

Malaise of clinical organ grafting

Professor Roy Calne, of Addenbrooke's Hospital, Cambridge, considers why organ grafting in the UK is in the doldrums.

MORE than 10 years ago an immunosuppressive regimen of the thiopurine Imuran, together with corticosteroids, was introduced and clinical organ grafting became possible. The actions of these agents are not fully understood; they can be toxic and sometimes they are totally ineffective at the maximum tolerated dosage. Nevertheless more than 20,000 kidneys have been transplanted in patients treated with Imuran and steroids, and the results are far from discouraging, especially in allografts between close relatives. Rejection remains the chief barrier to progress, but the quality of the organ when grafted is also very important. In grafts between identical twins where there can be no rejection and the organ, coming from a live donor, should be in perfect condition, there is an 86% chance of the graft sustaining the patient's life at two years and the longest period of survival after operation is now more than 18 years. If a kidney is grafted from a blood relative who is not an identical twin, the figures fall to 70% and 15 years, and with a cadaver donor (in which case both rejection and the condition of the organ are likely to raise problems) the figure is 48% and 11 years.

Two inter-related factors are responsible for the present malaise, namely the lack of a significant advance in the control of rejection and the poor therapy offered to patients, compared with what could be possible using existing techniques.

Then years ago the mood of surgeons and immunologists was full of optimism. They felt that if results such as those described above could be obtained with the earliest immunosuppressive agents investigated, surely more effective and less toxic drugs would soon be available. Moreover, immunology, which had been stagnating during the previous three or four decades, was given an immense boost. The work of Medawar and his colleagues led to the successful recruitment of brains and funds into transplantation biology. As had been anticipated, this focus of interest soon bore

fruit in the form of knowledge of cellular and humoral immune mechanisms. How disappointing it was to realise that this new light revealed that phenomena that had seemed simple were in reality excessively complicated and that almost every attempt to apply successful experimental techniques of graft prolongation in inbred rodents to outbred animals including man led to failure. As Medawar has stated the "tyranny of the skin graft in the inbred mouse" held back progress in organ grafting. Allografted skin does not behave like vascularised organs, and the controlled parameters of an inbred rodent strain do not resemble the immense variation of antigenicity and immunological response seen in man.

Much hope seemed justified when it was shown that antilymphocyte serum prepared in the rabbit against mouse lymphocytes would prevent the rejection of skin grafts from widely disparate donor strains and even from other species. Yet, many years after its first application to patients with kidney grafts, it is still not clear if antilymphocyte globulin (ALG) therapy adds significantly to the therapeutic index of Imuran and steroids; there is no doubt, however, that some batches of ALG can be dangerously toxic and can potentiate the risks of infection especially to viruses and fungi.

Tissue typing was another endeavour which seemed to have a bright future. A new and very complicated system of serologically defined antigens present on lymphocytes and many other tissues was discovered. They are certainly relevant to the outcome of graft survival. The genetics of this system and even the chromosome responsible have been demonstrated elegantly. Nevertheless complete matching of these tissue types in siblings only permits survival of skin grafts for some 20 days compared with 7 to 10 days when the grafts are mismatched. It is clear that there must be other important antigens that are not being detected, since the grafts are always rejected. Application of tissue typing to clinical kidney grafting has also been disappointing, except in grafts between siblings. If donor and recipient siblings are of identical tissue type, there is an 80% chance that the transplant will function normally after two years. Fully matched grafts between unrelated people do much better than unmatched grafts, but the influence of typing between unrelated donor and recipient when the match is only partial is weak, and most surgeons pay more attention to the clinical considerations and the quality of the organ than to the matching. Tissue typing and direct cross matching of recipient serum against donor cells is of importance in patients

previously sensitised to transplantation antigens as a result of rejecting a previous graft, receiving blood transfusions or following pregnancy. Sensitised patients must receive a kidney from a donor to which he does not already possess heightened immunity, otherwise aggressive rejection is likely. As more transplantation antigens are defined by new techniques, tissue typing will become more relevant, but in practice the likelihood of finding a perfectly matched donor organ will become increasingly difficult.

Most workers have felt that the ideal form of immunosuppression would be specific only for the donor in question, so that the patient would not be subjected to increased risks of infection. Laboratory models of specific 'desensitisation' using transplantation antigen and antibody preparations have been described, but to date there has been little success in their clinical application. It may be necessary to monitor the reactivity of the recipient towards donor antigens in order to treat the patient with an effective 'recipe'. Such speculations are for the future, but it is important to remember that half of the patients receiving random, unmatched, unrelated cadaver kidneys do well and since the dosage of immunosuppressive agents can often be reduced to relatively safe maintenance levels, it is likely that these patients have come to terms with the graft antigens to allow for a peaceful and profitable co-existence that probably involves natural donor-specific unreactivity.

