Middle Articles

CONTEMPORARY THEMES

Cadaveric Kidneys for Transplantation

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British Medical Journal, 1969, 2, 565-568

Of the 2,000 to 3,000 young people who die each year in England and Wales from irreversible kidney disease only 10% are offered treatment in the form of transplantation or dialysis. This is a tragedy, since these two forms of treatment can restore a majority of patients to a healthy and happy existence. The reasons are complicated, but those who would argue that this country is not wealthy enough to provide treatment have a weak case, since the provision of a hospital bed at £50 per week for a patient dying of uraemia is far less economical than a kidney transplant, which can restore him to the community as a breadwinner. The cost of both transplantation and recurrent dialysis is decreasing and will continue to do so in the future. The Department of Health is in the process of establishing 25 dialysis units, each capable of treating 30 patients in the unit and of training a variable number of people for home dialysis. At the same time renal transplantation units are being established to work in collaboration with these dialysis units, since it is now realized that the two procedures are inextricably linked and collaboration between the two can treat the largest number of patients satisfactorily.

Tissue-typing facilities are improving and there is a direct correlation of a good tissue match with the behaviour of the transplant. In the future it is likely that transplantation will be considered as unethical if the match between prospective donor and recipient is shown to be poor.

A national health service should provide the best available treatment to all patients in need, but efforts to provide therapy for the large number of people who require it are doomed to failure unless there is a definite change in the attitude of the public and, even more so, the profession towards the provision of donor kidneys. Irresponsible reporting of some of the heart transplants has resulted in public concern about the integrity of the profession in its care of the dying. This, together with the Human Tissue Act—which has ambiguities and is generally unhelpful in the development of transplantation—and the uncooperative attitude of some coroners have made it extremely difficult to keep transplantation units in the United Kingdom fully supplied. The personal tragedies of those denied treatment are not fully appreciated by those who work outside dialysis and transplantation units, since they do not come into close contact with the patients and their relatives, who know that treatment could be made available.

Below is outlined the procedure that has been evolved in obtaining cadaver kidneys for transplantation at Cambridge. An attempt will be made to persuade those who at present are uncommitted that it is a medical responsibility to think of transplantation and to help provide donor organs from their patients who have died after receiving all the care and medical attention that was possible in their lifetime.

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Permission and the Law

To be useful for transplantation a kidney needs to be removed and cooled within one hour of death. Before a surgeon can remove an organ from a cadaver it is necessary—according to the present Human Tissue Act (1961)—for him to obtain permission from the relatives, unless the donor had stated in his lifetime that he wished his organs to be transplanted after death. If the donor has given permission it is not necessary to ask the relatives, though obviously they would be consulted if available. If the patient is in a terminal condition and it is clear to the relatives that the prognosis is hopeless—in spite of his receiving all possible care—then the relatives may be approached and asked if they would give permission for removal of kidneys for transplantation after death. There is no official form for this permission and it is not even necessary for the permission to be signed; I frequently obtain permission by telephone, but prefer to write on a piece of paper, "In the event of my relative's death I give permission for organs to be removed for transplantation." If this is then signed the form can be put in the hospital notes. Alternatively, permission may be obtained immediately after death.

According to the Human Tissue Act (1961), before organs can be removed from a cadaver it is necessary for the doctor to make "such reasonable inquiry as may be practicable" that neither the deceased nor his relatives would have objected. "Such reasonable inquiry as may be practicable" has not been clearly defined. There is only one hour after death in which to remove the kidney, so inquiries can be made only during that hour if the kidneys are to be used. The relatives are also not defined. In practice the next of kin would seem to be the most suitable person to approach.

There is no definition of death in the Human Tissue Act (1961); a legal definition would be unsatisfactory, since it is a medical and not a legal matter. It is, however, advisable that death be diagnosed by a doctor or doctors independent of the transplantation team by means of whatever criteria they think fit. Usually these are based on the cessation of spontaneous heart beat and respiration, after any attempts at resuscitation which were considered to be indicated have been made.

Many suitable donors die from causes that make them coroner's cases; therefore in addition to the relative's permission for removal of organs it is necessary to have the coroner's consent as well. The coroner alone, however, cannot give permission for organs to be removed from the body in a coroner's case, nor can organs be removed from such a body unless the coroner is agreeable; thus the coroner can forbid the removal of organs from the body.

A coroner will withhold permission if he believes that removal of organs for transplantation will interfere with his statutory

duty in investigating the nature of death. Many coroners now adopt an enlightened view so as to help transplantation, which is quite possible without any interference with the coroner's duties. The coroner depends on his appointed pathologist for the necropsy report, and if the surgeon removing the organs is in contact with the pathologist then any abnormality in the organs or in the abdominal cavity will be reported to the coroner's pathologist. Of course, if the organs themselves are diseased they will not be used for transplantation. If there is any doubt the coroner's pathologist is directly consulted.

