brain death is not being misdiagnosed, but that the problems lie in the conceptual foundations of the whole-brain definition. Though clinicians can tell which patients have permanent loss of all brain function, there is no consensus over whether or why this means they have died. They claim that defenders of the whole-brain definition have yet to make a convincing case for equating loss of all brain function with the end of life. However, the fact that it is irreversible and that patients will never regain consciousness would seem sufficient reason to many to equate brain death with the end of life.

Youngner *et al* (1985) say that little attention has been paid to the disturbing effects of organ retrieval on staff members in intensive care units. They claim staff members are concerned that organ donors are not dead, despite the declaration of brain death. By ignoring such concerns they believe that we may unwittingly magnify societal resistance to organ donation. Organ donors have total and irreversible loss of integrative and cognitive brain functions but their cells, tissues, organs, and organ systems remain alive – albeit with various support mechanisms. Family members are often less intellectually and emotionally prepared to accept death in the face of so much apparent life. Intensive-care personnel, themselves, may feel confused about having to resuscitate a patient declared dead. To minimize problems Youngner and associates suggest:

1. Provide education so that all relevant staff know that human death and brain death are synonymous and stress the positive aspects of organ transplants, e.g. feedback concerning healthy recipients.

2. Protect vulnerable and inexperienced staff from the organ donation process and do not force staff to take part in it.

3. The body of the deceased should be cleaned and covered so that relatives can see the person at peace – rather than leaving the body in an undignified and disrespectful state.

Table 1 **Organ donor supply shortage**

Organ transplanted	*Transplant operations in 1989*	*Waiting list at 13.1.91*
Hearts	295†	234
Heart-lung	94	224
Lungs	39	75
Livers	295	54
Pancreas	9	5
Kidneys	1854*	3804‡

† includes 32 'domino' procedures (i.e. where the patient is both a recipient and a donor).
* includes 122 kidneys from living donors.
‡ includes 15 awaiting a kidney and pancreas transplant.

brain tumour). However, taking an international perspective, the head injury death rate in Britain per million population is less than half that of most European countries, North America and Australia. In addition the incidence of fatal head injuries per million population has been slowly falling in most countries. These factors together conspire to exacerbate the shortage of donor organs in the UK.

Organ supply and the USA

The United Network for Organ Sharing (UNOS) provide data showing that 4,059 people died while awaiting an organ transplant between January 1988 and March 1990, in the USA. 'The shortage of donor organs was primarily responsible for needless death.' (Peters, 1991) Throughout 1990 there were over 20,000 people on the organ transplant waiting list. In February 1990 22,340 people were on the waiting list; just over 18,000 of these requiring a kidney. During 1989 there were 8,905 kidney transplants performed in the USA; nearly 2,000 of these from living-related donors. Peters (1991) suggests that organ supply has reached a steady level with no increase in the number of donors during the past three years. Thus, organ supply appears to be the main constraining factor in many developed nations' transplant programmes.

Obtaining consent

Organ supply is the major limiting factor in organ transplantation. However, nearly a half of potential donors do not become actual donors, the most important reason being the refusal by relatives to use the deceased's organs. Occasionally, relatives are not even approached; although this is rare, it is an important problem when organs are in such short supply.

Wallwork (1989) argues that the style and professionalism of the approach towards the relatives is paramount. He believes refusals could be avoided by adopting a sensitive and professional technique. In contrast, Gentleman *et al* (1990) suggest that refusers may be the minority who are unwilling to donate organs for transplantation so consent may not be particularly dependent on the commitment and persuasiveness of the requester. However, a confidential audit of all deaths in intensive care units in England initiated by the Department of Health, indicated a 30 per cent refusal rate by relatives for organ donation, and a further six per cent where organ donation was not discussed with the family of a potential donor. Gore *et al* (1991) found a similar proportion of refusals and non-discussions, and claimed that the number of donor hearts could have been doubled over the six month period they studied. They estimated that the organ suitability from brain dead potential donors in intensive care units was 63 per cent for hearts, 95 per cent for kidneys, 70 per cent for livers and 29 per cent for lungs.

The shortage of donor organs does not seem to arise from a public distaste for the very idea of organ donation. In fact, a Gallup poll for the British Kidney Patient Association, quoted in the Guardian (9-5-90), found that 73 per cent of respondents would agree to their kidneys being used for transplantation, although only 27 per cent actually had a donor card and only seven per cent were carrying one on them at the time.

The purchase of organs from live donors has occurred as an extreme method of attempting to increase organ supply. The 1990 Human Organ Transplant Bill made it a criminal offence to be involved in payment for the supply of transplant organs with a £2,000 maximum fine. The aforementioned Gallup poll found that only five per cent of the general public agreed with the idea of buying and selling kidneys from live donors. Thus, any defence of the purchase of organs would go against both civil law and public opinion.

Medical considerations

Medical management of the organ donor has received relatively little attention in the past. However, early donor recognition, rapid diagnosis of brain death and maintenance of physiological haemostasis before and after brain death are essential components for ensuring a maximum supply of optimally functioning donor organs for transplantation. Complications that result from neglect of routine general care of potential donors can lead to needless rejection of organs and tissues that were otherwise suitable for transplants.

Patients who are brain dead or expected to progress to brain death can be considered potential multi-organ donors until excluded.

Increased organ supply through multi-organ donation from a single donor is rising, but there are wide regional variations. The survey by Gentleman *et al* (1990) of a Glasgow neurological unit found that 16 of the 24 consents in 1989 were for multiple organ donations, but in only half the cases were organs other than the kidneys used. The reasons for this apparent wastage are manifold. Short ischaemia time and distance between the donor hospitals and transplant centres are bound to cause logistical problems. Some cadavers are deemed medically unsuitable to donate organs, commonly due to infection, malignancy, and other advanced disease. However, some that were considered unsuitable by their doctors may have been accepted by the transplant team. Many became unsuitable due to hypotension – with more vigorous medical support fewer may have reached this stage.

Surveys in England and at the Glasgow unit have shown that 26 per cent of patients identified as possibly brain dead were not tested for brain death, although in Glasgow half of these either had medical contraindications to donation or asystole occurred before testing could take place. Prolonging ventilation to maintain potential donor organs in good condition raises ethical and resource issues. Gentleman *et al* found that in patients where ventilation was stopped before death because of a hopeless prognosis only 12 per cent had a contraindication to donation. Many anaesthetists and nurses are not prepared to ventilate such patients with the specific intention of providing donor organs. They are reluctant to embark on major intervention with no prospect of helping the patient. This was the view of staff in Glasgow, although it is not the policy followed in all hospitals.

Bodek (1989), has suggested the requirement that donor hearts be entirely free from disease is too idealistic and impractical in the current medical era. Donor hearts with minimal heart disease are better than no hearts at all, he believes, and argues for broadening the criteria to include, for instance, previous infarction or single coronary vessel disease.

Increasing the proportion of kidneys from live donors is a potential method of reducing the transplant waiting lists in the UK where, in 1984, the figure was only 12 per cent. In addition Newstead (1989) suggests that the UK may benefit from following the Dutch example of harvesting organs from cadavers following cardiac arrest. The Dutch report the same graft survival at one, two, and three years in kidneys harvested from non-heart-beating donors and brain dead (heart-beating) donors. Newstead claims that the chances of a patient with end-stage renal failure being offered a kidney transplant would improve about five-fold if such a system were adopted here.

Roels *et al* (1990), on behalf of the Leuven Collaborative Group for

Transplantation, reported on 423 primary cadaveric kidney grafts in nondiabetic adults, performed consecutively between February 1983 and June 1989. Patients were divided into three groups according to donor age. Firstly, those under 30, secondly, those 30-49 years, and finally, those 50 or over. The study did not reveal any negative impact of donor age on patient or graft survival. The authors concluded that older recipients should be transplanted preferentially with kidneys from elderly donors. Donors over the age of 50 years could contribute significantly to the pool of available kidneys.

Prospects for the future

Various ideas and strategies have been suggested to increase the availability of organs. By the late 1990s, for example, heart transplant patients may have a choice from at least four different artificial hearts expected to cost between $30-50,000 each. The National Heart, Lung, and Blood Institute, at Bethesda, Maryland, has awarded separate contracts worth over $5.5 million for the development of a permanent wholly implantable artificial heart. The artificial heart is currently only seen as a bridge until a suitable donor can be found.

Research and interest is also being focused on transplants from animals to humans giving the prospect of organs of reliable quality being available in bulk. However, the ferocious organ rejection associated with this type of procedure must be overcome for this to be a realistic possibility.

Until recently the mainstay of liver preservation was cold storage in Collins solution for periods of up to eight hours. Increased preservation times have been reported using 'UW' solution at the University of Wisconsin Medical Center. This has raised flexibility in working hours and reduced the need for very close co-operation between the donor and recipient surgical teams. Cryobiology – the science of freezing tissues and organs at extremely low temperatures without damaging their structure or function – may hold considerable potential for increasing the supply of donor organs. However, the Medical Research Council is to stop funding its Cambridge based cryobiology group; this action is seen by some as denying any UK chance of advancement in long-term organ preservation. The cryobiology group leader, Dr David Pegg, defended the work of his team saying it had contributed to an American technique for preserving livers four times longer than previously possible. An organ and tissue bank had also been planned for the group's laboratory.

In conclusion, organ shortage may be reduced by various methods, although it will probably always remain a limiting factor. Certainly, at present the available organs must be used as efficiently as possible.

THE IMPACT OF CYCLOSPORIN

Background

The success of organ transplants is limited primarily by rejection of the allograft – the grafted organ from another person. The immunological nature of allograft rejection was demonstrated as early as 1943 by Gibson and Medawar, and by the early 1950s Medawar's group had shown that the immune system could be modulated to prevent rejection, bringing about prolonged skin graft survival in experimental animals. This work laid the foundations for the development of immunosuppressive therapy.

The discovery of cyclosporin constituted a landmark in the history of organ transplantation. Rejection of a foreign body is one of the normal protective functions of the immune system and is essential for the maintenance of the integrity of the body. Cyclosporin is an immunosuppressive agent able to prevent the immunological reactions associated with organ transplants, that would otherwise lead to organ rejection. There is no doubt that the introduction of cyclosporin has improved transplant graft survival and thus has been an essential factor in the expansion of transplantation during the past decade. It has been so effective in suppressing the human immune response against allografts of all types that it became nick-named 'the magic bullet'.

Cyclosporin, derived from a fungus extract, was discovered in the Microbiology Department of Sandoz Ltd in Basel (Switzerland) in 1970. The earliest clinical study was conducted by Sir Roy Calne and associates at Addenbrooke's Hospital, Cambridge in 1978. Cyclosporin was found to significantly improve survival following kidney transplantation. Subsequently both liver and heart-lung transplants have become a clinical reality through the use of cyclosporin.

Cyclosporin is probably the most powerful of the available drugs for preventing rejection, with the best risk-benefit ratio. Nephrotoxicity is the major problem associated with cyclosporin. However, initial concern about delayed severe kidney damage and extreme hypertension were largely alleviated by the gradual recognition that even with major reductions in dosage cyclosporin could still provide excellent immunosuppression during the post-transplant months.

All modern protocols of immunosuppression now include cyclosporin. Most transplant centres have evolved protocols using various combinations of drugs to reduce adverse drug reactions while maintaining improved graft and patient survival. Cyclosporin is often used in combination with prednisone and/or azathioprine which permits a more flexible immunosuppressive regimen and minimises

complications, while maintaining adequate overall immunosuppression.

Cost

First *et al* (1989) point out that treatment with cyclosporin improves the survival of transplant patients, but at a financial cost. The annual cost of conventional immunosuppression was $1,000-2,000 per patient, with cyclosporin added this figure became $5,000-8,000. In 1988 in the USA use of cyclosporin added $105.2 million to the cost of immunosuppressive treatment, while the additional cost in 1991 is estimated at $245.8 million. First and associates reported on the use of cyclosporin with ketoconazole in renal transplant patients. The combination was not toxic and the cyclosporin dosage could be reduced significantly while still maintaining effective immunosuppression. Within six months of starting ketoconazole therapy the cyclosporin dosage was reduced by nearly 80 per cent and in those patients followed up for one year the reduction was up to 84 per cent of the original level. Since ketaconazole co-administration is not restricted to renal transplant therapy, such a scheme adopted nationally within the USA would produce a potential saving of over $100 million per annum for all solid organ transplants.

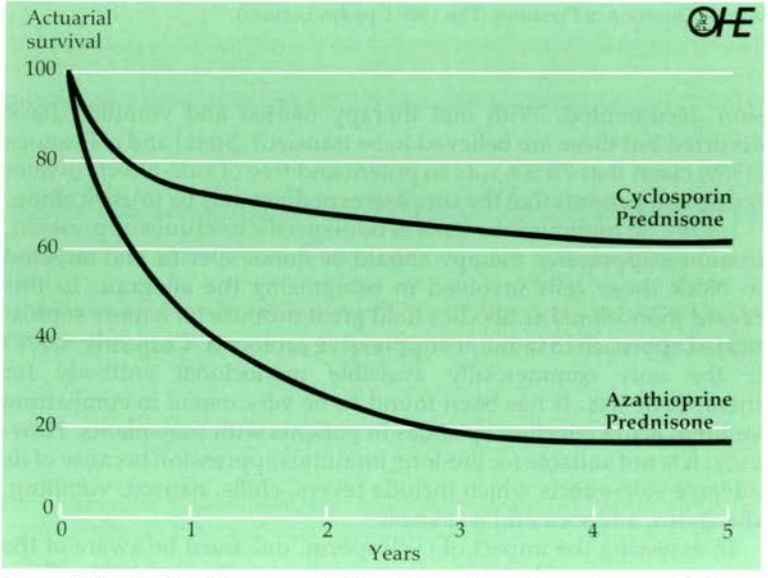
Huisman *et al* (1989) undertook a retrospective analysis of primary renal transplants between 1979 and 1988, to examine the effects of previous pregnancies on outcome following conventional immunosuppressive treatment compared with cyclosporin. One hundred and thirty-eight patients had received azathioprine and prednisone as immunosuppressive therapy between 1979 and 1982 and 274 had received cyclosporin (1983-88). The overall five-year graft survival rate was 56 per cent for those on 'conventional' earlier immunosuppressive therapy and 66 per cent for those on cyclosporin. However, the survival rates of women who had never been pregnant and men did not differ between treatments, with a combined rate of 62 per cent. For women with previous pregnancies the figures were 37 per cent for those on conventional therapy and 77 per cent for those on cyclosporin. Huisman and associates therefore suggested that, in primary renal transplants, cyclosporin be restricted to women with previous pregnancies. They claim this would improve cost-effectiveness without adversely affecting five-year graft survival figures. It would be interesting if subsequent research were able to confirm these findings, since there may be important cost implications if cyclosporin were to be exclusively reserved for women who have been pregnant. Such action, however, may not necessarily improve cost-effectiveness, since it has been demonstrated that the effects of cyclosporin usage are reflected

in shorter postoperative stays and a reduction in the use of certain ancillary services. A study at the University of California, San Francisco, suggests that the use of cyclosporin is associated with substantially lower costs for transplantation, compared with previous immunosuppressants (Showstack *et al*, 1989). Thus, while cyclosporin undoubtedly increased expenditure on immunosuppression, it may be related to a reduction in the overall costs of transplantation.

