

In a Small Iowa Town

849 Copies

IN A SMALL Iowa town more than 50 years ago, I was with an old Irish priest who was unable to complete a requiem mass that, for him, meant everything. He wept instead, and explained to those gathered that his heart was too full to go on. Father O'Toole taught me then to guard against moments like now when feelings can betray us by destroying the power of speech.

Thus, I will be impersonal, if that is possible on an occasion like this. I can only say that no day will go by in the rest of my life when I will not think of, and be strengthened by, what has happened this week. It is the kind of debt that few people incur and none can pay. Thank you for coming here.

Transplantation is the common bond that brought us together in the first place and has kept us together since. How new this field really is, and how unexpected. In 1961, the Nobel Laureate, Burnet, wrote in the *New England Journal of Medicine* that "much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success. . . ." This pessimistic view was published only a year before the avalanche of successful clinical renal transplantations in 1962 and 1963 that extended such procedures beyond the occasional identical and fraternal twin cases of the mid- and late 1950s. Developments since then in transplantation have revolutionized the practice of medicine. It is the effect of these burgeoning successes upon both society and medicine that I want to discuss today.

WHY MEDICINE HAS CHANGED AND HOW

Why has there been such an impact on medicine? Up to now, transplantation techniques have been expensive. Relatively few lives, probably less than 100,000, have been actually saved.

A Change in Philosophy

The reason is that transplantation has made possible a fundamental philosophic departure in the way that health care is delivered. Until 50 or 60 years ago, practitioners of medicine observed and presided over lethal diseases, powerless to provide much more than a priestly function. This began to change with increasingly specific drugs such as antibiotics, but for most organ-specific chronic disorders, a rear guard strategy was all that could be offered. Patients with failing kidneys, livers, or hearts could be treated with diet, medicines, or with operations that often were illogically designed. Suddenly, with the advent of transplantation, it became possible for the first time in human history to provide exactly what was needed, a completely new organ. Those who in small groups sat around small tables in the early 1960s and discussed renal transplantation understood perfectly how high the stakes were or could be.

But immunosuppression was too poor to apply this thrilling concept widely until the 1980s. Then, with the introduction of cyclosporine, it became obvious that a great escape hatch had not only been formed but that all future judgement in the care of organ-specific diseases would have to be in the new perspective of possible eventual organ replacement. Nowhere was this more clear than in liver disease, in which mutilating operations in the portal hilum such as portacaval shunts were virtually abandoned overnight since they jeopardized eventual candidacy for liver transplantation. Similar examples with renal and cardiac disease easily could be cited.

To many physicians, thoughts turned back to what might have been. How much more complete might the world have been if Mozart had been treated with renal transplantation instead of dying of glomerulonephritis at the age of 34. Or, closer to home, what might have become of that little girl so mourned by Father O'Toole 50 years ago in a small town

in Iowa. The people who could be most helped by transplantation were those with the greatest potential, often at a young age, who had been doomed by failure of a single organ system but with all other organ systems intact. Now, they could be saved. It was like a miracle.

Administrative and Educational Changes

In addition, transplantation has forced a change in the way that medicine has been taught and organized. The breadth and depth of expertise required to be at the State of the Art, much less progressive, in transplantation, have gone beyond the grasp of single individuals. Interdisciplinary teams have been formed within medical schools and hospitals that have cut across classical departmental and divisional lines. These new alliances have changed the face not only of practice but of research and have had wide-ranging influence on the development of other special fields.

Research Potential

A special note should be made about the extraordinary influence of transplantation on both basic and clinical research. Modern immunology has been in partnership with, not sponsorship of, transplantation. Our understanding of autoimmune diseases and the appropriate treatment of these disorders owes much to observations after transplantation, an undertaking that first creates and then attempts to control the autoimmune disease known as rejection.

Nowhere has the research potential of transplantation been more evident than with liver replacement. Although all liver transplantations are therapeutic, every such operation also is a potential incisive experiment in basic physiology. With the treatment of some inborn errors of metabolism such as type I glycogen storage disease, cure of the disorder by provision of the missing enzyme with the new liver was highly predictable. In other disorders such as Wilson's disease, classical hemophilia, and hypercholesterolemia, more

was learned about the true nature of the original disease by the discriminating study of a single human liver recipient than by all of the prior investigations over many years put together.

Finally, such a simple question as what are the necessary conditions for optimal revascularization of a transplanted liver has led to a major breakthrough in an understanding of liver physiology and of the influence that the so-called hepatotrophic hormones such as insulin have upon liver structure, function, and the capacity for regeneration. This subject is being treated elsewhere in this symposium.

Thus, transplantation became the Pandora's box of 20th-century science.

