A RECIPE FOR TRANSPLANTATION

by

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I am greatly honoured to be invited to give the Scott-Heron Lecture for 1983 but feel very inadequate to follow the distinguished doctors who have preceded me.

The interest in the kidney was first aroused by a young woman with bilateral staghorn calculi, while working as a house surgeon with the late Mr. Cecil Woodside. Mr. Woodside was a general surgeon who had a special interest in the kidneys and particularly in renal stones. He removed huge stones from kidneys of the patient, Mrs. Brigid Kelly. Later when they recurred in the left kidney he carried out a left nephrectomy. I am glad to say that the stones did not recur in the remaining kidney and Mrs. Brigid Kelly still remains well with excellent kidney function at the age of 70. Mr. Woodside was greatly interested in the pathogenesis of kidney stones and encouraged me to continue my interest which led eventually to the formation of the Renal Unit at the Belfast City Hospital in 1959.

I cannot describe this work without acknowledging the help, encouragement and support of my husband, Max Freeland. Dr. Terence Fulton in a kind tribute to him at the Opening Address in October 1982, commented on the helpful influence he had exercised on generations of medical students. I met him just before I graduated and the help, encouragement and support which I received from him is beyond estimation.

The work which I will describe belongs to the whole team associated with the Renal Unit of the Belfast City Hospital. The whole project depends on the able and devoted work of the nursing and technical staff in equal measure with that of the medical members of staff. Moreover we are greatly helped by the support of the laboratories, radiology, indeed the whole of the medical support services. Not only this, but the work would be impossible without the co-operation of the intensive care units in other hospitals. We owe a particular debit to the Respiratory Intensive Care Unit and the Neurosurgical Unit of the Royal Victoria Hospital.

It was shown by Ullman in Vienna as long ago as 1902 that the kidney of a dog could be transplanted from its normal site into the neck and urine would be produced, demonstrating that the kidney did not require a nerve supply. He was able to demonstrate that a kidney from another dog, or even from a goat would also produce urine in the new host but does not appear to have carried his experiment further. Carrell, also in Vienna, in 1902 confirmed Ullman’s observations and went on to transplant a kidney from a dog to a bitch, removing the bitch’s own kidneys, and the bitch remained well with good kidney function for some days but ultimately the graft ceased to function. Williamson carried out a similar experiment in 1923, and his description of the appearance of the kidney graft provides a classic description of rejection.
Transplantation of human kidneys was attempted in Boston from 1951 onwards, using "free" kidneys or cadaver kidneys. In 1954 Murray and Holden reported four human cadaver grafts, three of which failed but one survived, apparently without using immunosuppression. In the meantime research into the nature of the rejection process had revealed that it ought to be possible to transplant kidneys between individuals whose genetic similarity was sufficiently close, without fear of rejection. This led to the first transplantation between identical twins in Boston in 1954. This operation was successful, and over the next five years transplantation of kidneys between identical twins was carried out in a number of centres in Europe and America. Some of these transplants failed for technical reasons but in none of them was there any evidence of rejection. It is obvious that few patients reaching end stage kidney failure are fortunate enough to have an identical twin, able and willing to provide a kidney. This led to research into how rejection might be prevented when the graft came from a less closely related individual.

In 1958 it was shown by Hamburger in Paris that whole body irradiation would prevent rejection of the grafted kidney, but it almost invariably led to death of the patient because of bone marrow depression followed by uncontrollable sepsis. Research then centred on the possibility of preventing rejection by a drug, or drugs, in the hope that this could be controlled more easily than was whole body irradiation. At the beginning of the 60's Murray and Calne in Boston used 6-mercaptopurine in dogs and found that while it was immunosuppressive it was also very toxic. Burroughs-Wellcome in New Jersey produced an analogue of mercaptopurine, azathioprine, which proved in dogs to be a good immunosuppressive, as well as much less toxic, drug. In 1962 azathioprine was used successfully to prevent rejection when a kidney taken from a patient dying during an open heart operation was transplanted into an unrelated individual. Despite several rejection episodes the kidney continued to function for two years. About the same time cyclophosphamide and actinomycin were given to prevent rejection but proved to be more toxic than azathioprine, which thereafter became generally accepted as the drug of choice for kidney transplantation.