The law is unsatisfactory, since seeking permission from the relatives who have suddenly been bereaved—particularly in the case of accidents—can cause a great deal of distress unnecessarily. Moreover, in such cases there will probably be a coroner's necropsy, which is scarcely ever objected to by relatives, and objections can be overruled by the coroner. A change in the law on the lines of those recently passed in Denmark, Sweden, and France is urgently required. It would be a great help in the development of transplantation if permission was automatically assumed to have been given unless active objection had been made. Safeguards would be needed so that those who do not wish their organs to be used for transplantation after death could register an objection on their own behalf and also on behalf of their children. A "contracting out" procedure on these lines would be preferable to the present "contracting in" system. Safeguards could be arranged as follows: (1) A central computer would be programmed with information of all those who objected to their organs being removed after death; this could be telephoned at any time of the day or night by the hospital; and (2) objectors could carry a card stating their views. It would still be helpful if those who actively wished their organs to be used for transplantation would carry a card stating this wish and also record their names on the computer.

Suitable Donors

Most people dying in hospital are unsuitable as organ donors because of disseminated malignancy, systemic sepsis, hypertension, or renal tract disease. The most suitable cases are those of primary cerebral tumours, which do not metastasize outside the skull, head injuries, cerebral haemorrhage, and myocardial infarction. The age of the donor does not seem to matter, though infant kidneys do not do well in adults. Despite the slight deterioration of renal function in old age we have nevertheless used kidneys from donors in their 70s, which have functioned satisfactorily in young recipients.

Tissue Typing

If blood is taken from the potential donor for any purpose before death, an aliquot should be sent for red cell grouping and tissue typing. Alternatively, blood can be removed immediately after death from the femoral vein or by cardiac puncture. Tissue typing takes two to three hours, but this can be done while the kidney is being removed and preserved. Since the value of tissue typing has been clearly shown and the techniques are rapidly improving to make the best use of available donors to treat the maximum number of recipients and to have a good match in every case collaboration between doctors covering very large densities of population will be necessary. So far as the United Kingdom is concerned this will probably mean collaboration within the whole of Northern Europe.

Professor van Rood, of Leiden, has developed an international collaborative programme called "Eurotransplant." Kidneys have been moved from as far as Belgium to Sweden for transplantation. It would be desirable for the United Kingdom to participate and for there to be a central information organization, which would record the tissue groups and red cell groups of all patients ready for transplantation. Tissue typing would be performed in regional laboratories associated with renal transplant units. The results of donor tissue typing

would be immediately telephoned to the central organization and arrangements would be made for the kidneys to be sent to the nearest satisfactory, matching recipients. Wherever possible the kidneys would be transported by road, but for great distances helicopters or aeroplanes might be needed. The cost involved would be small in relation to the gain of a good tissue match, particularly in recipients of rare tissue groups. It is considered humane and correct for helicopters to save men drowning at sea; so to use the same means to save someone dying of kidney disease would seem in principle to be no different.

It is essential that hospitals not performing renal transplants should nevertheless collaborate closely with their regional transplantation units to help provide organs for transplantation. This would seem to be a reasonable obligation, since the whole region depends on the transplant unit to treat its patients with renal failure. If a patient died in one of these hospitals, blood for red cell grouping and tissue typing would be sent immediately to the regional typing unit, while the kidneys were removed locally.

Five millilitres of blood is taken for red cell grouping in an ordinary plain tube and allowed to clot. Twenty millilitres is put into a universal container containing glass beads for tissue typing. The bottle is then gently inverted repeatedly for 20 minutes so as to defibrinate the blood. It is then transferred at room temperature to the tissue-typing laboratory, where the lymphocytes are separated and tested against cytotoxic or agglutinating histocompatibility antibody-containing sera, or both.

Kidney Removal

As soon as the donor has died and permission for removal of organs has been given, the corpse is transferred to an operating-theatre or, failing this, to a room with good lighting where a sterile operation can be performed. It is valuable to have a kidney-removal set of surgical instruments and drapes permanently autoclaved and ready for immediate use, together with perfusion fluids at 4° C. in a refrigerator. The whole abdomen is prepared with 2% iodine in spirit. A transverse incision is made from loin to loin across the abdomen about 1 in. (2.5 cm.) above the umbilicus (Fig. 1). The peritoneum is incised lateral to the splenic flexure of the colon (Fig. 2). The colon and spleen are raised and the kidney gently mobilized. It is very important not to pull the kidney excessively, otherwise the arterial intima will fracture and cause obstruction to the artery following anastomosis. The renal vein is defined, clamped at the cava, and divided (Fig. 3). Much blood will escape from the cut renal vein, but it is preferable not to clamp it, otherwise it may be damaged. The vein is then gently dissected towards the kidney. The adrenal and gonadal vessels are ligated and divided.