WHY AN IMPACT ON SOCIETY?

When one man flew, as impractical as this was at first, the prospect of leaving the ground below and soaring like a bird was open to all men and women. The human condition rose to a higher level. Not to fly again was inconceivable, even though it may have been against all instincts.

So it was with transplantation, an even more unnatural event. As with flying, transplantation violated some of society's deepest taboos. Why? The mores or religious codes that govern us usually have a real basis of bitter lessons long forgotten but with lingering shadows. One need go no further back than to the discovery of kuru, the disease in New Guinea caused by a slow-acting virus to realize how a civilization can be wiped out by systematically exposing a human population to infected human blood and tissues. With kuru, the mode of spread was cannibalism. It may have been more than a Freudian slip in 1964 when an editorial in the *Annals of Internal Medicine*, criticizing the ethics as well as the practicality of clinical renal transplantation, began with the highlighted word "cannibalizing."²

It is obvious that there is no more intimate human contact than with transplantation in

the true nature of the discriminating study of recipient than by all of over many years put

the question as what are for optimal revascularized liver has led to a understanding of the influence that the hormones such as structure, function, regeneration. This sub-where in this sympo-

became the Pan- science.

ON SOCIETY?

is impractical as this of leaving the ground bird was open to all man condition rose to gain was inconceiv- have been against all

plantation, an even with flying, trans- of society's deepest or religious codes ve a real basis of but with lingering further back than to e disease in New cting virus to real- be wiped out by human population and tissues. With as cannibalism. It a Freudian slip in n the *Annals of* ting the ethics as inical renal trans- highlighted word

no more intimate ransplantation in

which the objective is to transfer living tissue under the most perfect possible conditions. The corollary is that diseases, including cancer, can be transplanted in the process. In the 1960s patients and health care personnel in transplant wards were infected in hepatitis epidemics worldwide, before serologic markers were discovered that permitted epidemiologic studies and prevention. Hardly a transplant surgeon in that era escaped infection. My chief research technician, a woman named Phyllis Nagel, died from hepatitis and so did many others. Eventually, it was proved that a hepatitis reservoir existed in the transplant wards and clinics, and measures could be taken to minimize the dangers.

An array of other viruses have been indigenous in transplant centers. Most recently, acquired immunodeficiency syndrome (AIDS) carriers have been found in every major transplant program in which screening of the postoperative recipient population has been carried out systematically. Many of these patients already had been infected before transplantation in the course of their original illness by blood transfusions and other factors. A few obtained the AIDS virus from infected donors before donor testing was available. In almost half, the time and circumstances of infection never could be determined. The conclusion is clear, as it was with hepatitis that precautions are crucial to prevent the transplant centers from being disease reservoirs from which other patients as well as health care personnel can be infected.

Now that preoperative transplant candidate screening for AIDS is being carried out widely, patients are being discovered in increasing numbers who present with failure of a vital organ and who are found during evaluation to be asymptomatic AIDS virus carriers. To their great credit, workers in transplantation have not precluded organ replacement in these patients, thus avoiding a moral dilemma of forcing a candidate to take a test that could, if positive, deprive him or her of live-saving treatment.

Decisions about what does or does not preclude candidacy for transplantation is not the sole responsibility of physicians. Society must play a role, and because of that I have brought the matter to your attention today. Society eventually pays the bills, and controls the resources, a subject to which I will return. Suffice it to say here that the real question is not why transplantation should impact on and be of interest to society, but rather how this impact has been felt.

HOW SOCIETY HAS CHANGED

The impact has been seen everywhere; in the law, in government, in philosophy, and in the perception of ethics. The leaders of all of the world's great religions have had to consider the implications of transplantation in their beliefs.

The new issues began to emerge 25 years ago. Before then, transplantation was not a practical therapeutic option. In 1962 and 1963, using the drug combination of azathioprine and prednisone, apparently healthy recipients of kidneys began to emerge from clinics in increasing numbers. Some are here today, a quarter of a century later.

The implications did not go unnoticed. In 1965, a meeting was convened at the Ciba House in London to consider what the early successes in renal transplantation truly meant. Of the 28 participants, a few also are here today. The symposium proceedings³ touched on all of the topics that still occupy our thoughts including human experimentation, living donation, informed consent, brain death, and allocation of scarce resources. Then 39 years old, I came to that meeting sure of everything. I left it certain of nothing.

To begin with, I had never previously questioned the propriety of living kidney donation, having been the principal proponent in the world of this practice. I left London a few days later with a brooding concern that promotion of living donation could be a subtle violation of human rights, even under the best of circum-

stances, and that free choice and informed consent might actually be unattainable.