Goodwin in 1962 reported that corticosteroid reversed rejection a number of times in a mother-to-child graft being treated with cytoxin (a drug similar to cyclophosphamide). Thereafter although their mode of action was unknown, and possibly mainly only anti-inflammatory, steroids were given along with azathioprine as the standard immunosuppression for kidney transplantation. Later attempts were made to develop a more specific weapon, antilymphocyte serum, against the small lymphocytes which infiltrate rejecting grafts. Antilymphocyte serum produced very promising results in animals but has been disappointing in human clinical transplantation. It is difficult to produce and standardize a satisfactory serum, and the use of antilymphocyte serum or globulin is still controversial even today.

Another factor which contributed greatly to the development of kidney transplantation was the invention of the Scribner shunt. This made it possible to use the same blood vessels for repeated treatments by the artificial kidney, so that a patient could be maintained for long periods, with improvement in general condition, until a kidney became available. This was later superseded by the arteriovenous fistula first suggested by Brescia in 1966. The discovery of the Scribner shunt in 1961-62 inevitably led to an interest in treating patients with chronic renal failure in those
units originally set up for the provision of treatment of acute renal failure. This happened in Belfast where patients were sometimes referred with renal failure of acute, or apparently acute onset, which in fact was due to irreparable kidney disease. In Belfast the earliest attempt to use a Scribner shunt was made in 1964 with the help of the late Mr. Megaw, and by the beginning of 1965 a patient was being successfully maintained, using the available facilities intended for treatment of acute renal failure.

In 1965, the DHSS in London called a meeting of those people already using haemodialysis, to decide whether the time had come to provide regular dialysis therapy for end stage renal disease. This was followed by the setting up of a Working Party with the brief of setting up a centre for regular haemodialysis therapy in each hospital region.

From the time of Murray and Calne's discovery that cadaveric transplantation was possible with the aid of azathioprine, it seemed that transplantation would prove eventually to be the way to replace kidney function but that good quality dialysis therapy was necessary to make the patients fit and maintain them until kidneys could be provided.

As a preliminary stage to setting up a kidney transplantation service here, occasional patients were sent to centres already transplanting in other parts of the United Kingdom, a form of "transplant brokerage." Over the years 1962-1968, 17 patients were "sold" to colleagues, most frequently to St. Mary's Hospital or to Roy Calne in Cambridge. Three of these patients are still alive, the longest one with a cadaver kidney still functioning excellently after 18 years, one of the longest in Europe.

During these years I was actively trying to obtain what I regarded as the minimum facilities for renal transplantation. The need for dialysis had already outgrown the small promises in Ward 9 even without transplantation. The late Mr. Megaw had generously allowed the use of a cystoscopy theatre for a 2-bed regular dialysis service and four patients were maintained without any additional medical staff and little in the way of equipment. By 1964 it was envisaged that the renal service would develop in the new Tower Block but in the meantime it was apparent that more space was needed. It became clear that the only way this could be provided was by the so-called "temporary" building now known as Renal I. In the meantime the Working Party of the DHSS had recommended the provision of a 10-bed dialysis unit for each hospital region, but the planning of our 6-bed unit to provide for acute renal failure and a small amount of treatment of chronic renal failure by dialysis and transplantation, was already at an advanced stage. It was decided to proceed with the original plan, providing the 10-bed haemodialysis accommodation as a second phase (which was ready for use by May 1972).

The first phase of the building was ready for occupation in July 1968, the part now known as Renal I. This contains 6 single rooms, a theatre and a 2-bed dialysis room, plus the usual offices (Figure 1). The unit differs very greatly from an ordinary ward. The individual patient rooms are situated between "clean" and "dirty" corridors, communicating with each. Entry of staff is via changing rooms as to a theatre suite, and all medical and nursing care is provided via the "clean" corridor. Disposal of all used items is via pass-through cupboards to the "dirty"
corridor. Each room has its own air supply and differential pressure ventilation ensures that air flows from "clean" towards "dirty" areas. This system provides good quality reverse barrier nursing, without the need for air locks, provided that the discipline of usage is properly carried out. This design allows the use of the unit to treat both patients with recent transplants as well as patients with acute renal failure who may be infected.

During the early part of 1968, with my colleagues, the plans for renal transplantation were worked out in detail. The legal aspects of transplantation were explored with the Legal Advisor of the Northern Ireland Hospital's Authority, and with the Belfast Coroner, the late Dr. Lowe.