In spite of this static background, clinical organ grafting is a worthwhile form of medical treatment that is not yet available to many patients in need. To be dying from failure of a vital organ function is as serious an affliction as any other lethal disease. When we spend huge sums of money without question on the treatment of cancer and operating on the elderly, why should organ grafting be attacked so often as an expensive luxury? Since organ grafts are seldom successful in those over the age of 50, most patients in need are of potential economic value to the state. Dying slowly in an expensive hospital bed is likely to cost far more than a transplantation operation which, if successful, will restore a breadwinner or housewife to the community. These financial matters do not take into consideration the suffering of the patients and their relatives if they are denied treatment. In the United Kingdom there are approximately 3,000 deaths a year from kidney disease in people aged five to 55 years. The DHSS has established 25 dialysis and transplantation centres. Most of the dialysis spaces are full and new patients cannot receive treatment since

only 500 kidney grafts a year are carried out. The majority of transplantation centres are performing less than half the number of grafts for which there are facilities. This is demoralising for the staff and patients, especially since the cause—namely a desperate shortage of donor kidneys—is potentially so easily soluble.

A kidney can be grafted from a live volunteer or a cadaver. Since the results of grafts from cadavers differ little from those obtained with grafts from unrelated live volunteers, only blood relatives are considered as donors. The operation for a live donor is not trivial and very often there is no suitable or willing familial donor. Removal of an organ from a dead body can do the deceased no harm and can be a gift of life to the recipient. Why then is there such a serious shortage? It has been suggested that in England the only thing more sacred than a live dog is a dead human body. This feeling for a cadaver may be an important subconscious reason for the lack of enthusiasm for organ donation after death. The precise details of what befalls a corpse are conveniently thrust out of conscious deliberation. Thus there has never been any serious opposition to the autopsy examinations ordered by coroners following most accidental deaths. The wishes of the deceased in his lifetime and those of his relatives have no bearing on the decision. All the organs are removed and examined, but these matters are not discussed by the relatives or the public. A request for organ donation does, however, require conscious thought on an unpleasant topic—death.

There are two categories of cadaver donor:

● Bodies brought into hospital dead. Here the diagnosis of death is straightforward, but there is urgency in removing the kidneys since if they are left in the corpse for more than an hour they will be useless. Once removed they are cooled and at 0 °C they can be kept in good condition for 12 hours. If they are perfused continuously with an appropriate cold oxygenated solution they can be preserved for up to 48 hours.

To comply with the Human Tissue Act of 1961, if the wishes of the deceased are known they are followed, otherwise the relative's permission must be sought. Often the relatives cannot be found in the limited time available. If they are traced it may be cruel to raise the question of organ donation at this moment of terrible distress, although sometimes this is not the case and the feeling that some good may result from their tragedy can give comfort. It is obviously preferable to know the wishes of the deceased—the simplest practical solu-

tion is to carry a kidney donor card as supplied by the Department of Health and Social Security. In spite of the fact that most people are in favour of organ donation after death, I doubt that more than a small percentage would carry a card, since it is a bother and its presence is a continuous *memento mori*.

● A body with a dead brain but an intact circulation, maintained by mechanical ventilator of the lungs. This category of cadaver donor is the only type from which heart or liver grafts can be used, because of their extreme vulnerability to ischaemic damage. After death of the brain, other organs and tissues die at different times depending on their oxygen requirements, unless the circulation is artificially maintained by oxygenating the lungs. Obviously all vital organ

grafts must be alive, otherwise they would be useless to the recipients. The organs of a decapitated body could be perfused and oxygenated with the heart beating, yet no one would consider the individual to be alive. Nevertheless there is so much superstition and folklore concerning the heart that many people consider the beating heart to be the cardinal sign of life.

How can this view be reconciled with the fact that it is routine surgical practice in open heart operations to stop the heart so that it can be repaired? During this period the patient is kept alive because his brain is perfused by an artificial heart-lung machine. Should the cerebral circulation fail, the patient will certainly die. Patients with brain damage from an injury, haemorrhage or tumour are

Kidney Donor Card

Your kidneys could help someone to live after your death

Keep the card with you at all times in a place where it will be found quickly

THE Department of Health and Social Security has recently stepped up distribution of kidney donor cards like these. Four million have been distributed, and although this does not mean that a similar number have been completed, hospital authorities

are finding that an increasing number of emergency cases, suitable for kidney transplant or research, are carrying the cards. Area health authorities are responsible for distribution, and the cards can usually be obtained from local hospitals.

I (full name) _____
 request that my kidneys be used after my death for transplantation or, if they are found unsuitable, for research.

Signature of donor _____ Date _____

The above-named person has discussed his/her wish with me and I do not object to that wish being complied with.

(Name of next-of-kin) _____

of (address) _____

Tel _____

Signature of next-of-kin _____ Date _____

resuscitated and assessed. If the damage is severe they stop breathing and this function is taken over by a mechanical ventilator. If after careful examination by experienced neurologists or neurosurgeons it is established that the brain is totally and irreversibly destroyed, then the ventilator is stopped since the perfusion of a corpse can be of no benefit to the deceased and would cause distress to his relatives and the nursing staff.

