

Ethics in New Medicine: Tissue Transplants*

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Conservatism in medicine is a posture of comfort. The physician who lets a patient go his way with little more than a squeeze of the hand, a pain pill, or a knowing look to the relatives, can console himself that it has been this way before. It is also the easiest way. Then when another physician comes along to state that a certain disease can indeed be removed, but by a new and difficult procedure after careful study by new biochemical discriminants, the conservative is disturbed. He sees his authority challenged. He feels a deep uneasiness that many of his ways may soon become outmoded, particularly if he is inexperienced in, or unable to understand or perform, the new procedure. He becomes outraged when he discovers that several of the new operations have resulted in fatality rather than cure. Therefore, with the strong conviction that he is protecting the welfare of his patient, he claims that this new departure is still only experimental, and therefore unethical.

Postgraduate education in medicine is devoted to surmounting this innate conservatism. It is a tribute to the medical profession that each year thousands of doctors return to sources of learning to refresh their sense of the "tried," if not always the "true" in the sense of widely proven. Practitioners who return periodically to hospitals, where challenge of the old is a way of life, find that they overcome this human tendency to entrench, crystallize and defend an unchanging art.

Nevertheless, the history of such positions against advance, positions taken on the ground of ethics, is long and illustrious. It ranges all the way from the use of ether in childbirth to the use of aseptic techniques in the operating room, from the prevention of puerperal sepsis by isolation to the removal of brain tumors, and finally includes even the repair of valvular diseases of the heart! An older and more conservative generation has each time looked askance at these new ideas and new procedures and, at some point in heated controversy, has declared them unethical.

And yet, some are! Some "innovations" are indeed quite unethical and unacceptable! How should we consider the transplantation of goat glands to restore the waning virility of the elderly male? Or the treatment of arthritis by irradiation from outer space? Or the administration of small doses of creatinine diluted in water, to raise the hopes of cancer patients . . . at a price?

How can the lay person, the legislator or the newspaper writer steer his way through such controversy? What values provide guideposts, what criteria are standards for acceptability in medical innovation? How is one to regard the newest entry in this field, an entirely new kind of surgery: the transplantation of organs from one person to another?

As new fields of clinical science emerge, they come under fire from many directions. The commonest criticism is that new procedures are experimental and therefore their employment in the care of patients is

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immoral. It accomplishes little to point out that all of medicine is in a sense experimental, and that most of the daily tasks in practice—large or small—are in a very real sense tentative, insecure. No one can ever take for granted his mastery over nature. One must always approach his conquest of natural forces with a high sense of risk, of uncertainty and of experiment. One must seek the same clever skill employed by the glider pilot who rides air currents that at one moment support him upward, and the next—if miscalculated—dash him against the hillside. This simple idea, that applied human biology involves the hazard of repeated experiment, applies to all of medicine and surgery. A few examples will suffice.

A surgical operation employs bacteriology in just this way. An open incision bares large areas of sterile human tissue to the invasive bacteria of the surrounding world. Cutting, sewing, dissecting the tissue, an operation becomes an experiment employing techniques of bacteriology to avoid bacterial infection. If performed properly, the tissues will heal without infection; if faults and breaks occur, there is infection. Soon after Pasteur and Lister showed the bacterial nature of infection, it became obvious that “every surgical operation is an experiment in bacteriology.”

When a physician gives his patient digitalis for the first time, he is carrying out an experiment in pharmacology. If he has misjudged the dose because of some unforeseen abnormality in his patient, he must readjust his prescription on the basis of the electrocardiogram and the heartbeat, working just as carefully as the scientist who manipulates a highly controlled system of variables in the laboratory.

Even such a commonplace operation as exploratory laparotomy for acute appendicitis, undertaken as an emergency in the midnight hours, harbors an element of experiment. “We are not sure what’s the matter with Johnny, but we better have a look. If it is acute appendicitis, we can remove the appendix; if it is not, we are running little risk.”

Each patient and each patient’s

disease is different from the last or the next. Each necessitates a rigorous approach to the phenomena of nature, of humanity and of illness. These in themselves are reasons enough for the continuing emphasis on biological science in medical education.

When we turn from these everyday uncertainties of medicine and surgery to the more troublesome aspects of entirely new treatments for critical illness, we pass from smooth sailing into choppy waters. The same experimental aspects are there, but now uncertainty is accentuated. The doctor can no longer tell his patient the chances of success or failure because he does not know them himself—nor can he minimize the risk.

