

Ethical Problems in Organ Transplantation*

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It would, I imagine, be generally agreed that the doctor's primary responsibility is to his patient; to try to preserve life, to restore physical and mental health, and to relieve suffering. At first sight this seems straightforward enough, but in practice it is often difficult to decide on the right course of action to pursue, partly because these various objectives are not always mutually compatible, and partly because there is sometimes no established effective treatment for the condition from which the patient is suffering. What degree of suffering should we be prepared to inflict on our patients in return for a faint hope of saving life? When, if ever, should we be prepared to try a new form of treatment which has never been tried before?

The Doctor's Duty

Despite its paramount importance, however, the doctor's duty to his patient is not his only responsibility; there are many other people to be considered.

In the first place there are those who may be affected directly or indirectly as a consequence of the patient's illness—for example, people coming into contact with a patient suffering from an infectious disease, or travelling in a vehicle driven by an epileptic.

Secondly, there are those who have, or at some future time are going to develop, the same disease as the patient. Here there is no problem if effective treatment is readily available; but this is not always the case.

Occasionally a satisfactory form of treatment is known but resources are lacking to make it available to everyone who needs it. I saw an example of this as a prisoner of war when we were faced with large numbers of our own men suffering from beriberi and other forms of deficiency disease but were desperately short of vitamins and vitamin-containing foods. It might be thought that the problem would scarcely arise in civilized countries in time of peace, but reports from even so wealthy a country as the United States suggest that a lack of sufficient resources is a limiting factor in the treatment of patients suffering from chronic renal failure by means of repeated haemodialysis.

Much more often, of course, the problem arises because there is no generally accepted and effective form of treatment. We may go a long way towards developing new methods by laboratory experiments, but the time inevitably comes when, if therapeutics is to advance at all, we must engage in clinical trials. As Bradford Hill (1963) pointed out in his recent Marc Daniels Lecture, someone must be the first to exhibit a new treatment in man, and someone, whether for good or ill, must be the first to be exposed to it. And, as the *British Medical Journal* (1962)

has reminded us, "If Jenner had not given the boy James Phipps cowpox and then subsequently attempted to give him smallpox the science of immunology would not have reached its position to-day, and if William Withering had not tried out the effects of foxglove infusion on his dropsical patients countless thousands of sufferers from heart disease would not have had the benefit of digitalis." Yet these, as the *B.M.J.* points out, were experiments on human beings, and they raise extremely complex ethical problems. Much helpful guidance is available—for example, the draft code of ethics on human experimentation formulated by the Ethical Committee of the World Medical Association (1962), the report by Dr. H. K. Beecher (1959) to the Council on Drugs of the American Medical Association, the privately circulated memorandum of the British Medical Research Council, numerous leaders in the *British Medical Journal* and other journals, and articles by individuals, including the lecture by Bradford Hill already cited. The various recommendations are, of course, not all mutually compatible, but taken collectively they provide much food for thought.

In many trials it is useful to carry out sequential analysis, and terminate the trial when the probability of an observed difference in response being due to an error of random sampling is less than some assigned value P . Unfortunately, however, as I have pointed out (Woodruff, 1963), Bradford Hill does not really come to grips with the very important problem of what value to assign to P , and this is largely true also of the other authorities. If the figure is set too high an erroneous conclusion may be drawn; if too low more people than necessary may be deprived of the better treatment. The value 0.05, which is often adopted, may be quite a good compromise in many cases, but it is certainly not always appropriate.

Thirdly, there may be one particular individual, other than the patient, to whom the doctor owes a particular duty, the classical example being the unborn infant when termination of pregnancy for therapeutic reasons is under consideration.

The advent of organ transplantation has brought us face to face with many of these issues in a particularly acute form, and has introduced a new category of individuals who have to be specially considered by the doctor—namely, transplant donors.