Research issues

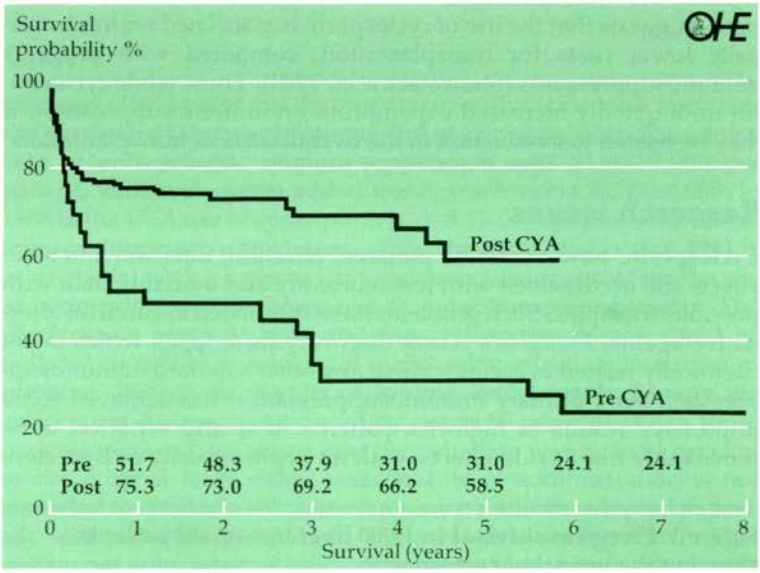
Cyclosporin, however, is no panacea; rejection, infection and side-effects still occur, albeit with less morbidity and mortality than with previous therapies. Such problems have stimulated a search for alternative agents. FK506 is a recent discovery from Japan which is not chemically related to cyclosporin or any other standard immunosuppressant. As a primary immunosuppressant it has achieved some impressive results in high-risk patients. It is also reported to be remarkably free of side-effects, with no nephrotoxicity or hyperten-

Figure 1 **Five-year survival in 1,000 liver transplant patients showing the impact of cyclosporin**



Source: Rolles K (1989) Summary of Clinical Data: Liver Transplantation In: Brent L and Sells R (Ed) Organ Transplantation: Current Clinical and Immunological Concepts.

Figure 2 **Papworth Hospital: Cardiac Transplant Patient Survival**



Source: English TAH (1988) Heart Transplantation and the National Health Service: A Question of Priorities (The 1988 Upjohn Lecture).

sion documented. With oral therapy nausea and vomiting have occurred but these are believed to be transient. Starzl and colleagues (1989) claim that FK506 was so potent and free of side-effects in liver transplant patients that the simplest expedient may be to use it alone.

Ideally, to minimise the risks of non-specific immunosuppression, immunosuppressive therapy should be donor specific and targeted to block those cells involved in recognizing the allograft. In this regard monoclonal antibodies hold great promise for a more sophisticated approach to immunosuppressive protocols. Currently, OKT3 is the only commercially available monoclonal antibody for therapeutic use. It has been found to be very useful in combatting sudden, acute rejection episodes in patients with transplants. However, it is not suitable for life-long immunosuppression because of its adverse side-effects which include fevers, chills, nausea, vomiting, diarrhoea, anorexia and weakness.

In assessing the impact of cyclosporin, one must be aware of the situation in the field of transplantation during the mid-1970s. There was at that time relatively little progress in transplantation, and the discipline was in a clinical and experimental doldrums. Results had

failed to improve and there seemed to be little that offered promise for the future. However, Calne's findings using cyclosporin in renal transplants provided the impetus necessary to renew enthusiasm. Cyclosporin transformed heart and liver transplants from experimental to effective therapy (see Figures 1 and 2) and aided increased success with kidney transplants. It provided an environment where heart-lung transplants could realistically be considered and improved pancreas transplant results. Whilst being aware of the shortcomings of cyclosporin – and hoping for far more sophisticated immunosuppressants in the future – one must also recognise the huge part cyclosporin has played in the growth of organ transplantation. The next generation of immunosuppressants must aspire to surmount the overwhelming problem of reduced resistance to infection, experienced in current practice, and also the cancer and ischaemic heart disease related directly or indirectly to immunosuppression.

KIDNEY TRANSPLANTATION

The kidneys, a pair of organs situated close to the spine in the upper part of the abdomen, constantly filter waste substances from the blood. They also regulate the volume and composition of the body fluids and produce a number of hormones, principally erythropoietin which stimulates the bone marrow to produce red cells. Kidney or renal failure leads to a build-up of waste substances in the blood; the resulting general 'poisoning' produces the clinical condition known as 'uraemia'.

Epidemiology of renal failure

Estimates of the incidence of chronic renal failure in the UK and other industrialised nations often exclude people with coincident diseases and ignore older people altogether. Selective estimates of about 40 new cases per million population per annum would increase by around 10 if all persons under 60 years old with co-existing diseases were included. If those over 60 years were also included (regardless of any other factors) the figure could reach 150 cases per million population per annum. Up to 100 new patients per million population could probably benefit from renal replacement therapy each year.

The Renal Association sponsored studies into the rate of preventable death from renal failure. Their findings suggest that a target of 75-80 new patients per million population for kidney transplantation would be an appropriate figure – nearly double the target set in 1987 for treating new patients in England and Wales. The UK Transplant Co-ordinators Association suggest that each year over 2,500 people develop chronic renal failure (about 50 per million population per annum).

Regionally, the incidence of chronic renal failure will vary depending on the make up of the local community. Those areas with many elderly people can expect a higher incidence than those areas with few elderly residents. Feest *et al* (1990) found an incidence of over 500 per million population per annum in those over 70 years, more than eight times greater than amongst those aged 20-49 years. It should, of course, be noted that many over 70 years old will have contraindications to transplantation. Melia *et al* (1991) also point out that the ethnic make up of the community will have an effect. An area with a high proportion of Afro-caribbeans can expect a high incidence of renal failure; for example, Camberwell was found to have a rate of 123.5 per million population per annum.

History of kidney transplants

The first successful experimental organ transplant was reported by Ullman in 1902. He managed to autotransplant a dog kidney from its normal position to the vessels of the neck. Later that year another doctor who, like Ullman, was based in Vienna, carried out a dog-to-dog kidney transplant. Jaboulay and his assistants in Lyon enacted the first recorded human kidney transplant in 1906. They completed two xenograft kidney transplants using a pig and a goat as donors, transplanting to the arm or thigh of the recipients with chronic renal failure, both of whom died within one hour of transplantation.

The first human kidney allograft transplant took place in the Ukraine in 1933 (Voronay, 1936). There was a major blood group mismatch and the patient died two days later. By 1949 this pioneering Soviet surgeon had effected six such operations without success, after which there was little new work until the revival of interest in the 1950s.

A Dane, Morten Simonsen, following on from the work of Medawar, reported on the mechanism of kidney rejection in 1953. Dempster, in London, re-examined this question in the same year. Both concluded that an immunological mechanism was responsible for failure, and also that the pelvic position of the kidney was preferable to a superficial site. Dempster discovered that radiation treatment delayed rejection.

Surgeons in Paris and London restarted human kidney transplants around this time. The Paris series included the first live related kidney transplant, the donor being the mother of a boy whose solitary kidney had been damaged in a road accident.[1] The kidney functioned immediately but was rejected abruptly on the twenty second day post-transplant.

Since no sustained function had been achieved, interest was beginning to wane when, on 23rd December 1954 in Boston, the first successful kidney transplant was performed. This, in fact, was the first successful human organ transplant of any kind with the donor and recipient being identical twins. The recipient eventually died eight years later from myocardial infarction.

The early attempts in Paris and Boston (from 1959-62) had used total body irradiation as an immunosuppressant. Sir Roy Calne, then a registrar at the Royal Free Hospital (London), found that an anti-cancer drug, 6-MP, provided superior immunosuppression. The first clinical success with chemical immunosuppression came in 1962, in Paris, when Kuss reported prolonged survival of a non-related donor

1 The Parisian series also included kidneys from guillotined prisoners.

kidney using 6-MP and prednisone. Derivatives of 6-MP were formulated, and BW57-322, later known as Imuran or azathioprine, proved more effective and less toxic in dogs.

Subsequently, combining prednisone with azathioprine became the standard procedure to suppress the immune system. Tissue typing became a routine process from 1962. Improvements in regular dialysis allowed better preparation for transplantation and permitted a return to dialysis if the graft was unsuccessful. In the late 1970s hopes of reaching the ultimate goal of routine, safe and successful kidney transplants were revived with the introduction of cyclosporin into clinical practice and the first effective clinical application of HLA matching (as explained in the next section).

Is HLA matching important in kidney transplantation?

Transplanted organs are rejected because the patient's immune system recognises foreign antigens – proteins on the surface of the cells in the transplanted organ. These antigens cause the formation of antibodies and are attacked in the same way as viruses or bacteria which are foreign to the body. Human leucocyte antigens (HLA) are inherited antigens on the surface of cells throughout the human body. A transplanted organ is recognised as 'foreign' if its HLA are different from those of the recipients body, which immediately starts producing antibodies to destroy it. HLA can be compared to ABO blood groups; they are, however, far more complex and although most people have only four, over 50 HLA have been recognised. It is therefore much more difficult to get an HLA match between donor and recipient than a blood group match.

The clinical importance of HLA matching remains controversial. Between 1981 and 1988 the proportion of centres giving HLA matching strong clinical importance rose from 33 to 37 per cent, while the proportion giving it little or no importance fell from 23 to 18 per cent (Brunner *et al*, 1989). Improved graft survival led to increasing scepticism about the usefulness of HLA typing and matching. Some argued that even if the HLA match was poor it was preferable to transplant a kidney available locally and use cyclosporin to prevent rejection than to exchange kidneys with another centre. Reports that prolonged preservation was detrimental to graft survival even when combined with cyclosporin gave additional support to the argument against exchanging kidneys between centres in order to get a better HLA match.

Claims that the benefits of exchanging well matched kidneys would be outweighed by the harmful effects of prolonged ischaemia were challenged by Opelz (1988) with the findings of the Collaborative

Transplant Study. The number of HLA mismatches was significantly associated with graft outcome in both local and exchanged kidneys. Where no mismatches existed there was an excellent mean graft survival rate at one year of about 85 per cent for both local and exchanged kidneys. One year post-transplant grafts with no mismatches had a 13 per cent higher rate of survival than those with four mismatches irrespective of whether they were local or exchanged. In addition for a retransplant, at one year, a no-mismatch exchanged kidney had an 81 per cent survival rate against 60 per cent for a four-mismatch local kidney.

These findings show that graft survival was not significantly affected by preservation involving cold ischaemia lasting up to 48 hours. Opelz argued that regardless of the duration of ischaemia in exchanged, well-matched kidneys, their outcome far surpassed that of local, poorly matched grafts. This even applied to patients receiving their second grafts where 187 well-matched exchanged grafts outperformed 90 poorly matched local grafts, even though local grafts had shorter ischaemia times (i.e. the time between procurement and transplantation). Opelz therefore recommended avoiding three or four HLA mismatches via greater application of kidney exchanges between hospitals.

The likelihood of finding a well-matched recipient locally is small but the chances are increased by exchanging kidneys. Since cadaver kidneys are in short supply it seems appropriate to promote HLA matching and exchanging in order to make the optimum use of the available kidneys.

Recent advances

One of the most important advances in recent years is the recognition that minimal immunosuppression is the best immunosuppression, in that, minimal immunosuppression does not jeopardize graft survival yet markedly improves patient survival. It is now seen as preferable to let the graft be rejected and return the patient to dialysis, with the possibility of a retransplant at a later date, than to overtreat an episode of rejection.

The 1980s saw considerable modification in immunosuppressive strategy. In 1981 azathioprine and corticosteroids combined were used for 90 per cent of grafted patients. By 1984 the majority were receiving either this combination or cyclosporin with corticosteroids while some 10 per cent were on triple drug therapy (i.e. azathioprine, corticosteroids and cyclosporin). In 1987 almost 90 per cent of kidney recipients were on cyclosporin (46 per cent with corticosteroids and 39 per cent triple therapy). The use of monoclonal antibodies had increased but was still relatively rare in the late 1980s (Brunner *et al*, 1989).

Surgeons at Dulwich Hospital, London, believe they are the first in the world to use antibodies to prevent rejection of transplanted kidneys. In their clinical trial patients given kidneys pretreated with antibodies showed rejection in only 18 per cent of cases compared with 64 per cent rejection of untreated kidneys. All patients were given the same immunosuppression; the antibodies were supplied by Cambridge University.