At the present time, the patient dying of kidney failure has but two things to look forward to, other than a lingering and unpleasant death. One is a program of repeated dialyses or “blood washings” (on the artificial kidney) at high cost, bringing no possibility of release from the shackles of repeated procedures, sensations of waste accumulation, and reattachment to the machine. The artificial kidney has brought new hope to many patients with short-term kidney disease capable of healing and recovery. But for highly destructive kidney diseases, such as chronic glomerulonephritis, chronic pyelonephritis and chronic polycystic disease, these repeated dialyses are but a series of temporary makeshifts—a way of staying alive but hardly a way of life.

The other choice is to have a kidney transplantation. This carries many uncertainties and several risks, both at the operation and later on, as well as hazards for the donor if a living donor is used. But despite these factors, kidney transplantation has reached the point where many patients are now alive and well, up and about, and at home and at work, free of repeated dialyses, but still on medication, with their transplants working well. To arrive at its present station, however insecure, this work has taken fifty years of gradual evolution and fifteen years of intensive research in America and Europe.

The first long-term survival after

homotransplant of a kidney (a homotransplant is a transplant between nontwin members of the same species) was in the spring of 1962, eight years after the first identical-twin transplantation. Up to the autumn of 1964, almost 500 kidney transplantations had been carried out in this country and abroad, involving many different relationships between donor and recipient. Of these, the large majority have been done since March, 1963; for these, no one can possibly claim “long-term survivors!” It is now, as this procedure is gradually emerging from a small and tightly controlled research study to more widespread use, that the ethical question is being raised: is it ethical to offer a kidney transplant to a patient dying of kidney failure?

“Good science is ethical science.” Applied human biology finds meaning only in assistance for human suffering. In viewing any new therapy as an experiment in human biology, it is possible to draw up certain guidelines that will support its ethical and moral climate. These guidelines are much the same for any medical advance or clinical research, but for each there are special problems and details to be served to meet the humane standards that all must seek.

The *first guideline* requires that the patient and his family be brought to an understanding of the alternatives through conversation and education. It is asking too much of a suffering patient to expect from him a final decision; he has neither the dispassionate view nor the background in biology required for such a decision. Yet he must be enabled to understand what lies ahead, what the possibilities are, and to enter the procedure of his own free will and clear assent. Even more important, this gives him a positive motivation to aid and assist his doctors. It is never possible to impose good surgical care on the unwilling; there is tangible gain in the confidence and cooperation that comes from education and understanding.

This education will tell the patient and his family what a transplant really is, how it is done, how it is sutured in place, the meaning of urine output, the use of immuno-suppressive drugs

and many other details. He should understand the risks, the question of timing, the utility of repeated dialyses, the various donor possibilities and the experience of the hospital group. Any patient with a good background in high school biology soon comes to understand a remarkable amount about any new medical procedure.

The newest operation needs the most ancient clinical judgment for its success; the *second guideline* is, therefore, that each patient must receive the best and most experienced medical care available. No operation or medical procedure can stand alone. It succeeds only with the assistance of all the rest of modern medicine and surgery, the help of many doctors, nurses, blood bankers, laboratory technicians, and the participation of that whole constellation of human activities encompassed in the modern hospital. While an isolated research institute may contribute much to the idea, its most effective implementation is in the skilled environment of a busy hospital service. Consultation among doctors provides the checks and balances that avoid excess of one view, or a one-sided bias in interpretation. When four or five keenly interested persons are concerned with the patient's care, under the guidance of one of their number, there is a healthy openness of view that exemplifies the freedom of communication and sharing of knowledge so essential to the care of complex illness.

Work on man must be the culmination of an effort, not its initiation; the *third guideline* is that preliminary study in the laboratory by the doctors doing the work (not someone else!) must yield enough skill in performance and likelihood of success to justify the attempt. The so-called "great advances" of modern medicine, no matter what their nature, have had a sound basis in laboratory work before they were moved to the clinic. This basic laboratory groundwork makes their clinical application not a mere adventure, but the establishment of a new routine. When this important guideline has been neglected, with an attempt to make the "great leap" straight from the test tube to the patient, tragedy

has resulted. The one example in the transplant field wherein the boundaries of ethical acceptance appear to have been crossed shows up at this point. The initial transplantation from chimpanzee to man was well based in laboratory work on blood grouping; but the subsequent series of attempts to place baboon kidneys (and even other organs, some of them obviously too small to do the job) in man, represented a premature step based on inadequate laboratory work. It is quite possible to set up experimental inter-primate heterografts (such as monkey to baboon, or monkey to anthropoid apes) which could have tested this fundamental hypothesis that immunogenetic acceptance might somehow be achieved more readily than with homografts.

