"It can't be done"

Roy Y Calne

In 1950, medical students in the UK were allocated patients for whom we had a special, personal responsibility and acted as advocate. I presented the case of a patient about my age dying of kidney failure. The senior consultant told me to make my patient as comfortable as possible, but, sadly, he would be dead in two weeks. I was appalled by this stark prognosis and, thinking in terms of gardening, I asked whether the patient could receive a kidney graft. The consultant said no, and, when I asked why not, I was told "it can't be done." I was perplexed because it seemed that there were only three plumbing junctions required—an artery, a vein and the ureter—and surgical techniques were available to accomplish these tasks. I had no idea of the phenomenon of graft rejection.

I returned to the subject in 1959 after hearing Peter Medawar give a lecture in Oxford explaining the immunological nature of graft rejection and the exciting experiments that he and his colleagues had done, showing "specific immunological tolerance"[1]. The concept of the developing immune system in the fetus, which would accept as a 'self-product' any potential antigen with which it came in contact, raised an important question not yet answered: could an adult immune system be temporarily returned to the fetal state while the organ graft was inserted, and could the immune system then regain its protective role, having accepted the foreign graft?

Hurdles to transplantation

Since 1959, my professional work has been focused on organ transplantation, and from the beginning it was clear that there were two separate series of problems to overcome. The first was technical and, for the kidney, this was solved by Joseph Murray with the successful transplant of a kidney between identical twins[2]. The second was immunological: the biological rejection of transplanted tissue. In 1959, while working at the Royal College of Surgeons in England, I found that total-body X-ray irradiation failed to prolong kidney graft survival, but the antileukemia drug 6-mercaptopurine prolonged renal allograft survival in dogs. Sir Peter Medawar felt this observation to be worthy of intense and prolonged study, and this proved to be the case[3], as it led to the introduction of azathioprine, the first effective clinical immunosuppressant.

I was fortunate to receive a Harkness Fellowship to study at Harvard Medical School in Francis Moore's Department of Surgery, where Moore himself was pioneering the technique of liver transplantation in dogs at the same time that Thomas Starzl was doing similar experiments in Denver. I was therefore exposed to the formidable technical obstacles to be overcome, but my work in Moore's department was concentrated on immunosuppression and on developing drugs given to me by the Nobel laureates George Hitchings and Gertrude Elion, who had synthesized 6-mercaptopurine. They suggested that I study a series of compounds, and one of them, azathioprine, turned out to be a little better than 6-mercaptopurine in terms of promoting graft survival[4]. Azathioprine was used in clinical kidney transplantation with results that were sometimes encouraging despite there being many failures. On returning to the UK in 1961, I continued with this work and was appointed the Chair of Surgery at Cambridge University in 1965.

Transplantation of the liver is a formidable operation, and for those attempting the procedure for the first time, when there was no previous experience, mistakes were made at every stage. But gradually a corpus of knowledge developed, and errors were recognized and subsequently avoided. Even in a healthy animal recipient the orthotropic operation is of great magnitude, involving removal of the recipient liver and thereby totally blocking the return of blood from the inferior vena cava and the intestinal portal system to the heart. The physiological disturbances were overcome experimentally by both Starzl and Moore in the late 1950s and early 1960s using independently developed blood bypass procedures.

The move to the clinic

The move of liver transplantation to the clinic was pioneered in 1963 by Thomas Starzl[5], but the results of the first pilot study were disastrous, and he decided on a moratorium while further experimental work was performed. In the clinic, only patients desperately ill were referred for consideration of this untried operation, and it is not surprising that some of these patients were unfit for an anesthetic, let alone a liver transplant. The anesthesia and the intensive care after the operation required complicated physiological considerations and special training for anesthetists and nurses, so that care of the patient after the operation by both surgical and hepatological teams remained at the same level of vigilance as during the surgical procedure (**Fig. 1**). Also essential was an in-depth understanding of the immunosuppressive drugs, none of which was perfect, having toxic side effects.

Our own interest in liver transplantation followed studies on the immunology of liver transplants and the unexpected acceptance of liver grafts that was observed between unrelated pigs without any immunosuppressive drug treatment. Usually, typical features of rejection were observed but they resolved spontaneously[6], an interesting and previously little studied phenomenon that presumably had similarities to the immune reactions that occur after a virus infection, when the powerful antibody and cell-mediated immunities are switched off after the infection has been defeated.