One of the main antigens which marks transplanted kidneys as foreign is found not on the kidney itself, but on blood left inside the kidney. Scientists at the Cambridge University, department of pathology, can now make antibodies which react specifically with the blood cell antigen. The kidney is treated with these antigens after it is removed from the donor and before it is implanted into the recipient. This helps eliminate the 'tell tale' blood cells and thus assist in preventing the kidney being recognised as foreign by the recipient's immune system.

Antigens on the kidney surface, however, cannot be eliminated without seriously damaging the kidney. To overcome this problem and to reduce further the chance of rejection the Cambridge team are trying to make antibodies against those blood cells within the patient's immune system which are responsible for recognising and attacking the kidney antigens. Only a small proportion of white blood cells are involved in this process. It is hoped to make antibodies able to destroy these cells selectively and not others, leaving the patient's immune system essentially intact and able to function normally in combating infections. If this can be achieved, transplant recipients may not have to take drugs to suppress rejection for the rest of their lives, which would considerably enhance their quality of life.

Kidney transplants in the UK and other European countries

Within the sphere of solid organ grafting, the area of kidney transplantation is of particular importance, because it is the most frequently conducted transplant. In the UK there are six kidney transplants for every heart or liver transplant, nearly twenty for every heart/lung transplant and approaching fifty for every lung transplant.

The UK has only 1.3 renal units per million population, compared with 4.4 in France and 7.1 in Italy; although continental units tend to be smaller. The relatively few units in the UK means patients may have to travel long distances with some communities being poorly served. There are 32 hospitals in the UK that transplant kidneys; organs for transplantation come from a much greater number of hospitals.

Table 2 **Kidney transplantation in Europe**

Country	*Cadaver grafts*	*Living donors*	*Total**	*PMP*	*Waiting list†*
Austria	288	37	325	43	142
Belgium	368	33	401	41	405
France	1,282	70	1,808	33	2,721
GDR	283	4	287	17	691
Italy	440	36	476	8	2,649
Netherlands	385	31	416	28	883
Spain	819	29	1,018	26	3,657
Sweden	268	87	355	42	230
UK	1,598	137	1,735	31	2,813
Total‡	8,729	988	10,681	17	26,429

* The total number of grafts for each country includes supplementary information. Therefore, the total may exceed the combined number of living and cadaver grafts.
† The waiting list was correct at December 1988.
‡ The total is for all 33 countries reporting to the EDTA.

Source: EDTA

In 1989 1,854 kidney transplants were reported to the UK Transplant Service and nearly 8,000 patients were on renal dialysis. Table 2 shows figures supplied by the European Dialysis and Transplant Association (EDTA) for kidney transplants performed in 1988 in nine European countries.

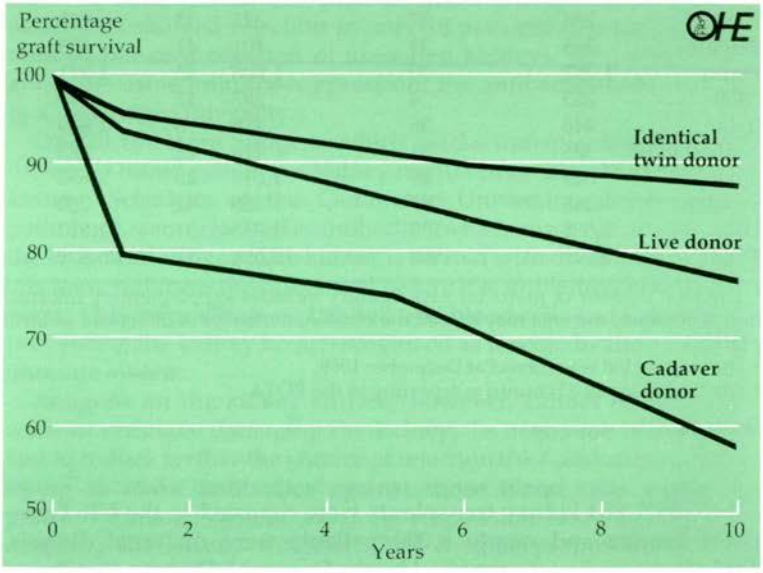
About 1 in 10 kidney transplants in Europe are on diabetic patients with secondary renal disease, the rest are for standard primary renal diseases.

Survival rates

Survival is measured in two ways; survival of the transplanted kidney itself, and survival of the recipient patient.

In the first six months after transplantation the death rates reported between 1984-86 were one third or less of those reported for 1974-76, despite the tendency in recent years for older and higher risk patients to receive transplants. Within the first two months of kidney transplantation less than half the deaths occur in patients with functioning grafts, but this increases with time post-transplantation. Cardiovascular complications accounted for about half the deaths in both 1974-76 and 1984-86, while most of the remaining deaths were consequent upon infection. Cardiovascular death was especially high during the first month post-transplant, while infectious causes peaked during the second month. The University of Wisconsin have reported a 95 per cent patient survival rate at five years

Figure 3 **A graph showing the average survival of three different types of first transplant kidneys**



Source: Gabriel R (1990) A Patient's Guide to Dialysis and Transplantation (4th Edition).

for nondiabetic recipients of a cadaver donor kidney. The corresponding figure for diabetics is 65 per cent, the lower survival being related to death from complications of diabetes.

The effect of the type of donor on the expected outcome is shown in Figure 3. In general a kidney from an identical twin will have a better chance of survival than one from a non-related live donor. The least successful graft survival rates are for kidneys from cadaver donors, which are the main source of kidneys. Table 3 compares graft survival of kidneys from cadaveric donors using triple immunosuppressive therapy (Minnesota 1984-88) against kidneys from living related donors (Hartford Centre, Connecticut, USA 1984-88).

Donnelly *et al* (1989) suggest that about 90 per cent of kidney transplantees can expect their graft to survive at least one year post-transplant, three quarters can anticipate five years and two thirds can foresee graft survival for a decade or more, if the graft is from a living donor. Despite advances in immunosuppression, the one-year survival of transplanted grafts from cadaver donors treated with cyclosporin is only approaching the one year survival rates of living donor grafts. Part of the explanation is that the recipients of grafts from living

Table 3 **Donor type and percentage graft survival at various intervals**

Donor type	*Years Post-transplant*			
	1	2	3	4
Cadaver donor	87	83	78	74
Living related donor	100	100	91	83

Source: adapted from Teraski 1988

donors are, in general, much younger than cadaver graft recipients. Survival after five years reported by the University of Wisconsin for grafts from living relations was about 95 per cent, whereas, cadaver graft survival was only 50 per cent (37 per cent in the case of diabetics). It is important to note, however, that these figures relate to the period 1974-81 and are therefore in the pre-cyclosporin era. 'Improved survival due to decreased risk of dying is likely to have resulted from a variety of factors and may reflect improved patient care, better organ preservation and surgical technique, progress in anaesthesiology, decreased use of steroids, the advent of cyclosporin and better lymphocytotoxic antibody preparations as well as newly developed anti-bacterial and anti-viral agents.' (Brunner *et al*, 1989).

The main disadvantage of using a living donor is the risk of mortality or morbidity to the donor. One in 1600 die in the USA and there is a 1-2 per cent chance of morbidity. Nevertheless, it may be necessary to turn to greater use of living donors if waiting lists are to be significantly reduced.

Economic and social aspects of kidney transplantation

Dialysis and transplantation are costly treatments, although costs vary from nation to nation. Essentially dialysis and transplantation are complementary treatments rather than alternatives, with dialysis therapy being used to maintain patients prior to a transplant. Transplantation is by far the cheaper option, especially when one considers that the vast majority of recipients are restored to full-time work, with consequent savings in pensions or benefits to the remaining family members.

Since in most countries (and certainly in the UK) kidney transplantation provides the most cost-effective solution it has been encouraged ahead of both haemodialysis and CAPD (Continuous Ambulatory Peritoneal Dialysis). CAPD, which became freely available in 1980, is used every day to remove waste products and water slowly but continuously. Patients receiving this treatment are free to walk about, work and continue normal activities, whereas haemodialysis

patients are restricted to sitting or lying down during treatment periods. Home haemodialysis, which was pioneered in Britain, has never become as popular in Europe or the USA. It has been suggested that home haemodialysis requires considerable instruction and 'know-how' to overcome the complexities involved in its operation, whereas CAPD is much more 'user friendly' and hence less demanding on the patient.

Data from the UK Transplant Service and several transplant centres give an approximate cost for transplantation of £10,000 with about £3,000 per annum thereafter for follow-up care (mainly, cyclosporin, immunosuppressive treatment). This compares with roughly £18,000 for hospital haemodialysis, £13,000 for CAPD and £11,000 for home haemodialysis per annum. Home haemodialysis is clearly cheaper than hospital haemodialysis; CAPD is surprisingly expensive due to the costs of the fluid.

A failed transplant works out a little more expensive than a year's in-centre haemodialysis. The advent of cyclosporin has led to significantly more expense in terms of post-transplant anti-rejection therapy, since it is three to four times more expensive than conventional immunosuppression, but also to fewer failed transplantations. Thus, the extra cost is largely negated. Simmons *et al* (1988) argue that patients treated with cyclosporin often experience a higher level of physical, social and emotional well-being than those treated with conventional immunosuppressants, who usually suffer a higher incidence of infections.

Professor Alan Maynard, director of the Centre for Health Economics at York University, in the 1990 Upjohn lecture, used the Rosser valuation matrix, which allows comparison of unhealthy states with the state of being healthy, to derive 'guestimates' of the cost per QALY (quality adjusted life year) of various therapies. According to his figures a kidney transplant has a cost per QALY, adjusted to 1990 prices, of £4,710. This compares with £17,260 for home dialysis and £21,970 for hospital dialysis. Table 4 summarises the relative costs of different renal replacement therapies. The new, and expensive, erthyropoietin (EPO) treatment for anaemia in dialysis patients, assuming a 10 per cent mortality reduction, costs £54,380 per QALY; with no increase in survival this figure is £126,290. On this basis kidney transplantation is unquestionably the most cost-effective treatment option. However, treatment with EPO therapy prior to transplantation can improve the outcome of a kidney transplant and thus its use may only be necessary for a short while prior to transplantation. Further, it has been argued that the main effect of EPO is to enhance quality rather than extend quantity of life.

In 1985 in the UK the breakdown of alternative therapies for renal failure was 50 per cent with functioning kidney grafts, 33 per cent on

Table 4 **Costs of renal replacement therapy**

	Cost/p.a. (£000s)	*Cost/QALY (£000s)*	*Total*
Kidney transplant	(10)*3	4.7	8,404
Hospital dialysis	18	22.0	2,556
Home dialysis	11	17.2	1,582
CAPD	13	–	3,529
Total†			16,071

* The figure in brackets gives the cost of a kidney transplant operation.
† The total refers to the number of patients alive, in the UK, on renal replacement therapy at December 1988.

haemodialysis and 17 per cent on CAPD. Only 15 per cent of all patients on renal replacement therapy used in-centre haemodialysis. For West Germany the respective figures were 14 per cent, 8 per cent and 7 per cent with 71 per cent on in-centre haemodialysis.

The policies adopted in Britain, with an emphasis on home dialysis and transplantation, have by accident or design resulted in a cost per life year gained lower than that of any other country. Wing (1990) concludes that 'the British system has been cost-effective but cruel', since older patients and those with multisystem diseases, notably diabetes, have been squeezed out. However, mere survival is but one criterion of success; quality of life is as important as quantity. Monetary cost and patient survival are very crude indices on which to decide the relative merits of alternative therapies. Evidence from the USA suggests that renal transplant recipients have fared best with nearly four fifths functioning at 'near normal levels' compared to three fifths of those on home haemodialysis and less than half of those on either CAPD or in-centre haemodialysis.

The greatest advantage of a successful transplant is freedom – freedom from repeated, perhaps tedious and disagreeable dialyses. Freedom, too, from restrictions on diet or the quantity of fluid that may be consumed. Holidays are possible without making complicated plans or having to return home or to hospital for dialysis treatment. Women's periods return to normal and they are capable of child bearing. For men potency returns. Thus, in many varied aspects of living, quality of life is greatly improved. It must be remembered though that such findings are subject to selection bias, in that those selected for transplantation are likely to be younger and fitter than those who remain on dialysis and can therefore expect a better outcome. Selection bias between dialysis and transplantation should also be taken into account when comparing survival rates.

Summary of key points

1. Kidney transplantation is the most cost-effective therapy for the treatment of renal failure.

2. Kidney transplantation is also the most desirable therapy because it allows a greatly enhanced quality of life over alternative treatments, i.e. various forms of dialysis.

3. Exchanging kidneys to obtain a better HLA match could be expanded in order to make optimum use of scarce donor organs.

4. To reduce the waiting list for kidney transplantation a greater emphasis on using kidneys from living donors may be required.

HEART TRANSPLANTATION

The function of the heart, a hollow muscular pump with four cavities, each provided at its outlet with a valve, is to maintain the circulation of the blood. Good circulation is essential for the health of every organ in the body and is largely dependent on the efficient functioning of the heart muscle and valves.

Epidemiology

The main indications for cardiac transplantation are dilated cardiomyopathy and ischaemic heart disease, both conditions in which the heart muscle is comprised. The prevalence of terminal ischaemic heart disease, while on the decrease, is still much greater than that of cardiomyopathy, even though the occurrence of the latter condition is on the increase. Therefore, demand for transplantation is influenced more by its suitability for treating ischaemic heart disease, than by any other factor. Ischaemic heart disease increases with age but older patients generally have contraindications to transplantation due to other disease.

The annual demand for heart transplantation in England and Wales for people under the age of 50, was estimated to be between 380 and 1,200 cases per annum, with a median of 790 (Buxton *et al*, 1985). This figure reached around 900 when Scotland was included. These estimates were very tentative and may not necessarily reflect the current demand for heart transplantation.