The decision to stop the ventilator has absolutely nothing to do with organ grafting. This was an accepted humane procedure before organ grafting was established. Once the decision has been made, however, and if it is likely that the case may be a suitable organ donor, there is then time to discuss the matter unhurriedly and sympathetically with the relatives, and the transplantation team can be prepared. In the USA and several countries in Europe, the organs are removed before the ventilator is stopped, since the intact circulation will ensure that the organ is in perfect condition. In the UK organs are usually not removed until after the ventilator has been stopped and the circulation has ceased. The heart may beat for up to an hour without oxygen; during this period all the organs including the heart are suffering severe damage — since the blood passing through them is becoming progressively depleted in oxygen and nutrients and is becoming increasingly acidic.

The British Transplantation Society recently published a report on the shortage of organs for transplantation, (*Brit. med. J.*, I, 251; 1975). It was concluded that apathy in the medical profession was the main cause of the shortage, but that this was aggravated by lack of public information, ambiguities in the law and an unhelpful attitude of some coroners. The report proposed that there should be minor changes in the law, and a code of practice to be followed by all transplantation centres.

Although the main clinical application of organ grafting has been the kidney, both the heart and the liver have been transplanted successfully and have restored moribund patients to normal lives. There are no substitutes for heart and liver function comparable with the artificial kidney. This lack of artificial organ support has held back progress. In spite of this handicap, Dr Shumway in Stanford has transplanted more than 70 hearts with results which are little inferior to those of kidney grafting. There are far more potentially suitable cadaver organ donors than are needed, but sufficient organs are unlikely to become available until it is assumed that after death it should be a routine procedure to remove organs for grafting. □

KENNETH MELLANBY



Paper chains

I FOUND the recent white paper *Food from Our Own Resources*, issued by the Minister of Agriculture, disappointing (Cmnd. 6020; HMSO). It makes no provision for the possible effects of a fall in the value of the pound sterling, which would make it impossible for us to continue to import food at the present rate, nor does it suggest the action that would be needed if a world food shortage threatened our imports. It does, however, make modest proposals for increasing our agricultural productivity—by enlarging our dairy herd, increasing the acreage under cereals, and growing some oil seed. Even if all targets are met, we will still be far from self-sufficiency and (at present prices) our balance of payments deficit will still be enormous.

The White Paper does imply that a greater improvement in yield and in our finances may result from research. Those scientists remaining in agricultural research (and whose work, it is hoped, will have this result) may, however, be surprised to read that the "National reorganisation [of research] in line with Lord Rothschild's recommendations is already taking effect in the closer integration of research and development with agricultural progress." Although the precise meaning of this curious example of Whitehall prose may be difficult to disentangle, it presumably means that agricultural research is becoming more and more effective. The sad thing is that the writer of the White Paper probably believes that this is true.

It is perhaps too soon to analyse the total effect on research—and particularly on agricultural research—of the Rothschild system, but it is disconcerting to find that there is such a divergence of views between the actual researchers themselves, and the administrators and committee members concerned with scientific policy. In our laboratories we see the number of the scientists at the bench decrease, and find the vacancies of those who leave (often to move into administrative

posts) remaining unfilled. Morale is lower than ever before, and complaints of time-wasting paper work, often at the behest of unnecessary committees, are widespread. Lord Rothschild criticised the research councils (to my mind, rightly) for wasting too much time and resources on committees, yet he has, no doubt unwittingly, caused the time spent on committees and working parties to be at least trebled.

The central feature of Lord Rothschild's proposals was the "contract". Money previously paid by the government to research councils has been transferred to executive departments who then pay the council for doing some particular piece of research. The idea was that this would make sure that work was concentrated where it was most needed. Now had contracts been the simple things suggested by Lord Rothschild, involving large sums to be spent on some wide field of work, the conditions simply and briefly set out on 'half a sheet of paper', the idea might have had some merit. But, unfortunately, the Civil Service has seen to it that many contracts are small, complicated and requiring the scientists involved to produce detailed 'project plans' and a constant flow of information to feed the computers which are playing an increasing part in sterilising originality at the laboratory bench.

The saddest result of all this administrative complication is that it has destroyed the enthusiasm of many research workers and has encouraged others to transfer to the administrative posts which seem to be so much more esteemed by the authorities. In the past, research for many was a way of life and workers often successfully chose problems which they believed were relevant and soluble. They were sometimes right, and they were then able to do much to see that their results were used, for instance, by the farmers. The trouble about the contract is that the scientist who has to carry it out may think it is for work which he cannot fully believe in. And he may well be right. But although in theory there are ways in which contractors can be persuaded to use their money wisely, few research workers believe that they will be very popular if they constantly shew that the authorities are incapable of selecting the best problems for investigation.

It is perhaps surprising that, though we have made many changes in the organisation of government-financed research in Britain, no one seems to have tried to find out how these have affected its efficiency. The impression certainly exists that no one is looking at all critically at the results of Lord Rothschild's recommendations. Surely someone should place a contract for such a study. □