Although pigs have been bred over hundreds of years to improve the quality of their meat, they are in no sense inbred, as are laboratory murine strains. The porcine liver graft could also protect other tissues such as kidney and skin from the same donor from being rejected. These observations were supplemented by many studies in inbred rats, and it was shown that, between certain strains, irreversible rejection occurred and, between others, there was little evidence

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Figure 1 R.Y. Calne, *The Liver Transplant Patient and The Tribute to the Compassion and Skill of the Intensive Care Nurse*. Oil on canvas, 4 × 3 ft. Commissioned by Goran Klintmalm of the Liver Institute in Dallas.

of rejection. Some rat liver transplants behaved in a manner similar to those in pigs, with rejection and then spontaneous recovery. Reports of these experiments provoked the *Lancet* to write a leading article entitled "Strange English Pigs"[7]. However, the phenomenon was not limited to the origin of the pigs and was repeated in other laboratories[8].

In the clinic, the hurdle of performing liver transplant in an exceedingly sick patient was difficult to overcome, and there were many failures. But when success was achieved, prevention of rejection seemed to be easier to accomplish than in cases of kidney and heart transplantation. In the largest clinical series in Denver, some of the patients initiated an important experiment without telling their doctors and deliberately stopped taking immunosuppressive drugs because they disliked the side effects. This noncompliance is a common phenomenon in recipients of all grafts, particularly teenagers and especially girls. Years later, these patients, who had become 'operationally tolerant', were studied and seemed to have accepted their livers without serious penalties. Coincidentally, some patients with viral disease and malignancies were regarded as too ill to continue immunosuppression, which was deliberately stopped. Some of these patients did not reject their liver grafts, others did. The procedure of weaning from immunosuppression was investigated extensively in the Denver/Pittsburgh series[9]. It became apparent that operational tolerance in some cases was extremely robust, with patients maintaining good function in their grafts for many years, whereas in other cases the tolerance was more fragile, and rejection could be precipitated by extraneous factors, for example, infection.

Two factors were, in fact, known. First, the liver is a major source of soluble human leukocyte antigen (HLA) class I antigen which can have a specific immunosuppressive effect, and approximately half of circulating HLA class 1 antigen in the blood of recipients of liver transplants is produced by the donor organ. Second, there is well-recorded trafficking of cells between the liver graft and recipient, particularly of passenger leukocytes and especially Kupffer cells, and it has been suggested that these play an important part in the relative lack of rejection of liver allografts, producing 'microchimerism', which may have a specific immunosuppressive effect[10].

Despite the failure to provide a complete picture to explain the phenomenon, the observations above confirmed the immunologically privileged status of the liver transplant experimentally and in the clinic.

In 1967, Starzl recommenced liver transplantation. Shortly after that, I performed the first liver transplant in Europe in 1968. I was given strong scientific support by Moore, who happened to be visiting Cambridge and who also scrubbed in at the operation as my first assistant, something for which I was extremely grateful[11]. This was the beginning of our program of liver transplantation in Cambridge, which linked up with Roger Williams's hepatology unit in King's College Hospital in London.

Immunosuppression

An important watershed moment in the management of all organ transplants was the introduction of cyclosporine, developed in the laboratory and first used in clinical organ transplantation in Cambridge[12]. Cyclosporin improved the one-year kidney graft survival from around 50% to more than 80%. This was seized upon by some of those who had previously been critical of the whole idea of transplantation, and they became enthusiastic supporters and performers of the procedure. Prior to the advent of cyclosporine, there were about ten centers seriously performing organ transplantation in the world; within a few years of its introduction there were more than 1,000, and the new problem of shortage of organ donors started to become apparent and has become increasingly worrisome ever since.

The introduction of cyclosporine into the clinic improved the results of liver transplantation. Another valuable immunosuppressive drug, FK506, or tacrolimus, was discovered in Japan and brought to the clinic by Starzl in Pittsburgh. Tacrolimus is a calcineurin inhibitor with a mode of action similar to cyclosporine. Another powerful immunosuppressant with a different mode of action and toxicity profile, rapamycin, was developed in Cambridge[13].