Transplant Donors

It is conceivable that one day it will be possible to meet all the demands of replacement surgery by animal donors. If so, the ethical problems, so far as I am concerned, will largely disappear. This is not because I am indifferent to the welfare of animals. Far from it. But I am convinced that we are of more value than many sparrows, or dogs, or cats, or monkeys, or even horses, and that it is morally justifiable to sacrifice animals in order to preserve human life, whether directly, as, for example, by providing grafts, or indirectly by virtue of

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the new knowledge gained from animal experiments. Of course, I would at once agree that anyone using animals for these purposes must act with a proper sense of responsibility; in particular, he must try to design his experiments so as to gain the maximum amount of information from the smallest possible number of animals, and must take all possible steps to avoid inflicting unnecessary suffering.

Until recently the use of animal organs for transplantation to man was not seriously envisaged. Now, as we know from reports in the daily press, surgeons in the United States at Denver and New Orleans have been attempting to treat chronic renal failure by transplanting kidneys from baboons and chimpanzees. So far as I know, however, no reports of this work have yet appeared in the medical or scientific press; whatever the future may hold, therefore, we must at the present time face up to the problems inherent in the use of human donors.

Salient Facts

In order to appreciate these problems better let us look briefly at the salient facts of the situation.

In the first place, many thousands of people die each year as a result of acute or chronic glomerulonephritis, pyelonephritis, or congenital disorders of the kidney.

Secondly, many of these lives could be saved by renal transplantation if means could be found of preventing immunological rejection of the graft and the reappearance in it of the original disease.

Thirdly, so far as human kidneys are concerned, there are only three possible sources: patients from whom a kidney is being removed for therapeutic reasons, living volunteers, and cadavers.

Fourthly, the results show that, at the present time, the therapeutic benefits to be expected from renal transplantation are very limited. This is illustrated in the accompanying Table, which is based on data presented at a conference held

survive indefinitely, the total proportion of transplants which do so will still be very small.

Transplants from cadavers, with a few notable exceptions, have yielded poor results, largely, it seems, because of the damage which occurs to the kidney during the terminal phase of the donor's life, or in the period between his death and the time when the transplantation is carried out.

With these facts in mind let us consider the ethical problems which may arise when human kidney transplants are obtained from the three possible sources mentioned above.

Free Kidneys

Kidneys which become available as a result of nephrectomy undertaken for therapeutic reasons are sometimes known as free kidneys, and at first sight would not appear to pose any ethical problems at all. Many such kidneys, however, are completely useless as transplants; indeed, if they appear useful the question arises whether nephrectomy was really justified. In some parts of the world a normal kidney is removed in the course of a Matson operation for hydrocephalus, but most British neurosurgeons appear to regard this procedure as obsolete. Fairly normal kidneys have also been removed in the treatment of arterial hypertension associated with renal artery stenosis, but to-day it is usually preferable to carry out some form of conservative operation on the artery unless the kidney itself shows signs of damage.

Kidneys from Living Volunteers

In allowing a living volunteer to donate a kidney we are exposing him to two risks: the risk of the operation, and the risk arising from the fact that he is sacrificing a spare part which he may one day badly need. To the best of my knowledge there have not been any operative deaths among volunteer kidney donors, and the risk is certainly small; it would, however, be unrealistic to assess it at less than, say, 0.5%. The

Cumulative Graft Mortality Table for Renal Homografts

Type of Donor	Proportion of Grafts Functioning after Number of Months Shown by Figure at Top of Column					
	0	1	3	6	12	24
Living monozygotic twin	28/28 (2/2)	26/28 (2/2)	26/28 (2/2)	23/26 (2/2)	21/25 (2/2)	18/22 (1/1)
" dizygotic twin	5/5 (0/0)	4/5	3/4	2/3	2/3	2/3
" non-twin	143/143 (10/10)	79/136 (7/9)	50/121 (4/8)	24/106 (3/8)	8/91 (3/8)	1/87 (0/7)
Cadaver	68/68 (1/1)	26/66 (1/1)	9/63 (0/1)	4/62 (0/1)	1/59 (0/1)	0/58 (0/1)
All excluding monozygotic twin	216/216 (11/11)	109/207 (8/10)	62/188 (4/9)	30/171 (3/9)	11/153 (3/9)	3/148 (0/8)

Each entry is in the form of a fraction. The numerator denotes the number of grafts functioning after the time shown; the denominator the maximum possible number of functioning grafts if every one had been completely successful.