A major part of the work of these meetings was the formulation of the recipe for transplantation (Table I). The recipe differed radically from the practice in the already established centres for transplantation in Europe and the United States. In 1968 most centres preferred to use living related donors rather than cadaver donors, and results of transplantation were vastly better using living donors. As the organization for cadaver donation is more complex we decided to prepare ourselves for the more difficult task. Our planning therefore provided for the additional problems related to the harvesting of cadaveric kidneys. We accepted the probability that most of the transplanted kidneys would develop acute renal failure, rather than functioning immediately as do most living related kidneys. The fact that postoperative haemodialysis would be needed did not seem to be a serious complication, which leads me to the next point, the organization of our clinical team.

In the establishment centres the transplantation service was entirely in the control of surgeons. Patients awaiting transplantation were maintained by regular dialysis therapy under the care of nephrologists. They carried out the investigations of family members in search for a living donor but took no part in the location of cadaveric donors. Once the patient entered the transplant unit the nephrologist relinquished all responsibility to the surgeons. One consequence was that should
TABLE I

Recipe for Transplantation

1. Cadaveric donors.
2. Organization of clinical team.
3. Preparation and assessment of recipient
   (a) bilateral nephrectomy
   (b) blood transfusion.
4. Tissue matching.
5. Transplant operation
   (a) anaesthesia: consultant
   (b) surgery
   (c) per-operative transfusion and IV therapy
   (d) avoidance of unnecessary drugs.
6. Immunosuppression.
7. Prevention of infection.
8. Caution in diagnosis of rejection.
9. Long-term follow-up.

post-operative haemodialysis be required this was carried out by doctors without experience in the management of acute renal failure.

Our plan envisaged transplantation based on a closely integrated team of nephrologists, surgeons, anaesthetists and the tissue matching service. The nephrologists were to prepare and assess the recipient providing full information for the surgical team who were to be briefed in advance of any special problems. This approach later paved the way for transplantation in patients without adequate bladder function, using an ileal conduit, and in diabetics. In 1968 it was only feasible to use ABO matching for distribution of kidneys. Such tissue typing as was then possible took longer than it was considered safe to keep the donor kidney so that the tissue typing result became available only after operation, and therefore was of academic interest only.

The surgical team prepared their techniques by carrying out a series of transplants in dogs. This was to provide practice in removal and perfusion of donor kidneys as well as of insertion of kidneys. A surgical technician was available to help with the perfusion of kidneys. The surgeons were responsible for drawing up lists of instruments, etc. required for the donor trays and the transplant operation trays. The Renal Unit theatre sister was to be responsible for their packing and sterilization. Special containers were made for the donor instrument trays, sterile perfusion fluid and sterile plastic bags to contain the perfused kidney, which were to be taken to the place where the donor operation was to be carried out, of course with full aseptic precautions. A supply of ice chips in which to pack the kidney in its plastic box, had to be arranged.

The nephrologists undertook the role of organization for procurement of donors, one of them being always on-call by bleep or by phone, to discuss with the doctor who was offering the donor the suitability and logistics of harvesting the kidneys. In due course the surgeon on-call was contacted and proceeded to harvest the kidneys
as soon as possible. The surgical team was responsible for all aspects of perfusion and chilling of the kidneys. In the meantime the nephrologist was to decide which recipient should receive the kidney, in 1968 on the basis of ABO identity and chronological order, also bearing in mind clinical need. At this stage only one kidney could be used locally and there was as yet no method of sharing kidneys, although we were able to take part in a kidney-sharing scheme, “The London Transplant Club,” by 1971.

The availability of our dedicated theatre facilitated the operation at a time when it was thought unwise to keep a kidney chilled for longer than 4 hours. The anaesthetists had previously agreed about the type of anaesthesia and agreed to provide a consultant on-call rota so that expertise was gained at the maximum possible rate. During the operation the nephrologist on duty prepared the immuno-suppressive drugs, and was to be available throughout to advise on blood requirements and drugs, and arrange details of early post-operative care.

The post-operative care was to be mainly the responsibility of the nephrologist who would prescribe all drugs used, to prevent confusion arising. The surgeon would be responsible for care of the wound itself, and the period of time for which wound and catheter drainage was required.

It can be appreciated that the nephrologists, from the very beginning, played a prominent role in the transplant situation. It is interesting to note that now in the 80's almost all transplant teams include one or more nephrologists. It must be admitted, however, that they do not usually play as prominent a role elsewhere as in Belfast.