Addenbrooke's hospital (Cambridge) estimated that about 10 per million population per annum in England need a heart transplant, which gives a figure in excess of 500 a year, below Buxton's median figure of 790. In 1989, 295 heart transplant operations were reported to the UK Transplant Service, and the number awaiting a transplant at January 1991 was 234. However, the waiting list may not be a reliable indicator of the number who could benefit from heart transplantation, since the waiting list excludes everyone over the age limit even though some might have benefitted from a transplant.

History of heart transplants

There was a sixty-two year gap between Carrel and Gutherie's pioneering laboratory work on canine cardiac transplantation and the first successful clinical heart transplant by Barnard in 1967. Orthotopic transplantation where the donor heart replaces the recipient heart in its normal location was first reported in 1958; prior to this heterotopic transplant of the heart to the neck or abdomen had been attempted. Early investigators had several problems to over-

come, including the development of a reliable and reproducible technique for transplantation, preservation of the heart during myocardial ischaemia, supporting the circulation including responding to the increased physiologic demands of exercise by the denervated heart, and developing methods for the diagnosis and treatment of rejection.

In the early 1900s Carrel, a French surgeon, and Gutherie, a US physician, performed a technically successful heterotopic transplant of a heart from a small dog to the neck of a larger one; the graft, however, only survived for two hours. It was not until 1933 that the next significant work on cardiac transplantation appeared. In that year Mann reported two different techniques of cervical heterotopic cardiac transplantation in dogs. His longest survivor lasted eight days, with an average survival period of four days. Mann felt that 'the failure of the homotransplanted heart to survive is not due to the technic of transplantation but to some biological factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs'.

In the 1940s, Demikhov believing that previous heart transplant models were inappropriate because they either resulted in an empty left heart or an excessively filled left heart, investigated 24 methods for placement of a heterotopic heart transplant. Following 250 operations in dogs, the longest survival was 32 days. He also attempted the first orthotopic transplants of both heart and lungs in dogs, most of whom died of technical failures.

A technique for orthotopic cardiac transplantation, which remains largely unchanged today, was described by Cass and Brock in 1959, and followed a year later by Lower and Shumway. Lower and Shumway carried out eight consecutive orthotopic transplants; five of the recipient animals survived between six and 21 days. Their findings were considered by most to be the first major advance in demonstrating the potential clinical role for cardiac transplantation. Lower and Shumway concluded that 'if the immunologic mechanisms of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal life span of the animal'. To investigate this idea, they undertook a series of orthotopic transplants; 20 received no immunosuppression and 25 received varying doses. The survival of the first group was between four and 21 days, and the latter group between six and 250 days. A decrease in electrocardiographic voltage was a reliable indication of impending rejection, and immunosuppressive treatment during such periods prolonged survival of cardiac homografts.

The first heart transplant into a human took place on 28 January 1964. A 68-year-old man dying of cardio-genic shock was taken to the operating room whilst a prospective donor at the same institution

with irreversible brain damage was close to death. However, with no brain death laws for guidance, the transplant team was unwilling to remove the donor from the ventilator to bring about cessation of cardiac function. So a chimpanzee's heart was excised and implanted instead, but it was too small to support the patient's circulation and he died after an hour.

On 3 December 1967, Denise Darvall was fatally injured in a car crash and taken to Groote Schuur Hospital, Cape Town. Ten hours after the accident artificial ventilation was stopped, leading to cardiac arrest. Her heart was transplanted into Louis Washansky. This, the first successful orthotopic homotransplant in a human, was carried out by Christiaan Barnard. The patient survived for 17 days, dying of pneumonia.

Following this success, 102 heart transplants at 17 centres throughout the world were performed in 1968. These attempts were on the whole disastrous; only a handful of centres continued cardiac transplants after 1969. In the USA, the programme at Stanford University was the only one to remain consistently active during the decade following the early and nearly universal disenchantment with heart transplants. The introduction of cyclosporin, however, led to a resurgence of interest in heart transplantation; the subsequent growth in the number of heart transplants undertaken worldwide is illustrated in Figures 4a and 4b. Figure 5 shows the associated increase in the number of heart transplant centres. The first successful transplant in a recipient under 1 year of age was performed in 1984.

Patient selection

In the UK, patient selection has traditionally taken the form of a two stage screening procedure of referral and assessment (Buxton *et al*, 1985). Typically patients consult both a local GP then a hospital consultant who refers appropriate patients to a transplant centre. In addition, a few referrals emanate directly from GPs, patient's relatives, or occasionally from patients themselves. On the basis of the referred information, transplant surgeons determine which patients are potentially suitable for transplantation. At Papworth Hospital, Cambridge, six out of every ten referrals are considered suitable for further assessment and about 75 per cent of those assessed are accepted for transplantation. A further 15 per cent with currently good prognoses are acknowledged to need a transplant eventually.

Potential cardiac transplant patients must currently fulfil the following criteria:

1. All patients should have 'end-stage' cardiac disease, which cannot be treated by further medical or conventional cardiac surgery.
2. The age limitation at Harefield Hospital, Middlesex, is up to

Figure 4a **Number of orthotopic heart transplants**

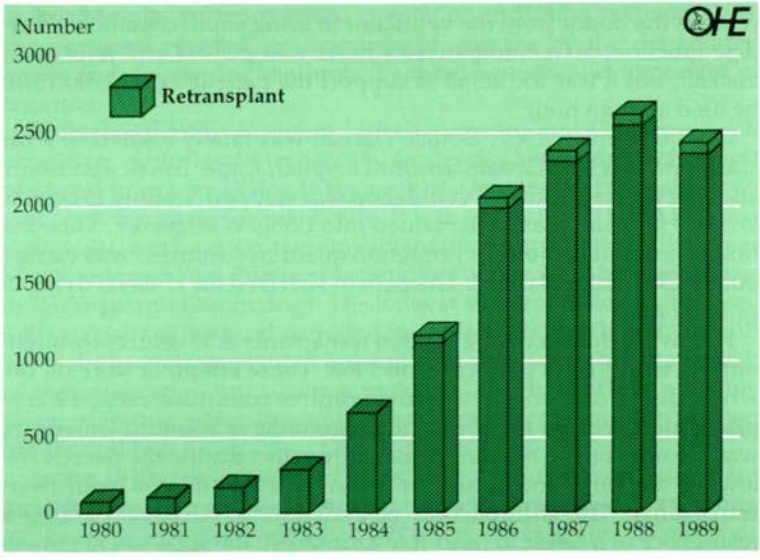
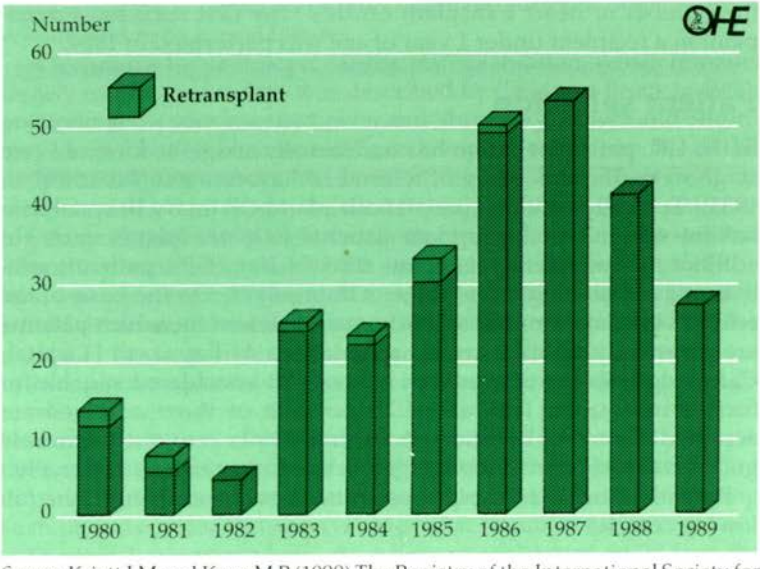
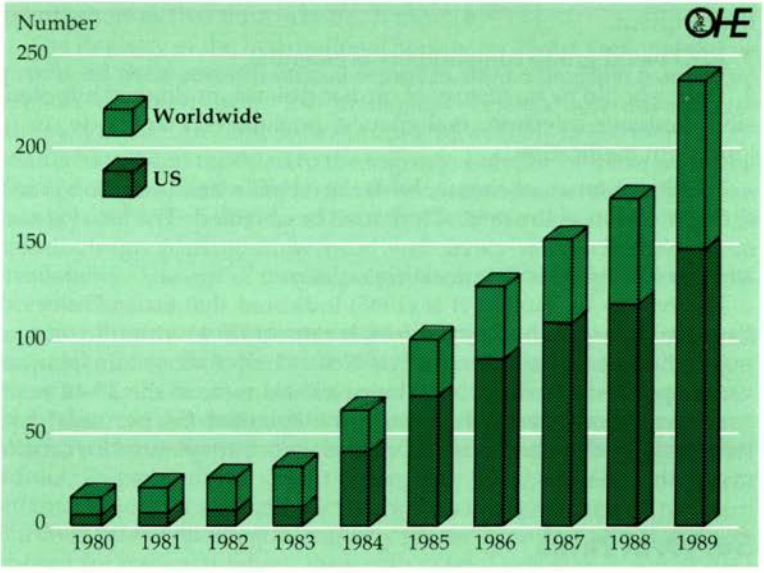


Figure 4b **Number of heterotopic heart transplants**



Source: Kriett J M and Kaye M P (1990) The Registry of the International Society for Heart Transplantation: Seventh Official Report – 1990 In: The Journal of Heart Transplantation Vol.9 p.323-330.

Figure 5 **Number of heart transplant centres by year**



Source: Kriett J M and Kaye M P (1990) The Registry of the International Society for Heart Transplantation: Seventh Official Report – 1990 In: The Journal of Heart Transplantation Vol.9 p.323-330.

around 55 years (although patients from 9 days to 68 years have been transplanted); the age range for Papworth Hospital is from adulthood to about 60 years. There are no hard and fast rules, however, and much is left to the surgeons' discretion.

3. There should be no active infection nor recent pulmonary infarction, although neither of these are absolute contraindications to transplantation.

4. Impairment of renal and hepatic function should be reversible and not caused by primary disease affecting these organs.

5. Without a transplant the prospective candidates should have a survival expectation of between 6 and 12 months.

6. Patients should be psychosocially stable with a reasonable prospect of rehabilitation.

During the period awaiting transplantation patients may stay at home, or in a local hospital or at the transplant centre, until a suitable donor heart becomes available. The criteria for the selection of donor hearts are as follows:

1. The donor can be up to 50 years of age.

2. There must be a compatibility of size between the donor heart and the recipient.

3. ABO blood group compatibility is essential.

4. There should be no history of cardiac disease, prolonged hypotension, systemic infection, malignancy, positive HIV antibody, or of long-term medication.

The donor must, of course, be declared brain dead (see Box 1) and the permission of the next of kin must be obtained. The heart is normally allocated to whoever has been waiting the longest, unless another candidate is deteriorating rapidly.

The review by Buxton *et al* (1985) indicated that transplantees at Papworth Hospital had a male:female ratio of 7.9:1, while the referral population had a sex ratio of 6.9:1. Nearly half of those transplanted were aged 45-54 years, while almost a third were in the 35-44 years age range. Just over half of those transplanted (51 per cent) had ischaemic heart disease and 36 per cent were transplanted for cardiomyopathy.

Survival rates

The UK

The overall survival rates since beginning the programmes at Harefield and Papworth Hospitals, up to 1985, were 73 per cent at six months, 69 per cent at one year, 61 per cent at two years, and 54 per cent at three years postoperatively (Buxton *et al*, 1985). However, these figures do not provide a sound basis on which to base future projections. It is more appropriate to consider only patients transplanted since 1983, for whom the survival probability at six months was of 82 per cent. This figure represents the survival rate achieved once cyclosporin had been introduced. In a paper published in December 1989, Papworth Hospital were predicting survival rates of 83 per cent, 80 per cent, and 77 per cent at one, two, and three years, respectively.

Other countries

At the Loyola University Medical Center, Illinois, of 137 patients transplanted between March 1985 and January 1989 the survival rates were 83 per cent, 78 per cent, 77 per cent, and 74 per cent at one, two, three, and four years post-transplant. The Dutch, by 1987, had undertaken 76 heart transplants with a one year survival rate of 86 per cent (van Hout, 1989). Since no patients died in the second or third years post-transplant, two- and three-year survival was also 86 per cent. To put these rates into some perspective it is perhaps useful

to note that the average survival for accepted patients is nine months without a transplant. Of course, the quality of life without a transplant, short as that time may be, is much lower too.

The Registry of the International Society for Heart Transplantation produced their seventh official report in 1990, compiled from information obtained from 230 transplant centres world-wide (148 situated in the USA and 88 in Europe). More than 12,600 heart transplants have been reported to the registry; only 360 of these were performed before 1980. There have been approximately 2,500 heart transplants undertaken for each of the last three years (1987-89). That this total has plateaued recently is probably due to limited donor availability. The age of transplantees during 1989 ranged from newborn to 78 years.

According to the Registry's report the current five-year actuarial survival after orthotopic heart transplantation is 72 per cent. This is significantly better than the five-year survival after heterotopic transplantation (54 per cent), which accounts for 1 in 40 heart transplants. World-wide, average one-year survival is currently 81 per cent for adults, 76 per cent for children over one year, and 66 per cent for infants. One-year actuarial survival after a retransplant is 49 per cent. Survival rates will depend critically on the type and age of patients chosen for transplantation, thus with careful selection survival rates in excess of the average figures are achievable.

Economic and social aspects

Costs

According to Buxton *et al* (1985), the costs per patient from assessment to discharge were about £11,000 at Papworth Hospital and £5,000 at Harefield Hospital. The average costs for the first six months were approximately £13,000, dropping to around £3,000 for the following six months. Cyclosporin was a relatively new introduction into heart transplantation when this study was conducted, but its cost on average has been estimated at over £1,500 per patient per six months. The six monthly costs after the first year post-transplant will now therefore be increased significantly. A recent estimate (1990) of the average cost within the first year of a heart transplant at Papworth was given as £10,000 by a transplant coordinator. This is below the 1985 figure and reflects more efficient operative procedures as experience grows.