I came to the meeting opposed to the concept of heart-beating cadaveric donors. I left convinced of the legitimacy of brain death. My fear had been that the terminal care of gravely injured and helpless victims would be jeopardized by virtue of planned or actual organ removal.

From the London discussions in 1965, it became obvious that acceptance of brain death could be expected to improve, not degrade, the quality of care for neurologically disabled patients. Until the 1960s, immediate assessments were made in emergency rooms about whether neurologically damaged patients could survive. Snap decisions were required whether to perform endotracheal intubation and whether to provide ventilatory support. With the acceptance of brain death, all patients could be so treated as the automatic first step. The gravity of the brain injury could be analyzed later by the neurologists and neurosurgeons under optimal diagnostic conditions. An earlier opinion of Pope Pius XII was discussed in London that held that ventilators and other means of extraordinary support could be discontinued if brain death was found to have occurred. Discontinuance of extraordinary support for brain dead patients was thought legal by four lawyers and jurists at the Ciba conference including Lord Kilbrandon, Chief High Justice of Scotland. Until this issue was settled, accusations of "murder" sometimes followed the detachment of ventilators.

The concept of brain death was popularized in the United States 3 years later by the so-called Harvard ad hoc committee. Laws were quickly passed in the United States and in many countries that gave legal sanction to what society had already decided. Thus, the face of the law was changed by transplantation. Warren Burger, later to become Chief Justice of the United States Supreme Court, remarked at a subsequent and similar medical ethics conference in 1967, "... it is not the

role and function of the law to keep pace with science . . . the law does not *make* discoveries as you do; the law evolves and evolves slowly. It responds rather than anticipates."⁴ By 1968, the law had responded, and it has continued to do so since.

Thinking back to that 1965 meeting, the thing that I remember best was concern for human rights and a determination that human experimentation should not blight this new field. Three of the 28 Ciba symposium participants had known degradation first hand in prison camps and concentration camps. Memories of atrocities, genocide, and war crimes trials were fresh.

The Nuremberg code and the Helsinki declaration of 1964 were used as the framework to judge what had already been done in transplantation and what might be considered next. The Helsinki declaration distinguished between nontherapeutic research designed solely for the objective of acquiring information as opposed to the use of unproven therapy in which the subjects who bore the risks were the same as those who stood to benefit. Transplantation was a classical example of therapeutic investigation. The risks and benefits of so-called innovative procedures could be weighed without equivocation for the first recipients of kidneys, livers, hearts, and other organs. Although stones could be thrown, there were no solid hits. What was done in transplantation in those days was sometimes foolish, but it was never ignoble.

In later times, there has been a tendency to construct formal and sometimes elaborate "human experiments" comparing different kinds of therapy. I once heard it seriously proposed that bonafide candidates for liver or heart transplantation should be randomized into those receiving therapy v untreated controls. I described such suggestions as randomized trialomania. This was a fair criticism. However, trialomania can present with more subtle symptoms, such as insistence upon carrying on randomized trials before learning how to use new therapeutic tools. There is no

better
opmen
clinea
ment p
ing a
experi
were c
with c
was r
rando
sure t
sourc
Ev
is ran
ized
the n
sis of
phys
to a
allow
selve
from
F
mer
vali
ran
pri
of
tre
onl
lar
Sc
ca
pr
al
ar
ag
of
rr
g
h
d
r
c

better way to discredit promising new developments. When cyclosporine was first used clinically, multiple, unanticipated management problems were encountered, necessitating a large number of pilot cases. With this experience, effective management schemes were evolved, including combination therapy with other drugs, especially steroids. There was no justification during this time for a randomized trial, yet nearly continuous pressure to conduct such a trial came from many sources.

Even worse than premature randomization is randomization after the fact. For a randomized clinical trial to be carried out ethically, the necessary starting point is a null hypothesis of no treatment difference. A question that physicians must ask before assigning patients to a randomized trial is whether they would allow therapy to be decided by lot for themselves or their family members if they suffered from the same disease.

Finally, a randomized trial is not an instrument of discovery, but rather a means of validation. The significance tests applied to randomized trials ordinarily are concerned primarily with preventing erroneous rejection of a null hypothesis. Thus, they will reveal treatment differences at an error level of 5% only for very large deviations or with very large samples. Because of these limitations, Schneider remarked acidulously that "significance tests are more adapted to preventing progress than to achieving it."⁵

The last issue already evident in 1965 was allocation of resources. Who could forget the article in *Life* magazine more than 25 years ago in which a group of wise men in the state of Washington were shown deciding who of many supplicants with renal failure would be given the handful of positions for chronic hemodialysis available in the world. The same debates about allocation of scarce resources rage today, but with the focus on the limited organ supply or the cost per transplantation.