When new immunosuppressive agents became available there was a tendency for clinicians to add them to previous protocols. This often led to severe toxicity, excessive immunosuppression, infection and a deterioration of clinical results. Our observation of liver tolerance in the pig with the spontaneous resolution of immunological rejection suggested to us that any approach toward achieving the goal of immunological tolerance would require active engagement of the immune system of the recipient with donor tissue. Excessive immunosuppression might prevent this engagement and prevent tolerance. We hypothesized that a window of opportunity for immunological engagement, or 'WOFIE', might be an essential step in the development of tolerance; so, in the clinic, efforts should be made to use immunosuppression at the lowest level that would permit graft acceptance. The pendulum has now swung toward minimalization of immunosuppression, and we have been particularly impressed with the use of the powerful antilymphocyte monoclonal antibody Campath-1H, developed by Waldmann's group in Cambridge, given as an induction treatment followed by a low-maintenance immunosuppression regimen. It has been slow to be adopted, but this so-called "prope"[14] or almost-tolerance has resulted in excellent quality of life for most patients; more than 80% of our patients had never had steroid treatment at any stage (steroids, used extensively as immunosuppressive maintenance drugs, can have unpleasant and dangerous side effects)[15].

Figure 2 R.Y. Calne, *Tribute to the Organ Donor—The Real Hero of Transplantation*, 2000. Bronze, approximately 18 in. One of a series of 12 castings.

Ethical issues

The shortage of organ donors has put enormous pressure on health resources by patients and doctors. The introduction of a new and successful treatment may be regarded as a therapy that should be available for all in need, but this is impossible for organ transplants. Fostering the culture of charity and compassion in organ donation is probably the most important approach to improving the number of organ transplants.

In Spain, the development of an outstandingly successful cadaveric organ donation program has been admired and emulated by some countries. It involves an 'opt-out' law on organ donation and the presence of medically qualified coordinators in all hospitals in Spain.

An opt-out law does seem to confer advantages, as it permits the removal of organs after death provided no objection has been made by the patient in his or her lifetime and that the views of grieving relatives are not over-ridden. In Singapore, the introduction of an opt-out law was followed by a tenfold increase in the number of deceased organ donations.

However, in most countries, it is not possible to obtain enough cadaveric organ donors, and living donors for liver grafting have been used, especially in Japan from parents to children. Gradually, the indications have been widened to adult-to-adult liver grafting, something that has precipitated worrying ethical matters, since removal of half a liver from an adult is a major procedure with a significant morbidity and mortality. In one report, for example, five liver donors themselves developed liver failure[16]. Four died and one was successfully treated by becoming a liver transplant recipient.

So, organ transplantation has led to an unprecedented break with traditional medical ethics, in that under certain carefully defined conditions a normal healthy individual may be harmed. Within a family, for a parent to donate a kidney or part of a liver to a child is not disputed, and this acceptance is usually extended to sibling-to-sibling donation and donation from other family members, including spouses. There is, however, a danger in any operation, and not only liver but even kidney donors have died. With liver donors, the risks are much greater, especially in adult-to-adult donation, and the concept of informed consent can be difficult to grasp for all concerned.

The gift of an organ is really a 'gift of life', and something as valuable as a life-saving organ is far more important to a suffering patient than wealth or power. To obtain an organ when a donor is not available puts stress on moral values. A rich person may travel to a poor country to pay for an organ from an impoverished donor or from a criminal subjected to capital punishment. There have been cases of people being abducted and their organs removed by criminal gangs, leaving the unwilling donor without a kidney or even dead. There have also been questions raised as to whether all patients who might benefit from an organ deserve to get a graft, for example, those suffering from alcoholic disease or self-induced drug abuse. There have been serious concerns regarding the quality of the organs that are offered, as well as about the age and health of the donor and recipient.

The transplant community is rightly concerned with these ethical matters, and even if they cannot all be overcome, defining and discussing the moral dilemmas that may arise in organ transplantation is a move toward improving the ethical background in which transplants are performed. Organ transplants have introduced new ethical worries for the community, but the organ donor—whether a live volunteer or a donor after death—is the true hero of organ transplantation (**Fig. 2**).

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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