A London teaching hospital estimated its costs for 14 heart transplants carried out in the financial year 1989/90 at approximately £18,000 each. They anticipated this figure to fall as their programme expanded. In the financial year 1991/92 they anticipate executing 50 transplants at a cost of around £15,000 each. (These figures ignore

pre-operative costs, but include follow-up treatment within the first year i.e. biopsies and immunosuppressive drug costs).

Quality of life

In order to assess changes in quality of life Buxton and associates used the Nottingham Health Profile (NHP). There are two parts to this profile. The first section assesses subjective health status by asking responses to 38 simple statements relating to pain, energy, physical mobility, sleep, social isolation and emotional reactions. The second section consists of statements referring to the effects of health problems on work, the ability to perform tasks around the home, personal relationships, sex life, social life, hobbies and holidays. Part one of the profile is analysed on the basis of a range of values from 0 to 100, whereas the second part is based on simple yes/no responses.

After transplantation all six dimensions in part one showed significant improvement at the 99 per cent level of confidence, with the greatest single improvement being in the degree of physical mobility. Similarly, the analysis of part two of the profile indicated that the proportion affirming that health problems affected aspects of their life fell significantly for all aspects covered. At the pre-transplant assessment 10 per cent were bed-ridden, over half could not walk 50 yards and about three quarters could not walk 100 yards. Over 90 per cent could not shop, garden, decorate, or clean; 98 per cent had stopped their active interests and 30 per cent claimed that even sedentary interests were affected due to poor concentration or tiredness. Overall 87 per cent reported a very poor quality of life. Within six months of transplantation 44 per cent had returned to work; by one year this figure had increased to 71 per cent, with a further 12 per cent having jobs open to them when they were ready to restart work.

One year post-transplant all surviving transplantees could walk over a mile and over half of these could manage a five mile walk. After two years post-transplant 75 per cent of survivors could walk over two miles. Within six months of transplantation most could shop, garden, cook, drive and carry out housework and car maintenance. Active interests were restored by 95 per cent after one year and by 100 per cent two years post-transplant. Eighty-eight per cent of heart transplant recipients said their quality of life was good and the remaining 12 per cent said it was better than before the operation. Buxton *et al* found 'evidence of a remarkably unrestricted lifestyle after transplantation and a near normal quality of life.' However, the incidence of chronic renal failure among heart transplant recipients, presumably as a result of cyclosporin therapy, is a factor which can interfere with the health and quality of life of transplantees.

The costs for transplantation are considerably more than for conventional treatment for ischaemic heart disease, such as coronary

artery bypass grafting (CABG). Such grafting costs just over £2,000 per patient and the NHP scores three months post-operatively showed no significant difference between transplanted and CABG patients. However, it must be remembered that transplantees tend to be in a worse state pre-operatively than CABG patients.

Cost per QALY

Estimates of costs per life year gained following heart transplantation or costs per quality adjusted life year (QALY) were not considered by Buxton *et al*. A study of the Dutch heart transplant programme provides such estimates, although differences in factors such as organisational structure, financing arrangements and patient care strategies which often result in substantial variations between hospitals within one country, suggest the estimates from Holland are unlikely to be applicable to the UK experience. However, that is not to say that such information is entirely without relevance for an analysis such as this.

The Dutch programme is a relatively recent one, having started in 1984; the analysis includes data obtained up to the end of 1987. The first year transplant costs are estimated at the equivalent of £43,648, falling to £11,559 in the second and third years. The costs without transplantation are estimated at £3,497 per patient for screening and £8,157 for the first six months on the waiting list. van Hout gives a cost per life year gained figure of £17,820 and a cost per QALY figure of £22,227. (The exchange rate at the time of writing (November 1990) was fl.3.235:£1).

The cost per QALY of a heart transplant at Papworth Hospital, Cambridge, at 1988-89 prices, has been estimated at between £6-8,000 (Professor Martin Buxton: personal communication). This figure corresponds to Professor Maynard's 'guesstimate' of £7,840 per QALY for a heart transplant, given during his 1990 Upjohn lecture. The heart transplant figures for the UK appear to be somewhat cheaper than the Dutch figures, although this may be as much attributed to differences in methodology, costing techniques, etc, as to more efficient transplants in the UK. Maynard's cost per QALY 'league table' also shows CABG at £2,090 per QALY for severe angina and left main vessel disease. For less severe single-vessel disease and moderate angina, CABG costs £18,830 per QALY. Thus, depending on the severity of heart disease conventional treatment may be more or less cost-effective than heart transplantation. It must be stressed though that heart transplant recipients cannot benefit from conventional therapy, a transplant is their only option.

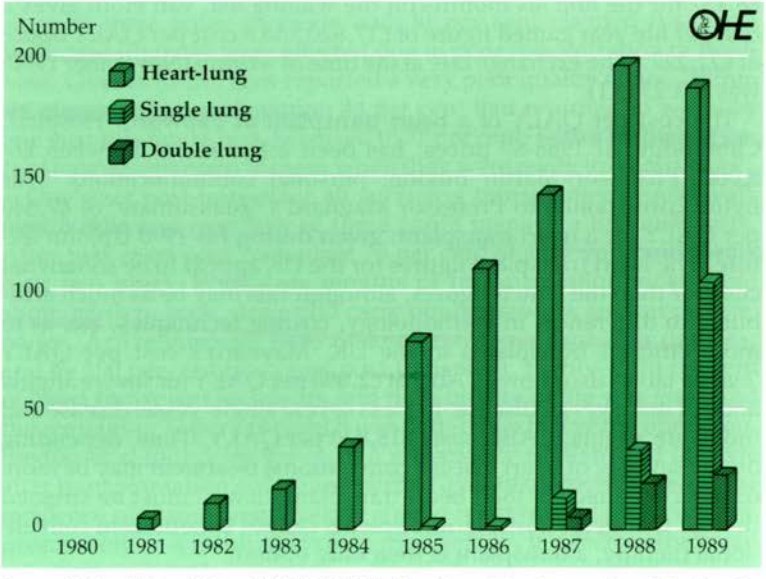
Summary of key points

1. The value of cardiac transplantation is clear in terms of improvements in quality and quantity of life for transplantees.

2. Costs of cardiac transplantation are not insignificant. Resources used in heart transplantation could be diverted to services for other patients, but services of unmeasured cost and unassessed benefit should not deprive transplant programmes of resources that clearly benefit patients.

3. For those requiring a heart transplant the alternative is invariably death within a matter of months.

Figure 6 **Number of combined heart-lung and lung transplants by year**



Source: Kriett J M and Kaye M P (1990) The Registry of the International Society for Heart Transplantation: Seventh Official Report – 1990 In: The Journal of Heart Transplantation Vol.9 p.323-330.

LUNG AND HEART-LUNG TRANSPLANTATION

The lungs are a pair of organs situated in the chest performing perhaps the most important function of vital activity: respiration. The lungs also act as a filter for the blood. The heart, is connected via large blood vessels to both lungs, so that any changes in lung volume cannot help but affect the action of the heart.

Isolated lung transplantation

Background

Isolated lung transplants for end-stage pulmonary disease have been attempted sporadically for over a quarter of a century, without notable success. The problems that have limited the success of lung transplants have now been identified and solutions, at least in part, achieved although there is still little evidence of long-term success. Lung transplantation was stimulated by the work of Veith, who studied and advocated the use of single lung transplantation rather than transplanting the heart and lung en bloc. However, to many, insufficient evidence of prolonged survival invalidates this opinion.

Recent success with the combined transplant of heart and both lungs suggests that this procedure may be the optimal choice for patients requiring a lung. There appear, however, to be several reasons for continuing with single lung transplantation. Firstly, surgical technique has improved considerably over the years and this factor combined with the introduction of cyclosporin has helped to eliminate some complications associated with healing. Secondly, any procedure involving simultaneous transplantation of both lungs requires a donor with two healthy lungs – a relatively rare circumstance. Thirdly, with earlier recognition and more accurate diagnosis of lung allograft rejection, it is probably inadvisable to replace a normal heart with a transplanted one in those with only end-stage lung disease. Finally, the use of single lung transplants could help make more efficient use of a scarce resource, that is, donor organs.

Transplanting both lungs appears to be surgically no less complex and physiologically more viable than transplantation of a single lung, but it does, of course, use two scarce organs instead of one. The lung is a much more difficult organ to obtain than other donor organs for several reasons. Firstly, even short periods of ischaemia of a donor lung can cause significant malfunction after transplantation. Secondly, pulmonary edema and pneumonia are common in prospective donors. Lastly, the size of the donor lung must be approximate to that of the recipient.

Figure 6 shows the increasing number of transplants undertaken which include the lung. Lung transplantation, however, is still in its

infancy so the extent of experience is relatively limited. Prior to cyclosporin no satisfactory immunosuppressant had been available for lung transplantation. Cyclosporin was seen to prevent rejection completely in occasional cases, attenuate it more effectively than standard immunosuppression in most recipients and often produce a milder and completely reversible form of lung allograft rejection. 'Cyclosporin has made therapeutic lung transplantation a real possibility.' (Montefusco and Veith, 1988).

Single lung transplantation

'It appears likely that lung transplantation for end-stage disease can achieve the same degree of success already accomplished with cardiac, hepatic and renal transplantation.' This was the opinion of the Toronto Lung Transplant Group in 1988, based on experience gained from 11 single-lung transplants in patients with pulmonary fibrosis. Such patients typically have a very poor prognosis with no patient, once accepted for transplant, surviving more than 12 months without a transplant; the mean survival time being 2.5 months. Patients up to the age of 60 years are considered as potential recipients, whereas donors must be under 50 years old with no history of heavy smoking.

Since single-lung transplants are technically easier to accomplish on the left side, this was done in nine of the eleven cases. There were two deaths in the immediate post-operative period, one in a rapidly deteriorating patient who received a donor lung that normally would have been deemed unsuitable, and a third patient died from chronic rejection at seven months post-transplant. The remaining patients experienced consistent, sustained improvement in lung function and physical performance following transplantation despite two or three rejection episodes in the first three weeks post-transplant.

The Group conclude that, 'after two decades of discouraging results, it is now possible to obtain clinical success with single-lung transplantation.' However, they also offer a cautionary note saying that 'the procedure must be considered highly risky', although not in their opinion, 'experimental'.

Recent advances

Bilateral single-lung transplants may offer hope to patients with end-stage pulmonary disease such as emphysema and cystic fibrosis. Whilst both lungs are replaced each is implanted separately. This has the benefit of allowing the patient to breathe with one lung whilst the other is being replaced. This technique was developed by the Washington University Lung Transplant Group and seven patients underwent the procedure between October 1989 and March 1990. All seven are reported to be on regular exercise schedules, without oxygen,

whereas preoperatively all had required oxygen supplementation, even when resting. They were now said to be enjoying active lives, in contrast to their severely limited existence pre-transplant.

Survival rates

The Registry of the International Society for Heart Transplantation collects data on lung and heart-lung transplants, as well as heart transplants. In their 1990 report the Registry received data from 58 centres throughout the world on almost 1,000 lung transplant procedures (including 785 combined heart-lung, 157 single lung, and 48 double lung transplants). They show actuarial survival of 60 per cent at one-year, for single lung transplantation and just over 50 per cent at two-years. Double-lung transplantation is less successful at just over 40 per cent survival at one-year. The Registry also has reports of 12 single lung retransplants. Of these, eight patients had a prior single lung and four had a prior combined heart-lung transplant. Operative mortality has been high for lung retransplantation; being 42 per cent for a single lung. One-year actuarial survival after retransplantation is calculated at 33 per cent for a single lung.

Heart-lung transplantation

Heart-lung transplantation was developed both for those people with primary lung disease and for those with primary heart disease and secondary lung disease. For patients having disease of the heart and lungs, often aetiologically and physiologically related, the en bloc heart-lung transplant is essential. Some surgeons, however, carry out the heart-lung transplant because they view this procedure as technically easier than a lung transplant, and therefore more likely to be successful.

Epidemiology

To gauge the potential recipient population for heart-lung transplants, Penketh *et al* (1987) reviewed the mortality in England and Wales from chronic lung diseases in patients aged 10-49 years. For the years 1979-84 the total number of potential heart-lung recipients varied from year to year between 145-185, although, due to various contraindications to transplantation (e.g. insulin dependent diabetes) the actual figure is estimated at 100 patients a year. The authors postulate that more patients with cystic fibrosis than with any other lung disease are likely to benefit from combined heart-lung transplants, especially as most now survive into adulthood. Estimates from Addenbrooke's Hospital, Cambridge, suggest approximately 3.5 per million population per annum require a heart-lung transplant, giving a total figure of just under 200 a year.

History of heart-lung transplantation

Attempts to transplant the heart and lungs of animals into the neck were made as early as 1907, but the first successful investigations were not until the late 1940s and early 1950s with the work of Demikhov. Demikhov obtained survival of over five days in two of his 67 experimental animals and, in so doing demonstrated the technical feasibility of heart-lung transplants. In 1961, six-day survival was achieved using a simplified, and currently clinically applied technique of anastomosis.

Denervation of the lungs, with consequent disruption of the respiratory pattern, appeared to be the common underlying fatal phenomenon in all these early experiments. However, experiments using baboons gave rather more promising results since primates, unlike dogs and other species, are able to maintain a normal respiratory pattern despite pulmonary denervation. In 1972 autotransplantation in baboons was reported, with five out of 25 living for over two years. The Stanford group in 1980 described long-term survival in 27 monkeys after cardiopulmonary allografting, using cyclosporin as an immunosuppressant, with most surviving for several months.