FIG. 1.—Incision. FIG. 2.—Incision in the posterior parietal peritoneum.

A search is now made for the main renal artery and any accessory arteries that may arise from the main trunk or independently from the aorta (Figs. 4 and 5). If they are arising independently from the aorta it will be necessary to take a Carrel patch, including the orifices of all the vessels—in continuity if they are close together, or separate patches for the individual arteries if they are far apart. To excise Carrel patches it is necessary to mobilize the aorta for a considerable length so as not to damage the opposite renal vessels. Following division of the renal artery at the aorta or removal of the artery with a Carrel patch the kidney is free apart from the ureter, which is followed gently to the pelvic brim where it is divided (Fig. 6).

FIG. 3.—Kidney and renal vein are brought into view. Renal vein is clamped and cut.

FIG. 4

FIG. 5

FIG. 4.—Renal artery is clamped and cut close to the aorta. FIG. 5.—If there are two separate renal arteries a Carrel patch is taken from the aorta.

FIG. 6

FIG. 7

FIG. 6.—Ureter divided and kidney removed. FIG. 7.—Kidney surrounded in cold saline and perfused. Great care is taken to avoid introducing air into the renal artery.

It is important not to strip the ureter from surrounding connective tissue, since the blood supply to the ureter may become tenuous and anastomotic vessels lie in the periureteric and areolar tissue.

The kidney is now placed in a cold dish containing sterile normal saline at 4° C. and is perfused to cool it further and to provide it with a stable intravascular environment (Fig. 7). We use Gelin's method, consisting first of a washout fluid of cold Rheomacrodex, which is infused into the kidney by gravity at about 1 metre of hydrostatic pressure; 200–300 ml. of this is necessary to get a clear perfusate from the renal vein. The perfusion then continues with a preserving fluid, also at 4° C., which consists of a mixture of 5% invert sugar and 0.7% sodium bicarbonate (Brunius *et al.*, 1968). These two fluids need to be mixed just before infusion, as they become unstable after a few hours.¹ The sugar and bicarbonate provide a buffered, calorie-containing, innocuous medium.

The arrangements of the drip-set for the perfusion have to be made carefully. The drip-sets, with suitable junctions, are joined to sterile extension tubing which has a tapered cannula at the end. The perfusate is introduced into the tube with care so that all bubbles are expelled, and then, with the perfusion running gently, the cannula is inserted into the renal artery and held there firmly but gently by hand, to avoid damage. Once in the renal artery, perfusion continues until the kidney turns pale and the perfusate emerging from the renal vein becomes colourless; at this point the perfusate is changed to the preserving mixture without removing the cannula from the artery. This is managed by means of a Y tube (Fig. 8). Where there are two arteries each one is individually dealt with in the same manner. If the kidney fails to perfuse satisfactorily it is probably unsuitable for transplantation, since intravascular thrombosis or autolysis may have occurred.

FIG. 8.—Kidney perfused with 5% dextran 40 until effluent from renal vein is clear. About 100 ml. of preserving fluid consisting of a mixture of invert sugar and sodium bicarbonate is then infused into the renal artery. These two solutions are mixed just before perfusion by transferring 1.4% sodium bicarbonate into the 10% invert sugar, making a final mixture of 5% invert sugar and 0.7% sodium bicarbonate.

¹ These fluids are prepared in a special pack by Pharmacia, arranged so that the invert sugar in one plastic container can be mixed with the bicarbonate in another without danger of contamination.

About 100 ml. of preserving fluid is infused into the kidney, which is then inserted into a polyethylene bag containing about 100 ml. of cold saline. The bag is occluded with an elastic band and inserted into another sterile polyethylene bag also containing a little cold saline. The second bag is similarly occluded, and the left kidney, in its two bags surrounded by cold saline, is inserted into a vacuum flask clearly labelled "left kidney." Ice cubes are gently packed around the outer polyethylene bag, which is not sterile on the outside. The exact time of death of the donor, the time of removal of the kidney, its anatomy, and its perfusion are recorded on a special form. The peritoneum lateral to the ascending colon is now divided and the right kidney is removed in a similar manner to the left, perfused, and preserved in the same way. Any anatomical abnormality is accurately recorded on the form.