Because I have never known how to divide

scarce resources, my approach has been always to try to eliminate the scarcity. Scarce transplantation resources have been expanded with increased cadaveric organ procurement through public education, and by devising procurement, preservation, and distribution techniques that have made more efficient use of the organ supply already available. Surely this is preferable to debating entry to candidacy based on irrelevant criteria such as age, race, educational status, role in society, or national origin as has been advocated from time to time. It is possible that animal organs, possibly as distant from the human as the pig, will be found to be clinically valuable within the next few years by exploiting clues and knowledge about xenograft rejection that are already available. Then, the resource dividers will yield totally to the resource suppliers.

Cost is the ultimate resource limitation either for the individual or for society. Until 1973, renal transplantation could not be offered to any but the most wealthy recipients except on clinical research centers. This was changed in 1973 by the federally mandated end-stage renal disease program.

Although this was one of the most altruistic legislative initiatives ever taken, it was not free of complications. The cost quickly escalated to the \$2 billion-per-year level. A potential economic aristocracy was created amongst physicians and/or surgeons who controlled "regional concessions" for dialysis, vascular access surgery, and transplantation. The struggles that have ensued for various franchises within the End Stage Renal Disease (ESRD) Program, including cadaveric organ procurement agencies, sometimes have been ruthless. The competition between hospitals for the economic and public relations advantages of transplant programs sometimes has had the appearance of corporate warfare.

The pawns could easily be the patients who can be dehumanized by joining a captive population that has extremely limited options. Recipients on a cadaveric waiting list may feel

that they cannot be demanding, express their true feeling, or deviate in any way from docile behavior for fear of jeopardizing their candidacy. I cannot tell you how many letters I have received from physicians or their assistants openly stating their ownership or proprietary relationships with their patients. It goes without saying that we are the servants, not the masters, of our patients and the same goes for the nephrologists, hepatologists, and cardiologists with whom we collaborate. Patients do not belong to doctors, to systems, or to hospitals. They belong to themselves.

Recent legislation such as the so-called Gore bill of 1984, and amendments of 1986 has mandated changes. During this spring and summer, great steps have been taken in the United States to ensure more fair, orderly, and efficient use of all the major organs. The task fell by federal contract to the transplant surgeons and physicians through their previously voluntary organization, the United Network for Organ Sharing (UNOS). Everyone gave up some of their previously unchallenged independence in order to accommodate the common goal of serving the people. On October 1, 1987, the new system went into effect. There is a parallel data component through which a complete cross section of the national program can be developed. This permits resolution of previously unanswered questions, and it will allow changes to be made systematically and intelligently in our future policies and practices. The timing of this international symposium on the eve of the new era is particularly significant. The location of the meeting in our city will be a source of pride to citizens of Pittsburgh for a long time.

THE SIMPLE PAST

It is easier for me to talk about the past than to face the future. The work we did was once so simple. That has all changed. What was a crusade when it was *not* a reliable way of treatment became a business when it turned successful. The magical days were gone, not overnight but over a quarter of a century. This may have been just as well since victories easily won are lightly held.

I do not really have a grand vision of what happened in the last 25 years, only details. I can see a thousand air strips rolled into one, days turned into nights, flashing lights, mournful sirens, pale faces drained of hope in donor hospitals, faces grown beautiful with restored vitality and visions of the future in the transplant centers. Someone once told me that the greatest gift of God was to see something of yourself, if only once, in the face of another human being. Those working in transplantation have known this experience in the best of times and this experience has made bearable the worst of times.

I have always been proud to be a surgeon. Sixty years ago, another surgeon wrote: "To give courage to those who need it, to restore the desire for life to those who have abandoned it, with our skill to heal disease or check its course, this is our great privilege. Ours are not the concerns of ordinary life. We who . . . are doomed to go in company with pain and fear and bloodshed have a higher mission than other men, and it is for us to see that we are not unworthy."⁶

T.E. Starzl

REFERENCES

1. Burnet FM: *N Engl J Med* 264:24, 1961
2. Elkinton JR: *Ann Int Med* 60:309, 1964
3. Wolstenholme EEW, O'Connor M (eds): *Ethics in Medical Progress: With Special Reference to Transplantation*. Boston, Little Brown, 1986, p 1
4. Burger WE: In Elkinton JR (ed): *The Changing Mores of Biomedical Research*. *Ann Int Med* 67:15, 1967 (suppl 7)
5. Schneider B: In Csomos G, Thaler H (eds): *Clinical Hepatology*. Berlin, Springer-Verlag, 1983, p 398
6. Moynihan B: *Br Med J* 2:621, 1927