The figures outside the brackets are based on the data reported from all centres at the Washington Conference on 23 September 1963. The figures in brackets represent the cases treated in Edinburgh up to 10 December 1963.

last September in Washington¹ at which an attempt was made to review all known cases of transplantation of the kidney in man.

The best results have, of course, been obtained with transplants from identical twin donors. Here there is no risk of immunological rejection, and the only hazard, apart from the small one of technical failure, appears to be that if the patient is suffering from some form of glomerulonephritis this condition may subsequently develop in the transplant.

The results with transplants from living donors other than identical twins rank next. Taking into account recent improvement in the results, it seems reasonable to assess the chances of such a transplant made at the present time functioning for a year as approaching 50%. On the other hand, only 2 of the 11 surviving patients whose transplants have been in place for more than a year have maintained normal renal function, so that even if, as seems quite likely, both these transplants

long-term risks entailed in sacrificing one of a pair of healthy kidneys are harder to assess, but once again, though probably small, they are not negligible. Moreover, while the life assurance companies do not as yet appear to be concerned about the matter, it is conceivable that if the number of voluntary donors were to increase greatly they might refuse to accept proposals from people contemplating such donations, or weight the premiums of those who have already made them.

The question therefore arises regarding the conditions, if any, under which it is proper to allow the donation of a kidney by a living volunteer. In discussing this matter it may be helpful to begin by suggesting some *necessary* conditions, and then consider whether or not they may be regarded as *sufficient*.

In the first place it must be established beyond reasonable doubt that the patient has gross and irreversible renal failure which it is not feasible to manage by other methods.

Secondly, the donor must be in good health and must possess two kidneys which each show normal renal function. It might be argued that one could proceed if a donor had one normal

¹ The report of this conference was published in the January 1964 number of *Transplantation*.

kidney and one which was nearly normal, provided that it was the better one which was left in place. This is open to objection, however, because the presence of an abnormality in one kidney increases the likelihood of a hidden defect in the other, and also because by transplanting an imperfect kidney the chances of success may be reduced to such a point that the donor's sacrifice is no longer justified.

Thirdly, the donation must be entirely voluntary. There must be no threats or bribes, open or implied, and whenever possible the patient should be kept in ignorance of the fact that transplantation is under discussion unless and until a decision is made to proceed.

Fourthly, the donor must be made fully aware of the risks he is accepting, and of the very considerable chance that his sacrifice will turn out to be of little or no benefit to the patient. Consent is not enough, for such is the trust which many people have in their doctors they will consent to almost anything which is put to them. What is required is informed consent, and this is possible only after full and frank discussion of the whole problem.

Finally, there must be no grounds for supposing that the chances of success are exceptionally poor in the case under discussion. It would seem unwise, for example, at present to accept a donor who is incompatible with the patient in respect of the ABO blood-groups, though it may become possible one day to relax this condition.

Few would deny that these conditions are necessary. But are they sufficient? Indeed, are any conditions sufficient?

Difficult Questions

The notion that a man should be prepared to sacrifice his life for his fellows is accepted by Christians and Humanists alike. We might or might not have the courage to walk out like Captain Oates into the Antarctic blizzard, but we all applaud his action. And if a man may sacrifice his life then why not a kidney? Yes, indeed; but what is to be said of those of us who permit others to do these things? The question is not whether the donor is right to offer to give up a kidney, but whether the doctor is right to allow him to do so.

My own answer to this question, which has been arrived at only after long and anxious consideration, is that it is sometimes right, assuming that the necessary conditions listed above are fulfilled, but that each particular case must be judged on its merits.

There is least difficulty when the patient and donor are identical twins of adult age, and the disease from which the patient is suffering is not of a kind which is likely to recur in a transplant. Here the prospects of success are excellent, and the situation is also particularly favourable from the psychological point of view. Unfortunately, however, the chances of a patient having an identical twin are only about one in 300, and even when this occurs both twins may be suffering from the same disease.