The exact locus of the laboratory in any advance of applied human biology depends on the nature of the work to be done. No dogma is effective for all. In cancer chemotherapy, for example, the only available animal model is the small laboratory rodent—rat or mouse. Spontaneous or transplantable tumors in larger vertebrates (permitting study and care resembling that in man) are but rarely available. In other fields, such as active immunization against poliomyelitis or measles, the final step somehow has to be made, and it is still a big one. It involves considerable hazard even though the circumstances are less spectacular than a surgical operation. The initial test with vaccines is made cautiously and with small doses. It should never be done on captive or primitive populations who cannot understand the risk.

In transplantation research this long step from test tube to man was taken only after a decade with the dog. The size of the dog, the size of his blood vessels, the ease of his care, the frequency with which blood and urine tests can be made, and the ability to judge fine gradations in his clinical status by physical appearance alone, have all made study in the dog basic not only to the science but also to the ethics of transplantation in man. Antivivisectionists please take note: there could be nothing more shocking than

moving straight from the rat to man with the transplantation of organs!

And finally, as a *fourth guideline* of the utmost importance, each patient's case must be studied, documented as carefully as possible, and made available to the general view. The study and documentation of each case must be so complete and accurate that any interested person can come to the hospital and spend a few days or weeks reviewing and challenging the procedure or the data—and learning from them. There can be no toleration of secrecy. Every compound used, every procedure employed, must be fully known and made clear. When the time comes, the collected experience must be published with everything displayed, results both good and bad, so that the openness of modern science can be satisfied. There have been no breaches of this faith in the transplant field. Several transplant centers have now banded together to place data on computers for complete analysis. Any doctor in the world may join this project, so that his statistics, his failures and his successes are freely made available for all to see.

But helpful as these guidelines are, no one of them fully answers the question unique to transplantation—what about the donor? For the first time in the history of medicine a perfectly normal, healthy person has now been subjected to the rigors of a major surgical procedure and the removal of an organ, to help another.

The principle of injury to one so as to help another is common throughout nature and is basic to the Christian ethic. Examples are not to be found in the protection of its young by hazard to the mother, or when one person has sacrificed himself to help another, in war or peace. But in these natural phenomena and altruistic events, there has never been a third party—the physician—*advising* the individual to take this risk. It has been an emotional rather than an intellectual decision, and a matter of personal choice.

Medical science began to invade this field about 1915, with the development of blood donation for transfusion. Here the injury appeared to be minor and the body had methods to

compensate. The hazard in blood donation lies not in any threat to the donor but in the threat to the recipient by the transmission of disease.

The initial step in organ transfer was taken in 1954, with the first of the identical-twin transplants. Up to September, 1963, thirty-three identical-twin transplants have been carried out in the world, of which twenty-two are still alive with kidneys functioning well. The success of identical-twin transplantation has become sufficiently assured so that it scarcely arouses a question of morality with regard to the recipient—who is dying from terminal kidney disease. But as it bears on the donor, the ethical problem is as pressing and urgent now as it ever was, and is just as severe for the identical-twin donor as it is for the unrelated person, or for the father, mother or brother who seeks to be a kidney donor.

There is no simple unitary ethical solution for kidney donation from a living person today. Nephrectomy (removal of a kidney) carries a risk and a mortality. When enough has been done, it will be found that one has resulted in fatality. When enough has been done, it will likewise be found that a subsequent injury to the opposite kidney has resulted in significant loss of function, shortening life. The likelihood of a donor's losing the use of his remaining kidney is very small, and has been estimated as being in the same range as an automobile fatality, yet probabilities and statistics are inescapable. Such a major procedure as nephrectomy will surely exact its price when finally enough have been done.

It is clear that the first priority in donor development lies in better methods for preserving kidneys from recently deceased persons—a situation that completely side-steps the use of the living donor. This is still a research problem (though many cadaver kidneys have functioned well), but it is a research problem with an ethical overtone. Until cadaver kidneys can be used for all, the living donor (closely related to the recipient) still yields the best chance for success. Some important principles appear to be as follows:

First, every effort should be made

to assure the maximum donor-recipient tissue compatibility. Despite advances in this area during the past year or two, the most reliable criterion is still that of close family relationship.

Second, one must be assured that both kidneys of the donor are quite normal, that there is no disease of the upper or lower urinary tract, and that kidney donation will involve only the risk of nephrectomy itself.

Third, the donor, just as the recipient, must understand the risks, the alternatives, the hazards, the discomforts, and most especially the uncertainties in the enterprise. If the donor is an identical twin, the prospects for success can be described with reasonable optimism. If any other relationship, then the prospects in all their uncertainty must be outlined clearly.