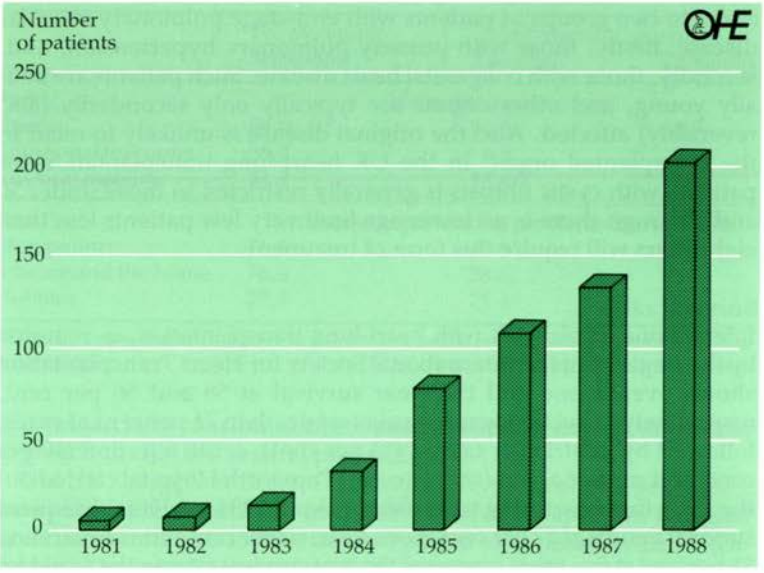
Early clinical experience was discouraging. In 1968 Cooley and associates attempted the first such procedure in a two-month old child who died 14 hours after surgery. The following year Lillehei performed the second such operation on a 43-year-old patient with emphysema and pulmonary hypertension; the patient died eight days later from pneumonia. The third heart-lung transplant took place in Cape Town with the patient dying 23 days post-operatively.

During the following decade various improvements were made in technique, rejection detection and immunosuppression, notably with cyclosporin, making heart-lung transplantation a more realistic treatment option. In March 1981 the first clinical programme was initiated at Stanford University, with the first successful transplant being on a 45-year-old woman with pulmonary hypertension. The number of heart-lung transplants performed increased considerably during the 1980s, as demonstrated in Figure 7.

Recent advances

Improved preservation methods, new immunosuppressive medications, and advances in technical capabilities have allowed innovative procedures to be developed. The 'domino-donor' operation has evolved as an extension of heart-lung transplantation in specific situations and as a result of the need to maximise the number of donor organs. In May 1987 the first 'domino-donor' operation was performed in the United States. A 28-year-old man with cystic fibrosis and end-stage lung disease received the heart and lungs of a donor and donated his own heart to another man with end-stage cardiomyo-

Figure 7 **Number of heart-lung transplantations performed by year**



Source: Heck C P, Shumway S J and Kaye M P (1989) The Registry of the International Society for Heart Transplantation: Sixth Official Report – 1989 In: The Journal of Heart Transplantation Vol.8 p.271-276.

pathy. Cystic fibrosis sufferers are particularly suitable for domino-donor operations since their hearts remain unaffected by the disease. More than 95 per cent of the deaths from this condition, in adults, result from lung infection or other pulmonary complications. There are currently 6,000 cystic fibrosis patients in the UK; thus there is a large pool of sufferers who could benefit from lung transplantation. Yacoub *et al* have pioneered the procedure in the UK at Harefield Hospital, Middlesex. The first cystic fibrosis patient was treated in September 1984. A further 27 transplants were carried out in cystic fibrosis patients up to October 1988. The hearts from 20 of them were used for domino heart transplants. All these patients were judged to have a poor life expectancy and quality of life prior to transplantation. Their actuarial survival was 78 per cent at one-year and 72 per cent at two-years post-transplant, figures superior to all other diagnostic categories of heart-lung recipients transplanted at Harefield.

Recipient selection

Indications and criteria for heart-lung transplantation vary from centre to centre, although uniformly the recipient has advanced pul-

monary disease, not amenable to conventional or medical therapy. At Stanford University, the operation has been restricted, deliberately, to two groups of patients with end-stage pulmonary vascular disease; firstly, those with primary pulmonary hypertension, and, secondly, those with congenital heart disease. Such patients are usually young, and other organs are typically only secondarily (and reversibly) affected. Also the original disease is unlikely to recur in the transplanted organ. In the UK heart-lung transplantation for patients with cystic fibrosis is generally restricted to those under 50 and although there is no lower age limit very few patients less than eight years will require this form of treatment.

Survival rates

International experience with heart-lung transplantation, as reported by the Registry of the International Society for Heart Transplantation shows overall one and two-year survival at 58 and 56 per cent, respectively. Infection was the cause of death in 71 per cent of cases, followed by ventricular failure (13 per cent), acute rejection (10 per cent) and cardiac arrest (six per cent). Papworth Hospital carried out the UK's first heart-lung transplant in April 1984, and its subsequent survival figures of 77 per cent at one year, 60 per cent at three years and 51 per cent at five years represent the best survival rates in the world for heart-lung transplants. These impressive results have been achieved by following a policy of careful recipient selection. It should be noted that Harefield Hospital's survival figures, mentioned earlier, refer exclusively to heart-lung transplants on cystic fibrosis sufferers, and thus do not provide an overall figure applicable to all transplantees.

For patients requiring a combined heart-lung retransplant, the operative risk was high at 52 per cent. After retransplantation one-year actuarial survival was 30 per cent (against 49 per cent for hearts and 33 per cent for single lungs).

Economic and social aspects

By January 1987 78 patients had undergone a combined heart-lung transplant at Harefield Hospital, Middlesex. The majority (2/3) were female with an average age of 23 years. The Nottingham Health Profile was administered by interview to these patients at assessment and at three-monthly periods prior to the operation. Post-transplant appraisal was via postal follow-up at three, six, nine, and 12 months. Thirty of the patients were ineligible for the study being overseas patients, paediatric cases, or too ill prior to the transplant to participate in the study. Of the 48 remaining patients, 32 had survived three months or more at the time of the analysis, 28 of these completed the profile. The results showed a significant improvement in both parts of the evaluation (see Table 5).

Table 5 **The Nottingham Health Profile as a measure of quality of life following combined heart and lung transplantation.**

	Pre-transplant assessment	*Post-transplant assessment at:* 3 months	12 months
Part 1:		Mean dimension score*	
Energy	76.0	14.5	4.7
Emotional reactions	39.2	6.5	1.2
Physical mobility	51.2	13.4	3.4
Part 2:		Percentage experiencing problems due to health	
Occupation	76.6	42.9	15.4
Jobs around the home	76.6	28.6	0
Hobbies	77.1	21.4	15.4

* The closer the number is to zero the fewer are the problems associated with that dimension. *Source:* O'Brien, Yacoub *et al*, 1988.

The researchers concluded that, 'post-transplant quality of life can approach that of the general population.'

The UK Transplant Service has estimated the cost of a heart-lung transplant at about £12,000 in the first year and Papworth Hospital have estimated £10-15,000 for the period of operation until discharge. The initial assessment adds a further £600 to this estimate and follow-up costs are approximately £5,000 per patient per year, on average. For cystic fibrosis sufferers the high doses of cyclosporin required to achieve therapeutic drug levels and the frequent courses of antibiotics used to combat infection, result in costs substantially above the average for heart-lung recipients. However, one must take into consideration here the high costs of conventional medical therapy for end-stage respiratory disease induced by cystic fibrosis.

Summary of key points

1. Whilst survival rates after lung transplantation are improving, they have not yet reached a level where the procedure can be considered routine.

2. More patients with cystic fibrosis than any other lung disease are likely to benefit from combined heart-lung transplantation.

3. The survival rates for cystic fibrosis sufferers are superior to all other diagnostic categories of heart-lung transplant recipients.

4. The 'domino-donor' procedure in heart-lung transplantation has evolved as a result of the need to maximise the number of donor organs.

5. Gains in quantity and quality of life after heart-lung transplantation have been clearly demonstrated.

LIVER TRANSPLANTATION

The liver is the largest internal organ in the body. It plays a vital role in regulating the composition of the blood and is the site of many essential chemical reactions in the body. In addition to forming bile (necessary for the absorption of vitamins D and E) the liver has a number of important functions e.g. production and storage of proteins, storing sugar and fats, detoxicating noxious substances, breaking down drugs and manufacturing and storing red blood cell components.

Epidemiology

There are four main categories of end-stage liver disease applicable to liver transplantation. Firstly, there are intrinsic diseases of the liver, such as inborn errors of metabolism. Since these diseases are congenital or acquired, many of the patients are children who may be cured by replacement of their enzyme-deficient liver. In some cases, transplantation of a second organ may also be necessary e.g. a combined liver and kidney transplant. Secondly, there are diseases caused by external agents affecting the liver; these agents can be toxic, viral, bacterial, traumatic, or parasitic. Alcoholic cirrhosis and hepatitis would be two such afflictions. Recently, such patients have been able to benefit from transplantation, whereas previously the majority died because of the low probability of obtaining a liver in the short time available between the patient's condition justifying a transplant and death. Thirdly, there are systemic diseases affecting the liver, such as primary and secondary biliary cirrhosis. Lastly, there are malignant diseases involving the liver, either primary hepatic or metastatic cancers. Such malignancies frequently recur in the transplanted liver.

American estimates of the need for liver transplantation range from 10-40 per million population per annum. Only a small percentage of patients dying from liver disease are viewed as being eligible for a liver transplant. For 1989 295 liver transplants were reported to the UK Transplant Service, with 54 on the waiting list at January 1991. This is clearly well below the US estimate, which even at the lowest end of the range (10 pmp per annum) would result in over 500 cases for the UK. A member of the Cambridge Liver Transplant Programme estimated the need for liver transplants in the UK at between 12 and 14 per million population per annum (about 700 cases per annum).

History of liver transplants

The application of modern surgical techniques and modern concepts to liver transplantation was first explored by Welch in the early

1950s. He experimented with heterotopic liver transplants (i.e. implanting the liver into a different site in the abdomen without disturbing the host liver). In the late 1950s Moore, in Boston, and Starzl, in Chicago, reported on orthotopic liver transplants in experimental animals. Despite technical difficulties, their work progressed rapidly and by 1958 short-term survival in dogs, limited only by rejection, had been achieved. Once immunosuppressive chemotherapy became available, the first protracted survival in dogs was reported using azathioprine, and soon after antilymphocyte globulin (ALG), as immunosuppressants. The first attempted clinical liver transplant was made in March 1963 by Starzl and was followed by other similarly unsuccessful ventures in Boston and Paris. There was then an interlude until 1967, when Starzl performed the first successful liver transplant, at the University of Colorado, employing azathioprine, steroids, and ALG as immunosuppressants. Calne was to perform the UK's first liver transplant in May 1968.

By the mid-1970s, Starzl in Denver and Calne in Cambridge were reporting a few long-term survivors following liver transplantation. However, the operation was unreliable and unpredictable and was therefore justifiably considered experimental. In 1978 Calne introduced cyclosporin, which helped to achieve survival rates of 80 per cent at one year post-transplant. 'There can be no doubt that the introduction of cyclosporin for clinical immunosuppression has been the most significant factor in the expansion of liver and heart transplantation.' (Gordon *et al*, 1988) The predominant impact of cyclosporin was to control rejection in the critical first six months after transplantation and so increase patient survival.

However, there were also technical improvements in the transplant procedure which were of great importance to the growing success of liver transplantation. During the 1980s the availability of the monoclonal antibody, OKT3, more extensive use of retransplantation, newer non-invasive diagnostic techniques, and sophisticated donor-recipient matching further boosted survival rates.

By 1980 there were about a dozen liver transplant centres in the USA and in Europe. It is only relatively recently, however, that liver transplantation has gained acceptance as a standard therapy. It will probably never be as widespread as kidney transplantation since it requires cadaver donors (at least for adult recipients), is not a paired organ, and the operation is technically very demanding.

Liver transplants in children

The procedure of using a living liver donor is only applicable where the donor is an adult and the recipient a child. Paediatric hepatologist, Dr Peter Whitington, director of paediatric transplant

services at the University of Chicago, estimated that about half the paediatric liver transplants carried out there will be segmental liver transplants involving a living donor. The first such operation took place between a mother and her 21 month old daughter in 1989 at the University of Chicago. There were several advantages to using this technique. Firstly, the operation could be planned so the child was not critically ill with liver failure or infection at the time; a problem facing most young children who are awaiting liver transplantation. Secondly, the liver did not have to withstand the damage associated with donor death, organ preservation and long distance transportation. Finally, compatibility between the mother and daughter should improve the chances of graft survival. Other centres hope to be performing living liver donor transplants in the early 1990s. There are, however, technical difficulties and hazards to the donor, in such procedures, which ought to be recognised.

The incidence of end-stage liver disease is high among infants relative to the supply of appropriate donor organs. This means that only the most desperately ill children get the available livers. Broelsch performed the first successful segmental liver transplant in 1986. In July 1988 he introduced the 'split liver' concept, whereby parts of one cadaver liver are transplanted into two recipients. By using these innovative techniques only one child on the liver transplant waiting list in Chicago has been lost before operation in the past three years.

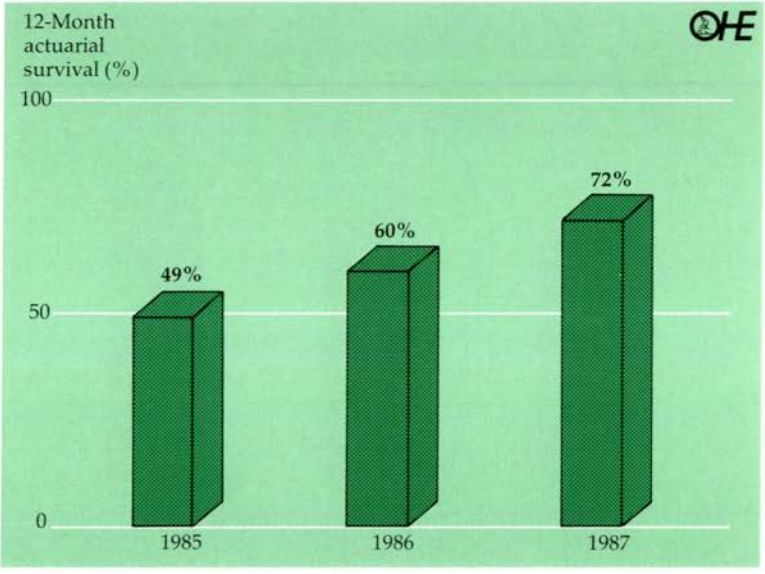
Prevention

In a recent article, in General Practitioner (September 1990), it was reported that Lombard, of King's College Hospital, London, speaking at the BMA annual scientific meeting, suggested that serum ferritin tests could be used to identify people likely to need a liver transplant in later life. Early diagnosis, would allow preventative measures to be taken before a liver transplant becomes necessary. Iron loading is often apparent in middle age only after cirrhosis has set in. Dr Lombard advises serum ferritin tests on patients with 'grey' facial pigmentation, sexual problems and lethargy.