In the case of twins who are under the age of 21 the decision is more difficult. If they are close to this age, and the healthy twin is sufficiently mature to be able to appreciate the issues involved, the ethical situation seems to me to be essentially the same as before, though it has recently been suggested that the legal position may be different. In the case of children or adolescents, however, it would seem quite wrong to proceed.

The situation which in my view ranks next is that in which a parent wants to donate a kidney to his child. Here the prognosis is much less favourable than in the case of transplantation from an identical twin, but in my view the procedure is justifiable if the necessary conditions are fulfilled, and if both parents, after frank discussion of the whole situation and adequate time for reflection, are agreed that they want to go ahead.

The next situation to be considered arises when the donor and host are siblings but not identical twins. The outlook appears to be much the same as for transplantation from a parent to a child, but from the psychological point of view the situation is perhaps less favourable, and many would-be donors in this category may have to be rejected on the grounds that they are young people with as yet undefined responsibilities.

My colleagues and I in Edinburgh have not accepted offers to donate a kidney except in the situations so far discussed. There are, however, circumstances in which it would seem proper to allow a husband to give a kidney for his wife or vice versa, though not, at the present time, if they had a young family. One might also, on occasion, consider allowing a volunteer to donate a kidney for a close personal friend.

What of offers from donors who do not fall into any of these categories? Many of these can be dismissed at once on the ground that the would-be donor is merely making a dramatic gesture without any real appreciation of the issues involved. Moreover, one must be especially critical when faced with offers from members of what Dr. Beecher (1959) has referred to as captive groups—for example, individuals serving a sentence of imprisonment. Indeed, a strong case can be made for refusing to consider all such offers, though I do not know that I would entirely rule out the possibility of accepting a kidney from someone who has committed a serious crime, and, after sober reflection, wants to make such a sacrifice as a sort of act of atonement. I do not think that this situation will arise often, but it is not one which can be dismissed as inconceivable.

Cadaver Kidneys

Cadaver kidneys suitable for grafting are difficult to obtain. Many subjects are unsuitable on account of renal disease, atherosclerosis of the renal arteries, gross infection, or disseminated neoplastic disease, and in others the kidneys are irreparably damaged during the last few hours of life—for example, as a result of peripheral circulatory failure. To make matters still more difficult, the kidney deteriorates rapidly after death, and is unlikely to function satisfactorily if the period between the death of the patient and the restoration of the renal circulation after transplantation is more than about three hours. Indeed, even with this interval severe tubular necrosis is inevitable, and it may take several weeks before the transplant begins to function properly. The situation is thus entirely different from that which obtains with corneal grafts, where a delay of six hours or so is of little consequence.

Generally speaking, the most suitable subjects are those in whom death has resulted from some form of accidental injury, from spontaneous subarachnoid haemorrhage, or during the course of a surgical operation. There is, however, often considerable delay in obtaining permission to remove organs for grafting in these cases, partly because the coroner or procurator-fiscal may have to be consulted, and partly because the next of kin are often not readily available. Moreover, even when the next of kin can be found they are often too upset by their sudden and unexpected bereavement to understand properly what is being asked of them. And if, as is sometimes done, the next of kin are approached before the patient actually dies, they may feel that hope has been abandoned prematurely.

A further difficulty arises from the fact that it is in just the type of case under consideration that it seems most appropriate to resort to extraordinary measures in the hope of saving life, including artificial respiration and cardiac massage. When this is done the patient either recovers, in which case he ceases to be available as a donor, or there comes a time when a decision must be made to abandon a lost cause and switch off the machines. It seems inevitable that the fact that someone else is waiting for this patient's kidney must to some extent influence the decision, since the longer the injured patient is connected to the machines the more his kidneys and other vital

organs are likely to deteriorate. It has been suggested that the difficulty can be avoided if the surgeons concerned with the transplantation are not called until those responsible for the injured patient are satisfied that he is dead, or at any rate that no possible hope of saving life remains. Owing to the shortness of the permissible interval between death and transplantation, however, the surgeons concerned with the transplantation must be given sufficient warning to enable them to make the necessary preparations for the operation, and those looking after the injured patient can scarcely fail to know that their unseen colleagues are waiting poised for action, or that their colleagues' patient is also waiting, hoping desperately for a graft that will give him a chance of survival.