Most patients awaiting transplantation are supported by dialysis but occasionally transplantation may be carried out just before dialysis becomes essential. Each body system must be carefully assessed so that problems may be anticipated. Hypertension must be controlled. When hypertension is not controlled by dialysis with the minimum of drugs bilateral nephrectomy is usually carried out. The original protocol provided for bilateral nephrectomy for all recipients, for control of hypertension, and removal of a source of potential infection or tumour. Although with time and increase in workload this policy had to be abandoned and bilateral nephrectomy used more sparingly, the bilaterally nephrectomized recipient is easier to manage in the early post-operative period. There is no uncertainty about the source of any urine passed, all of which must come from the new kidney. A late benefit of bilateral nephrectomy is the very low incidence of hypertension, compared with patients retaining their own kidneys.

Blood transfusion is worth some detailed consideration. The anaesthetists were perturbed about the marked anaemia of most patients with end-stage renal failure. It was agreed by the team that all patients should be given transfusions to prevent symptoms of anaemia. The need for transfusion was increased by the policy of bilateral nephrectomy. Now about the time we were planning transplantation, hepatitis B began to appear in renal units in other areas and transfusion came to be regarded as potentially dangerous to staff and patients. It was discovered also that some patients responded to transfusion by developing antibodies against antigens in the transfused blood. There developed a strong body of opinion that patients awaiting transplants should not be transfused, this despite evidence from transplants
that transfusion improved graft survival. We considered many times from 1970 onwards whether we should discontinue blood transfusion, but as we were obtaining good graft survival decided to continue to transfuse, albeit somewhat more sparingly. In 1973 Opelz and Terasaki reported that graft survival was better in transfused than in non-transfused patients. This report was criticized on the grounds that it contained data from a large number of centres, but over the next few years experiments in rodents, dogs and rhesus monkeys all suggested that prior transfusion led to improved graft survival although admittedly hyperacute rejection occurred in some animals. Gradually the evidence accumulated in human transplantation that transfusion improved graft survival, and this is now generally accepted.

Tissue matching, apart from ABO, played no part in the early disposition of grafts as it was available only retrospectively. Nevertheless, graft survival was good from the beginning. Although we now prefer to obtain a 2 (out of 4) antigen match or better, this is because it makes it easier to carry out a second or even third graft should this become necessary. Regular checking for cytotoxic antibodies was added to the programme later.

To return to the recipe: The importance of high quality anaesthesia can not be over-emphasized. Until quite recently all anaesthetics for transplantation were given by consultants. Problems with anaesthesia have been remarkably few despite the fact that many of the patients have ischaemic heart disease of serious degree and all are anaemic. It is important that the blood pressure should be kept slightly high, in the range usual for these patients, and must not be allowed to rise unduly or fall.

Time does not permit me to go into the details of the operations for removal and insertion of the donor-kidney. For those unfamiliar with the subject the kidney is inserted into one or other iliac fossa, using the internal or external iliac vessels for vascular supply. The ureter is joined by one of several methods into the bladder lying conveniently near. Problems with the vascular anastomoses are relatively rare despite the fact that none of the surgeons have training in vascular surgery. Surprisingly, complications related to the ureter, including urinary leakage, sloughing of the ureter and late stenosis are fairly common. In Belfast, but in relatively few other centres, a capsulotomy along the convex border of the kidney is carried out routinely to help prevent rupture of a kidney swollen by acute tubular necrosis or rejection.

Great care is taken over the fluid balance during operation and post-operatively. Electrolyte fluids are given in small amount at the beginning of operation to permit administration of anaesthetic and immunosuppressive drugs. Thereafter blood loss is replaced generously with whole blood. It may be important that all unnecessary drugs are avoided. We do not give mannitol, frusemide, anticoagulants, prophylactic antibiotics or anti-fungals, although many other centres use them.

The immunosuppressive drugs are of crucial importance. In 1968, as indeed today, there was no general agreement about immunosuppression. A list of immunosuppressive therapy then in use is shown in Table II. It seemed to us best to commence with the simplest method, using azathioprine and steroid only, but the problem was the dosage. I obtained the protocols from St. Mary’s and Cambridge, both of whom had successfully transplanted my patients. Cambridge used much
TABLE II

*Immunosuppression in use in 1968*

1. Lymphatic duct drainage.
2. Irradiation of graft.
3. Azathioprine.
4. Azathioprine plus steroid.
5. Antilymphocyte serum.

TABLE III

*Immunosuppression for Renal Transplantation (Belfast Regimen)*

Initial immunosuppression:
- Imuran 5 mg/kg body weight—slowly;
- Hydrocortisone 200 mg;
  (given intravenously as soon as possible after intravenous infusion is commenced).

Remainder of first 24 h:
- No further Imuran;
- Hydrocortisone 200 mg given intravenously at 0 + 6, 0 + 12 and 0 + 18 h.