Survival rates

There are now about 100 liver transplant programmes worldwide undertaking around 5,000 liver transplants per annum. Most centres have seen improving results in the past four or five years. Of 172 patients immunosuppressed with azathioprine and prednisone between 1963 and 1981, actuarial survival at five years post-transplant was 20 per cent (Rolles, 1989). This figure increased to 65 per cent of the 1,000 patients treated with cyclosporin and prednisone

Figure 8 **European liver transplant registry data for 12-month actuarial survival**



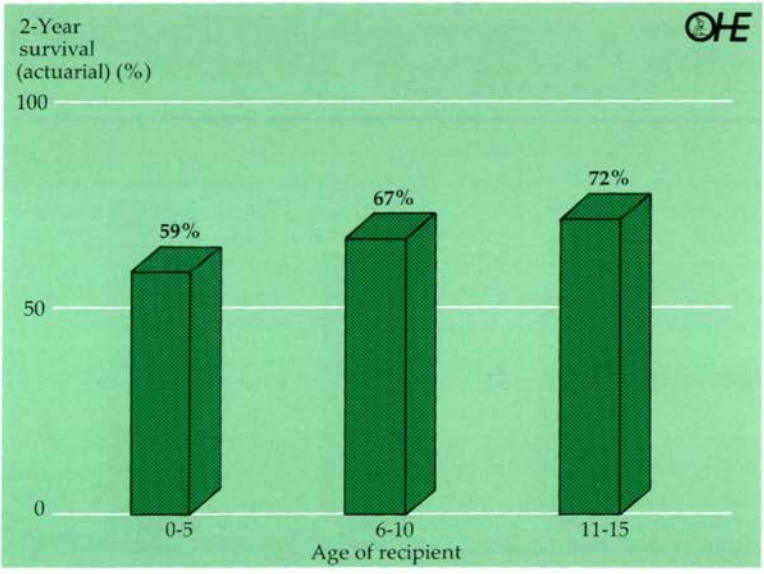
Source: Rolles K (1989) Summary of Clinical Data: Liver Transplantation In: Brent L and Sells R (Ed) Organ Transplantation: Current Clinical and Immunological Concepts.

between 1981 and mid 1988.

The European liver transplant registry which began accumulating data in 1985, has indicated a marked improvement in one-year actuarial survival from 49 per cent to 60 per cent in 1986 and to 72 per cent in 1987 (see Figure 8). Some recently established smaller centres, pursuing a policy of careful case selection, are achieving one-year survival figures in excess of 80 per cent. For paediatric transplants, the European liver transplant registry has identified a correlation between the age of the child and the rate of survival. Two-year actuarial survival for children aged 0-5, 6-10 and 11-15 years, are 59 per cent, 67 per cent, and 72 per cent, respectively as shown in Figure 9.

There also appears to be a correlation between the number of transplants a centre carries out and its success rate. Centres performing less than one a month seem to have significantly fewer patients surviving a year than those centres conducting from one to over five a month (64.3 per cent vs 80.7-84.9 per cent) (Foster and Burton, 1989). The type of liver disease leading to the transplant may also affect the outcome as shown by the one and five year survival figures

Figure 9 **Survival of children undergoing liver transplantation, by age**



Source: Rolles K (1989) Summary of Clinical Data: Liver Transplantation In: Brent L and Sells R (Ed) Organ Transplantation: Current Clinical and Immunological Concepts.

Table 6 **Indications for liver transplantation: survival data 1988**

Diagnosis	*1-year*	*5-years*
Primary biliary cirrhosis	69	65
Other cirrhoses	56	50
Sclerosing cholangitis	77	77
Fulminant hepatic failure	78	78
Malignancy (HCC)	71	36
Biliary atresia (paediatric)	90	88

HCC = hepatocellular carcinoma.

Sources: UCLA Registry, Calne, Slooff, Pichlmayr.

for different indications given in Table 6. With liver transplants the more severe the stage of the disease the less likely one will survive a year after transplantation.

Controversy surrounds the expediency of transplanting patients with liver cancers. Results are generally poor; the tumour often recurs and can progress rapidly in the presence of immunosuppressive therapy. Since donor organs are scarce, some centres will only transplant those with non-malignant liver disease (Pichlmayr, 1988).

With improving results there has been a trend towards earlier referral and operation. This is an important component in the increased survival rates, since the more healthy the patient is at the time of transplantation the higher the chances of a successful operation.

Economic and social aspects of liver transplantation

The substantial cost of liver transplants is an issue that needs to be addressed as more transplants are contemplated. Some recent estimates from the USA have cited a 'mean working figure' of $150,000. Williams and colleagues have claimed that the mean cost of hospitalisation for the last twelve months of life for their patients dying of liver failure without transplantation was $45,643. Their figure for the cost of transplantation was $92,866 giving a net transplantation cost of around $47,000. To this figure they added the mean cost of first-year follow-up care and professional fees, the net one-year cost being estimated at about $79,000. Although the immediate costs of liver transplantation are considerable, the reward is also high. Death from liver failure is expensive too, and nothing is returned to society. Most patients requiring a liver transplant are either children soon to enter, or adults in, the productive years of life.

The above figures may have little relevance to the UK. The cost of a liver transplant in the UK has been estimated at between £15-18,000 by the UK Transplant Service, with follow-up costs ranging from £3-5,000 per annum. In 'Liver Transplantation: The Cambridge/King's College Hospital Experience', edited by Sir Roy Calne, a UK figure of between £15,000 and £20,000 was quoted for the total costs of the procedure in 1987, including the donor operation and transport. Calne claims that the cost of a successful liver transplant, resulting in a fully rehabilitated patient who returns to work, is small in comparison to the costs incurred by repeated hospitalization of a dying patient plus the continuing cost of caring for the dependents. A 1990 estimate of £20,000 for the average costs within the first year for a transplant by the Cambridge liver transplant programme was given by the transplant co-ordinators at Addenbrooke's hospital.

Colonna *et al* (1988) surveyed liver transplantees at the University of California, Los Angeles, School of Medicine. Fifty-eight of 60 questionnaires were returned. Only 32 per cent of adults were working full- or part-time before liver transplantation; this increased to 75 per cent after transplantation. Post-operatively 93 per cent of adults reported normal or only mildly restricted activity compared with 39 per cent pre-operatively. The frequency and duration of hospitalisations was reduced from an average of 3.07 during the six months preceding the operation to 0.87 in the most recent six months after the transplant.

Subjective assessments of quality of life were also surveyed. Before liver transplantation 47 per cent felt their quality of life was intolerable, 27 per cent felt that it was poor, 13 per cent satisfactory, and only 13 per cent felt their quality of life was good or excellent. After transplantation no-one felt their quality of life was poor or intolerable, in fact 67 per cent thought it was excellent, 27 per cent good and seven per cent satisfactory. Seventy-five per cent of patients were completely satisfied with the overall transplant experience, and 25 per cent were very satisfied. All the patients said that they would, and some have, recommended liver transplantation as a means of survival to others with end-stage liver disease. Colonna *et al* conclude that their 'data indicate that the patient can anticipate that the quality of that survival will be excellent.'

Summary of key points

1. Liver transplantation has recently become an established treatment for end-stage liver disease.

2. Liver transplant results are improving continuously, both in terms of the survival and the quality of life of recipients.

3. The relative costs and benefits are not yet as clear cut for liver transplantation as they are for kidney or heart transplants.

4. Many patients requiring a liver transplant are either children or young adults so the reward to society as well as to the patient of a successful transplant is high.

PANCREAS TRANSPLANTATION

The pancreas is a secreting organ situated behind a loop of the small intestine, below the stomach. Its two most important functions are the production of pancreatic juice, the most important of the digestive juices, which is secreted into the small intestine after partially digested food has left the stomach; and the production of the hormone insulin. Inadequate production of insulin leads to diabetes mellitus. The only absolute indication for a pancreatic transplant is to arrest or prevent the sequelae of diabetes.

Epidemiology

In the industrialized world there are about 80 new cases of Type 1 (insulin-dependent) diabetes diagnosed per million population each year. Of these approximately half are at risk of developing severe secondary complications. The vast majority of diabetics have non-insulin-dependent diabetes (Type 2 diabetes). Assuming that pancreatic transplantation would be the favoured option for the former group, and allowing for an exclusion rate of one in four due to contraindications, this would result in around 30 new patients per million population per annum who might ultimately benefit from a successful pancreatic transplantation.

No country, including the UK, even approaches this level of activity in pancreatic transplantation. The UK Transplant Service had evidence of only nine such transplants for the whole of 1989. Indeed only 45 have been undertaken at Cambridge in a programme which has been active for over a decade. The total world wide experience now amounts to just over 2,000 pancreatic transplants.

Aim of pancreas transplantation

The aim of a pancreas transplantation as a treatment for diabetes mellitus is to establish an insulin independent state and thereby halt or prevent the progression of the complications of diabetes that can afflict the eyes, nervous system, kidneys, heart, brain and legs through thickening of the arteries. A transplant may also improve the quality of life for diabetics, by releasing them from dependence on insulin injections. The decision to perform a pancreas transplant in a diabetic depends, first, on accurate identification of the risks from progressive and debilitating complications and, second, on the balance between the risks of transplantation and the benefits that may accrue from a long-term successful transplant.

Pancreas transplantation is not performed to save a life but to improve the quality of life for the recipient. It is analogous to kidney

transplantation where the objective is to obviate the need for dialysis and prevent the complications of chronic uraemia in patients with end-stage renal disease. Pancreas rejection can be followed by a return to exogenous insulin therapy, just as rejection of the kidney can be followed by a return to dialysis.

Before the insulin era commenced, diabetic coma was the cause of death in nearly two thirds of Type 1 diabetics. Insulin, introduced in 1922, has led to markedly improved longevity; however, diabetics still die earlier than non-diabetics. Diabetes is a potentially devastating disease and the risk of developing complications can vary substantially between individuals. The age at which diabetes begins and the duration of the disease are important risk factors. Women tend to be more at risk from complications, as are smokers, people with high blood pressure, and those with a degree of hyperglycaemia. However, it is not possible to predict with certainty which diabetic patient free from complications will develop them in the future. Whilst blood glucose levels appear to be related to diabetic complications, the nature of the relationship remains unclear.

History of pancreas transplants

Brooks and Gifford (1959) were the first to describe pancreatic transplantation in a large animal model. In the following years the technical details in the dog model were worked out, thereby providing the setting for clinical trials. The first clinical pancreas transplant was performed by Lillehei and Kelly in December 1966 at the University of Minnesota. The operation was a combined kidney/pancreas graft, the patient being a very ill, uraemic diabetic woman. She immediately became normoglycaemic and insulin independent, but died after two months from a combination of rejection and sepsis.

Between the end of 1966 and 1973 Lillehei and his associates performed 13 pancreatic transplants – most of which were combined with a kidney transplant. The results were disappointing with only one of the pancreas grafts functioning for over a year. Some technical improvements throughout the 1970s, the use of living donors for segmental pancreatic transplants and the acceptance of non-uraemic diabetic patients for single pancreatic transplantation, have led to a more widespread adoption of pancreas transplants. There are many challenges that remain in the area of pancreas transplantation, but with sustained effort they may not be insurmountable.

Current issues

As more pancreas transplants are performed, the criteria for recipient selection are being modified. Many centres are now considering earlier

transplantation of diabetic patients to restore normoglycaemia and hopefully avert or halt the advance of secondary complications of the disease. The successful experience with living related donors may increase its application to suitable donor-recipient pairs. However, some donors have suffered from impaired glucose levels or have become diabetic themselves.

Recent findings have revealed that the techniques used during multiple organ harvesting may be deleterious to subsequent pancreas function. Attention needs to be focused on the specific requirements of the pancreas during these procedures and currently research on preservation techniques is taking place.

Surgical techniques have changed considerably since the first clinical pancreas transplant in 1966. Segmental pancreas transplant came into vogue after the early failures. However, no great long-term gains were made and the move recently has been back to whole pancreas allografts with segments of the duodenum attached. The Cambridge programme, initially adopted the duct occlusion method in 1979, then from 1982-84 used the enteric method and from 1984-88 employed the paratopic technique which was pioneered and developed at Cambridge and only used there. Currently, a bladder technique is being utilised by the Cambridge programme. Thus, there is as yet no universally accepted technique.

In the past many grafts were lost because pancreas rejection was diagnosed too late. New advances mean that impending rejection should be noticed earlier and appropriate immunosuppression instituted before it is too late. The use of cyclosporin as the primary immunosuppressive agent has been associated with improved graft survival. In the future immunosuppression will probably increasingly include monoclonal antibodies such as OKT3, ALG (antilymphocyte globulin), and ATG (antithymocyte globulin), used alone or in combination with cyclosporin.

Research is being focused on replacing the pancreatic function by using of mechanical or electronic devices. Investigation into insulin infusers suitable for implantation has been an important area of research. Such devices usually consist of an insulin reservoir and pumping device to give a continuous infusion of insulin, perhaps with an additional capability to accommodate meals. The development of electromechanical devices to replace normal pancreatic function is conceptually easy but has been difficult to achieve in practice. Technical difficulties and poor long-term reliability of these devices has so far limited their utilization.