But surely the most important thing, as mentioned above, is to move away from the living donor entirely. This requires intensive study of cadaver organ procurement, and the definition of those factors in the recently deceased that bias the health of the remaining tissues. When the brain and heart are dead, then the patient is said to be "dead," even though many of his tissues are still alive, respiring in a blood stream increasingly devoid of oxygen, accumulating acid, but still alive for a few more minutes and salvageable for life in a new host. The care of the dying patient must never be compromised by impending tissue donation. The finest tissue bank in the world is the body of a person recently deceased from causes not damaging the health of transplantable tissues. Death from certain types of injuries, heart disease or brain tumors has provided many useful tissues. If cancer, infection, chronic vascular disease or just plain old age enter the picture, then the organs are of little use or actually dangerous to another. Herein lies a whole new field of endeavor in which we, as doctors, need the help of lawyers and legislators to give us legal guidelines to steer us through the uncertainties.

It is ironical to find that while tissue transplantation itself is being called into ethical question, in point of fact it is giving an entirely new meaning to

human generosity as living persons or families of those recently dead make free donations of tissue for the assistance of others. The ethical lesson of kidney transplantation may turn out to be on the side of the Good Samaritan rather than the Evil Scientist!

It is a curious fact that although the general questions of ethics are not appropriate for examination by the methods of science, nonetheless a strong ethical flavor runs through all of science—"good science is ethical science." What are these features within science which give it ethical stature?

"Experiment is perilous and decision difficult." In that well-worn phrase, "perilous" and "difficult" indicate two of the ethical values in scientific experiment: courage and persistence. Other values have to do with rigorous personal honesty in viewing and displaying the results of scientific research, without prejudice, with a dispassionate discrimination, and with the self-discipline required to make a judgement valid. Those who enjoy the privilege of science must spend many years acquiring an education so as to make their work meaningful. Ethical values in science include also such things as openness of communication, exchange of information, avoidance of secrecy, willingness to educate the young and the avoidance of selfish gain.

Every few years the public is affronted by some spectacular example wherein a self-styled scientist has kicked over these traces, and sought a quick victory over nature by disobeying these inner ethics of science. But science is a stern taskmaster; transgressors are brought to a bitter judgment.

Examples are to be found in those goat-gland transplants. Though hardly science in any term, they were most assuredly devoid of the ethical content of careful study, openness of method, documentation, and analysis of results. The Nuremberg trials showed us another failure of ethics in experimentation. When a so-called "scientific experiment" was conducted wholly at the expense of the welfare of human beings, nothing good came of it. Even

the experimenter himself was finally debased and prostituted.

Most recently in the public press there has been described a flagrant example, where in science has shown that its own inner ethic must indeed be obeyed and respected. A person of previous scientific achievement has evidently tried to convince the public of the effectiveness in cancer treatment of a compound the identity of which he kept a secret—and indeed it truly was a secret, because as it now turns out, he himself did not know what it was! Instead of education and openness, careful trial, clear publication, controlled results, documentation of good and bad clearly shown for all to see, advocacy here was on the basis of hearsay about a secret and unknown compound, based on testimonials from random patients. A travesty on all the guidelines we have discussed! And then, with a fitting irony, downfall came through the study of a scientist working in the laboratory and obeying the basic ethic of honesty and rigorous examination. While examining this highly publicized “cancer cure” by infrared spectroscopy, he found it to be creatine—a commonplace material present in large amounts in the bodies of all cancer patients.

The study of patients is always more difficult and complicated than the study of controlled experiments in the laboratory. Sick people can be difficult, demanding, biased and fickle; controls are hard to conceive and devise. The patient's own emotional involvement and that of the doctor himself often provide false evidences of success. Persons working in clinical research (research in patient care) are as much in need of special education for this complex work as is the physiologist working under highly controlled conditions in the quiet of his laboratory. Five years ago, the field of tissue transplantation was in a very difficult phase of clinical research. Then came the demonstration of immunosuppressive pharmacology by scientists working with the New Zealand white rabbit. There was then a period of advance clear for all to see as studies in the dog confirmed their findings and were moved to man. But now again the

field of tissue transplantation has been advancing more slowly, awaiting its next stepwise upward progression. As this is written, several new modifications are coming along, any one of which might make tissue transplantation safer and more effective. Until then, the toilers in this vineyard must work with the methods they have, respecting some such guidelines as these, for ethics in the pursuit of *veritas*.

It is most appropriate to raise ethical questions at a time like this, not only to strengthen and shore up the procedures of each group working in the field of transplantation but also to challenge the critic and put him on his mettle to show cause why this particular advance of medical science should be any more suspect than another. The laboratory scientist tends to be critical of the clinician, the physician of the surgeon; these petty chauvinistic antagonisms should never cloud the real issues of ethics and acceptability in applied human biology.

Tissue transplantation, like other advances of the past, will react to the welfare of mankind if explored and exploited within the ethical bounds of science itself. Honesty and self-discipline must be held as values of the same importance as the very essence of all medical ethics: the welfare of the patient.