Maintenance immunosuppression:
(a) No significant function;
- Imuran 1.5 mg/kg body weight daily;
- Prednisolone 20 mg daily.

(b) Creatinine clearance of 30 ml/min or greater;
- Imuran 3 mg/kg body weight, given as a single dose;
- Prednisolone 20 mg daily for first 6 months. Dose is gradually reduced thereafter to 10 mg daily, if there are no signs of rejection.

Anti-rejection therapy:
- Prednisolone 200 mg, reducing in 3 or 2-day steps through 150, 100, 75, 50 to 20 mg per day.

NB: Extreme care is taken in making diagnosis of rejection.

more steroid than did St. Mary’s who gave larger doses of azathioprine. It was decided to use the lower dose of both drugs. St. Mary’s were then giving 10 mg of prednisolone twice daily from the second 24 hours onwards, whereas Cambridge gave 75 mg daily until diuresis occurred. It was only some years later that I discovered that St. Mary’s increased their dose of steroid soon after I contacted them, because of unsatisfactory graft survival. The dosage we used at the beginning is shown in Table III. The initial maintenance dose of prednisolone was 10 mg bd but was reduced much more gradually than in St. Mary’s, using three month steps.

As it seemed more logical to give the steroid as a single morning dose as being less likely to lead to adrenal suppression, this policy was followed from the third patient onwards. No other changes have been found necessary. The much lower dose of steroid given in Belfast compared with other centres is shown in Figure 2, where the area under the curve gives the total dose. It should be remembered that these are maintenance doses, patients in whom rejection occurs receive much more.
Moreover, some of the centres illustrated combine this therapy with antilymphocyte globulin, local irradiation of the graft, sometimes splenectomy or lymphatic duct drainage, all of which carry their own hazards.

The gratifying fact is that in the 80's transplant centres all over the world have reduced their dosage of steroid, encouraged by our good results using such relatively low doses, although many still use more than we give. Our own experience, and research, strongly suggests that in many patients even lower doses than we use may be sufficient.

I do not have time to consider treatment of rejection in detail but it is not remarkably different from that in use elsewhere. The dose of prednisolone is increased to 200 mg daily reducing in 3 day steps through 150, 100, 75 and 50 mg back to 20 mg daily. We originally gave a single intravenous dose of actinomycin C but this was not obtainable after 1972 and no other drug was given in its place.

The seventh point in the recipe is the prevention of infection. This seemed very important because the commonest cause of death following transplantation was then, and still is in many centres, infection. The majority of the infections appeared to be due to the usual types of hospital organisms though it was becoming clear that
unusual infections may occur. The known high incidence of hospital infections dictated the design of Renal I, illustrated in Figure 1. The design certainly provides protection but the sparing use of steroid may be of at least equal importance. Table IV shows the steroid-related complications encountered in the first 220 patients transplanted. Only five patients died from infection, only two of whom died during their first admission. It is of some interest that of the rarer infections commonly reported in association with transplantation we encounter cytomegalovirus, candida and herpes frequently but without fatalities, there has been one case of pneumocystis and two of tuberculosis. None of the rarer infections known to occur in immunosuppressed patients have been seen.

The cumulative survival curves for first cadaver grafts, produced by the UK Transplant computer is shown in Figure 3. Each curve represents the results of one unit and is anonymous except to the unit concerned. The top line represents the Belfast results. These results have held through 14 years for 297 kidney grafts.

Finally, the normality of our patients is noteworthy. At least 20 of the male patients have fathered children and 6 of the women have had normal babies by the vaginal route. One patient completed the Belfast Marathon in 1982 and 1983.

The recipe used in 1983 differs very little from the original of 1968. The main difference is that tissue matching is now a pre-operative procedure, permitting matching of donor with recipient. The sharing of donor kidneys through the UK Transplant Service, and with Eurotransplant and Scandiatransplant, facilitates good tissue matching. On the surgical side improved kidney perfusion with modern perfusion fluids has meant that many kidneys now function immediately and almost no kidneys fail altogether to function.

Future improvements in kidney transplantation will depend on better methods of immunosuppression. Already another immunosuppressive drug, cyclosporin A, is being widely used but as yet the serious side effects associated with its use suggests that it is too soon to change our recipe for immunosuppression.
Fig. 3
Cumulative actuarial survival curves for survival of first cadaver grafts in UK centres.

2. ALL N.O.M.D.S. CENTRES

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