Phase 1 trials of human pancreatic islet transplantation in patients with renal failure and Type 1 diabetes are to commence this year at a new Oxford transplant centre. These trials follow nearly 16 years of research directed at the immunological, physiological and technical

problems of pancreatic islet transplantation in experimental models of diabetes in several species and in man.

Survival rates

Pancreas transplantation has been performed over 2,000 times in patients with insulin dependent diabetes since 1966. Most of these operations (about 4/5) have been carried out in the last six years. Surgical problems are formidable with between 20 and 30 per cent of pancreas transplantations being technical failures, and as a consequence the techniques have varied considerably.

From December 1966 to June 1989, 2,004 pancreas transplants were reported to the International Pancreas Transplant Registry, 1,604 of which were carried out after 1984. One-year actuarial patient and graft survival were 81 and 46 per cent, respectively. However, since 1985, these figures read 88 and 55 per cent, respectively. For the 1,604 transplants since 1984, the technically successful cases (1,253) yielded a one-year graft survival rate of 66 per cent. Analysis by era for 1966-77 (64 cases), 1978-83 (336 cases), 1984-5 (384 cases), and 1986-89 (1,220 cases) gave one-year graft survival rates of 5, 26, 40, and 56 per cent, respectively. The patient survival rates were 39, 71, 80, and 87 per cent, respectively. These improvements may reflect better preservation methods and immunosuppressive regimens, and the minimization of the number of HLA mismatches through the growth of HLA typing should enhance graft survival. Graft survival rates were influenced by HLA typing with DR antigens; no mismatches produced significantly higher graft survival rates than those mismatched for one or two DR antigens. Although pancreas graft survival rates were highest in recipients of a simultaneous kidney transplant, at 58 per cent, patient survival rates were lowest in this group, being 83 per cent at one year. Patient survival was 88 per cent at one year for recipients of a pancreas transplant alone (although the graft survival rate was only 35 per cent) and 91 per cent for recipients of a pancreas after a kidney transplant, where the graft survival was 41 per cent at one-year.

The relatively disappointing results of pancreas transplantation may to some extent be self-perpetuating because only patients in a poor state are referred for transplantation giving less chance of a successful outcome. This leads to poor results meaning that doctors are still reluctant to refer patients until their quality of life becomes very poor – with no other feasible alternative treatment. If patients were operated on at an earlier stage the results would probably improve; however, the reverse of this must occur i.e. results must improve before better patients are referred for transplantation.

Results are continuing to improve but as yet pancreas transplant-

ation cannot be considered an applicable therapy for all insulin dependent diabetics. Nevertheless, its application is going to spread with programmes planned at both St. Mary's Hospital, Portsmouth, and the John Radcliffe Hospital, Oxford. There are active programmes at Cardiff and Cambridge although neither centre has vast experience of pancreatic transplantation, 45 having been carried out at Cambridge since the programme began in 1979.

Economic and social aspects

Alberti (1987) suggests that graft survival and function are too short and the problems of immunosuppression too great to consider pancreas transplantation as a realistic treatment for diabetes. Pancreas transplantation can establish a euglycaemic, insulin independent state for years, if not indefinitely. However, this is achieved only at the cost of chronic immunosuppression thus pancreas transplants are limited to recipients whose diabetes would cause complications more serious than the potential side-effects of immunosuppressive drugs, or patients already immunosuppressed because of a previous or simultaneous kidney transplants.

Johnson *et al* (1990) ask the question 'does pancreas transplantation really improve the patient's quality of life?'. They see the key issues as being: gaining control over their lives, having a positive self-image, vocational or employment changes, sexual activity and loss of fear of complications or rejection. They studied 17 patients transplanted at the Mayo Clinic during the period December 1987 to January 1989. Fifteen still have pancreatic function, one rejected and one died. Fifteen recipients received both a kidney and pancreas, two had a pancreas only having received a kidney previously. Using the Karnofsky scale (see Box 2) patients were assessed pre-transplant

BOX 2 Karnofsky Index

1. Normal: no complaints, no evidence of disease.
2. Able to carry on normal activity; minor signs and symptoms of disease.
3. Normal activity with effort: some signs and symptoms of disease.
4. Care for self: unable to carry out normal activity or do active work.
5. Requires occasional assistance but is able to care for most of own needs.
6. Requires considerable assistance and frequent medical care.
7. Disabled: requires special care and assistance.
8. Severely disabled: hospitalization indicated although death not imminent.
9. Very sick: hospitalization necessary.
10. Moribund: fatal processes progressing rapidly.

and at various periods post-transplant. The results showed a significantly improved quality of life after transplantation.

The assessment system used requires the individual to rate their quality of life (QL) from 1 to 10 (with one being the optimal rating). Pre-transplant no patient considered life normal; the highest rating was QL 2 assigned by one patient and three ascribed a QL 3 rating to their predicament. Three months after transplantation 60 per cent rated themselves QL 1, 2 or 3; six being in category 1. The authors concluded that 'the transition from being seriously ill to a 'normal life' may sometimes be a slow process, but nevertheless it does happen. This study shows that pancreas transplantation does, indeed, improve the patient's quality of life.'

Pancreas transplants are, however, expensive operations. A member of the Cambridge transplant unit estimated a figure of between £20-30,000 per transplant. With graft survival rates at around 50 per cent this represents a costly procedure, with great uncertainty attached to the outcome. To put this figure into some perspective it must be remembered that the complications attached to diabetes also have considerable costs. For instance, blindness induced by diabetes could mean a home help visit up to 3 times a day to facilitate insulin injections. A successful pancreas transplant should enable a return to full-time work and the ability to lead a 'normal' life.

Summary of key points

1. The aim of pancreas transplantation is to establish an insulin independent state in diabetics and thereby halt or prevent the progression of the complications of diabetes.

2. Approaching a third of pancreas transplants are technical failures; this factor partially accounts for the relatively poor graft survival rates, with about one in two failing within the first year post-transplant.

3. Analysis by era shows that graft and patient survival after pancreas transplantation are improving, but have yet to reach a level whereby this procedure can be considered a routine operation for insulin dependent diabetics.

4. Successful pancreas transplantation can result in a transition from being seriously ill to leading a normal life.

5. Pancreas transplants are expensive procedures; with poor graft survival rates such expense may currently be difficult to justify.

DISCUSSION

'The history of medicine is that what was inconceivable yesterday and barely achievable today often becomes routine tomorrow.' (Starzl *et al*, 1982) In a dynamic field such as transplantation, any conclusions drawn from an analysis may only be applicable at the time of writing. With the advent of new drugs, better surgical techniques, improved organ preservation methods, and so forth, the situation is inevitably going to alter in the near future, making previous analyses partially or wholly inapplicable. Also, the situation may vary from nation to nation due to differences in patient selection criteria, categories of disease treated and immunosuppressant regimes employed, to list but a few. Such differences may even be apparent between hospitals within a country. Thus, any findings may apply to the 'average' hospital, rather than be true for individual hospitals.

There must also be some degree of uncertainty when attempting to extrapolate or forecast benefits into the future. A 30-year, or so, follow-up period would allow detailed documentation of actual survival, but this would be of little use to policy makers of the day. A major obstacle to any evaluation of transplant operations is that a rigorous control group does not exist and so we have to rely on 'counter factual' judgements to postulate what would have happened if no transplantation had taken place.

As transplantation becomes a generally accepted and proven modality, questions of efficacy and safety are superseded by new issues dealing with patient selection, organ procurement, ethical and legal implications, cost effectiveness and so forth.

There are clearly marked differences between various transplant operations. Kidney and pancreas transplants, for example, are not the sole life-saving approach, in the way a heart, liver or lung transplant can be, but are performed to improve the quality of life for the recipient. The various transplant procedures are therefore not directly comparable.

Critics have argued that transplantation is a 'false technology' because it does not address the cause of the problem or look into methods of disease prevention, it merely provides a costly and technically demanding solution. Some commentators have argued that because of this transplantation should not be a funding priority within the NHS. Such sceptics have suggested that resources allocated to heart transplantation, for example, would be better utilized for preventative health care measures. They seem to lose sight of the fact that preventative measures are of uncertain value, whereas transplants have been economically evaluated. Health education, promoting preventative health care (concerning issues such as, diet, exercise and lifestyle), is, however, important and should be encour-

aged as this may avert the need for a transplant operation in those cases where the cause is preventable.

Undoubtedly results will continue to improve as progress is made in all aspects of transplantation. However, judging from past experience there appears to be little promise of a reduction in overall costs as, for example, new and more sophisticated immunosuppressive drugs are likely to be even more expensive than existing ones, although cost per life year gained may fall as results improve. There is evidence to suggest that new technologies can become more cost-efficient as medical teams become more proficient and experienced. Sayell *et al* (1989) see this as 'a learning effect for transplant teams over time'. They also suggest that economies of scale may be achieved at larger facilities.

With finite NHS resources, a judgement to treat one patient inevitably means not treating another patient – rationing is unavoidable. Policy makers have to make difficult choices concerning the most humane and rational way to allocate these resources. As new technologies continue to be successful in extending and improving the quality of life, knowledge of costs becomes more crucial as one modality is contrasted with another to make a decision as to which services should be provided. It is necessary to ascertain the relative benefits of competing therapies and devote resources to the treatments offering the best value for money. Table 7 provides a brief overview of the survival rates and costs associated with the transplant procedures discussed in this paper.

Table 7 **Survival rates and costs of the various transplant procedures.**

Organ	*Survival 1, 5 yrs*	*Cost*	*Per annum*	*Cost/QALY*
Kidney	87(94), 75(83)*	£10,000	£3,000	£4,710
Heart	85, 82	£15,000	£3,000	£7,840
HLT	77, 51†	£17,000	£5,000	–
Liver	72, 66	£20,000	£4,000	–
Pancreas	49(82)	£25,000	–	–

The figures in brackets give patient survival data, where such a breakdown is applicable.

* For kidney transplants the second set of survival statistics refer to four years post-transplant.

† It should be noted that the heart-lung survival data refers to Papworth Hospital, Cambridge, which has the best results in the world. Thus, overall survival figures for heart-lung transplants are lower.

Sources: adapted from Teraski, International Registry, UCLA Registry, Calne, Slooff, Pichlmayr, Maynard.

From this analysis it would appear that kidney transplants give the best value for money followed by heart transplants. The increasingly better results from liver transplants are encouraging and probably warrant its continued expansion. Heart-lung and certainly lung and pancreas transplants are more contentious issues. However, their continued development is likely to lead to a time when all solid organ transplants can boast fine success rates and become accepted as routine procedures. 'Organ transplantation has come a long way in the past 30 years but it still has a long way to go. There is little doubt that the advances over the next ten years or so are likely to prove even more remarkable than those we have already seen.' (Morris, 1991)

SUMMARY OF MAIN ISSUES

Kidney transplantation

1. Kidney transplants are probably the most clear cut example of a cost-effective transplant. The graft survival rates are high at around 75 per cent at five years post-transplant for a cadaver kidney donor, rising to over 90 per cent for an identical twin donor. The patient survival rates are even higher because the recipient of a failed transplant can then return to dialysis treatment.

2. A kidney transplant costs about £10,000 in the first year compared with around £11-18,000 for dialysis per annum, depending on whether the dialysis is CAPD, home or hospital based. Thus, savings accrue from the first year and increase thereafter with follow-up costs, after transplantation, estimated at £3,000 per annum.

3. It must also be noted that the recipients are able to enjoy a high quality of life; in many cases returning to full-time work. Of the transplants considered here kidneys are both the cheapest and most successful.

Heart transplantation

4. Heart transplants are carried out on patients where there is no alternative therapy open to them. A transplant is their last hope for continued life. Results have persistently improved and the current five year survival is about 80 per cent.

5. The post-transplant quality of life is generally very good with most recipients leading a fairly unrestricted lifestyle, many returning to productive employment.

6. Whilst the costs involved in this procedure are not insignificant, many people may feel that the expected outcome justifies the resources used.

Lung and heart-lung transplantation

7. Lung and heart-lung transplants have a survival rate of about 60 per cent at one year, although Papworth have achieved a heart-lung survival rate of 77 per cent at one year and 51 per cent at five years.

8. The cost at Papworth has been estimated at between £15,000 and £20,000 in the first year for a heart-lung transplant.

9. Whilst the results of heart-lung transplants are quite encouraging from some centres, lung transplants have generally proved to be rather disappointing.

10. For the patient there is no alternative hope for additional life, and if the transplant is successful it has been shown, certainly for heart-lung recipients, that the quality of life attainable 'can approach that of the general population.' (O'Brien *et al*, 1988).

11. It must still be questionable whether lung and heart-lung transplants should be considered as routine 'service' procedures rather than continuing research projects, given that the outcome is far from certain and the substantial resources involved, could be used elsewhere in the health service. However, it also likely that over time the efficacy of these transplants will continue improving.

Liver transplantation

12. Liver transplants like heart, heart-lung and lung transplants are carried out when there is no other treatment available. It is slightly more complex to evaluate, though, since survival rates are associated with the type of disease being treated and the stage of the disease.

13. Good results are achievable, particularly, when the transplant is carried out in an experienced centre, at an early stage of the disease, and where the disease does not involve a malignancy. With careful patient selection the likelihood of a successful outcome is greatly enhanced.

14. A successful liver transplant can enable the transplantee to enjoy a high quality of life, however, liver transplants are relatively expensive procedures and the survival rates are lower than for those receiving kidney or heart transplants.

Pancreas transplantation

15. Pancreas transplants are still at an experimental phase with very few carried out in the UK; the total being in single figures for most years.

18. Pancreas transplantation may be hard to defend when one in two grafts fail within the first year. For the successful transplantee, however, a greatly improved quality of life can result with freedom from insulin injections and the complications that diabetes can foster.

19. At the current state of the procedure it would seem that there is little evidence to support the considerable cost involved. Of course, the situation may change in the years ahead, especially when one considers the extensive research going into this area at the moment; this is particularly true with regard to islet transplantation, which may be the way forward.

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