The dilemma thus remains, however much we seek to apportion the responsibility, and I see no hope of escaping it entirely, but there are three ways in which the situation might be improved. In the first place, it would be helpful if people who want their organs to be available after death for purposes of transplantation should make this known to their next of kin, their doctors, and their legal advisers. Secondly, it should be possible to improve methods of resuscitation so that terminal deterioration of the kidneys and other vital organs is reduced to a minimum. Finally, it would help greatly if we were able to develop methods which could be instituted promptly after death for preserving tissues and organs in a viable state before they were removed from the body, thus avoiding the present necessity of having the prospective recipient ready and waiting to receive the graft.

It has been suggested that kidneys might also be obtained from those whose death is the result of judicial execution. For my part, I would reject this source entirely. In the first place, the number of such cadavers would, fortunately, be small, and I think it is extremely doubtful whether the authorities would agree to make them available. Secondly—and here, of course, I am simply expressing a personal opinion—I

think it would be deplorable to do anything which might create a vested interest in such a barbaric practice as capital punishment.

Experimental Work with Other Organs

I have been speaking up to now of transplantation of the kidney. As you know, however, there has been a great deal of experimental work on transplantation of other organs, and attempts have already been made in a few cases to transplant the liver, lung, and heart to human patients. The technical problems here are indeed formidable, though I do not think they are insuperable. It is clear, however, that one cannot look to living volunteers for these organs, and, in the case of the liver in particular, the permissible interval between death of the donor and transplantation is even shorter than in the case of the kidney. All the various difficulties that we have been considering therefore arise in even more acute form.

I have left you with many questions, and only a few very sketchy answers. You may feel that it would have been better not to have raised these issues at all, but the fact of the matter is that, whether we like it or not, they raise themselves. In the practice of medicine there is no turning back, and not much opportunity for standing still. Medicine serves mankind, and the needs of our fellows drive us on.

The opinions expressed are my own, but I would like to record my deep gratitude to colleagues who have shared the responsibility of making decisions in all our cases of renal transplantation.

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Mortality in Relation to Smoking: Ten Years' Observations of British Doctors

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General Discussion

In the preceding sections we have set out our observations. We turn now to their interpretation. We have to consider, as is true in nearly every problem of human epidemiology, observed *associations*—in the present instance between smoking habits and features of mortality. We have to decide from these associations, together with all other available evidence in man and animal, whether association implies *causation*.

In so doing we can consider our rates of mortality in at least two ways: (1) we can calculate the *absolute* difference between them, and (2) we can calculate the *ratio* of one to the other. For example, we have found death rates per 1,000 per annum from cancer of the lung of 0.07 in non-smokers, 0.93 in cigarette smokers, and 2.23 in cigarette smokers of 25 or more cigarettes

a day (Tables 23 and 24). With these figures we can say that the excess mortality in cigarette smokers over non-smokers has been 0.86 deaths per 1,000 and in heavy cigarette smokers over non-smokers 2.16 deaths per 1,000—that is, the absolute differences. Alternatively we can say that the death rate of cigarette smokers from cancer of the lung has been thirteen times the rate of non-smokers, and that the death rate of heavy cigarette smokers has been over thirty times the rate of non-smokers—that is, the ratios.

Both these ways of looking at the data are legitimate, both have their uses. If we wish to know how many extra deaths will result from smoking (presuming for the moment causation) then clearly we must calculate the absolute differences. We may, of course, find that quite a small proportional rise in mortality from a common cause of death, such as coronary thrombosis, has a greater effect upon total mortality than a pronounced rise for a less common cause, such as cancer of the lung. But, despite Berkson's (1959) opinion, it certainly does not follow that this best measure of the effect upon total mortality is also

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