The kidneys are now transported to the nearest transplant centres where there are recipients of a suitable tissue match. The abdominal incision in the cadaver is closed. Any abnormalities noted by the surgeon will be reported to the coroner's pathologist if the case is under the coroner's jurisdiction.

The removal of a kidney is not an easy operation; it is often performed by relatively inexperienced surgeons in the middle of the night with few assistants and perhaps poor equipment. Kidney removal sets should include deep retractors, long scissors, and clamps. Suction apparatus is very useful to remove the blood that accumulates when the renal vessels are divided. If the kidney is damaged in any way it is important that the nature of the damage be recorded on the form provided. The best way to train surgeons in the removal of kidneys is for them to spend some time at a transplant centre learning the techniques. Furthermore, it is advisable that they should know something of the operative procedures performed on the recipient, to enable them to appreciate how the manner of removing the kidney can modify the insertion of the organ.

Kidney Preservation

With simple surface and perfusion cooling, as described above, it is possible to keep a kidney for seven hours with very little deterioration of the parenchyma. Seven hours is sufficient to move a kidney long distances by road in Britain and anywhere

in Northern Europe by helicopter or aeroplane. Longer methods of preservation, which would allow kidney transplantation to be done as an elective procedure rather than as an emergency, require complicated continuous perfusion apparatus. Belzer *et al.* (1967) described a perfusion apparatus which enabled consistently good results to be obtained over a 72-hour period of preserving dog kidneys, which functioned well after being reimplanted. Any perfusion system, however, has the disadvantage that if anything goes wrong with the apparatus the organ may be irreversibly damaged. There is also a danger of introducing infection while the organ is being fitted to the apparatus.

Conclusions

If organ transplantation is to provide the therapy of which it is potentially capable far more collaboration within the medical profession will be necessary. To help provide a kidney requires a considerable amount of work on the part of all concerned. It is difficult to think of the possibility of transplanting organs after a great deal of time and care has been spent in trying to save a patient who eventually dies. It is not easy to remember that his kidneys might help somebody else, yet delay will make the organs useless. Obtaining permission from the relatives—and also from the coroner if the case is under his jurisdiction—and finding an operating-theatre together with assistants and equipment for organ removal and preservation all need considerable time and effort. In addition numerous telephone calls will have to be made to the transplant centre and tissue-typing laboratory. Nevertheless, to see patients with good functioning renal transplants back at work and leading normal lives makes it clear that the effort is worth while and does not differ in principle from the efforts that medical men normally make in trying to help their patients.

Figs. 1–7 are reproduced by courtesy of the *British Journal of Urology*.

REFERENCES

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CONFERENCES AND MEETINGS

Control of Tropical Endemic Disease—Anglo-French Symposium

[FROM A SPECIAL CORRESPONDENT]

A joint meeting of the Royal Society of Tropical Medicine and Hygiene and the French Société de Pathologie Exotique was held at Manson House, London, on 15 May to discuss the control of some of the great endemic diseases of the tropics. Opening the morning session Professor P. C. C. GARNHAM, F.R.S. (London), welcomed the French visitors.

Malaria

Dr. G. PRINGLE (Liverpool) described a malaria control investigation in an area of 2,000 square miles (5,180 sq. km.) on the Kenya-Tanzania frontier. Huts and dwellings were sprayed with dieldrin at a rate of 0.8 g./sq. metre on the first application and 0.5 g./sq. metre subsequently, applications being spaced at intervals of

eight months. The scheme was started in 1955 and completed in 1959. During this period malarial transmission was reduced considerably, and did not increase significantly for some six to eight years after spraying finished. This prolongation was attributed to reactivation of the residual dieldrin on the walls during the wet seasons. For five years after the vector control by spraying dieldrin there was statistical evidence that the population was healthier. Human fertility was not affected.

Referring to the resistance of anophelines to dicophane, benzene hexachloride, and the cyclodienes, Professor J. R. BUSVINE (London) said that so far resistance to organophosphorus and carbamate insecticides had not appeared, though this was likely if these were used extensively. He had examined the control schemes used throughout the

world, and had concluded that where resistance did occur in a given vector it seldom extended throughout the entire geographical range of the species. He was not sure whether this was due to the restricted occurrence of the genes for resistance, to differences in ecology, or to different operational control procedures. The eventual extension of localized resistance must be expected if the same insecticides were used continually. Despite many years' search only the organophosphorus and carbamate insecticides had shown any promise—most others were too expensive, not persistent enough, or developed resistance in the vector.

Chemoprophylaxis

Professor G. CHARMOT (Bobo-Dioulasso, Upper Volta, West Africa) said that chloro-