THE CLINICAL REALITY AND PROMISE OF TRANSPLANTATION

I am honored to be asked to deliver this address, but find it a difficult task. The clinical reality of transplantation is fairly straight forward, but to discuss its promise is somewhat more complex.

Hippocrates gave us some advice applicable to addresses such as this, although he was describing the practice of medicine when he said,

> Life is short and the art is long.
> Each occasion is fleeting.
> Experience is fallacious and
> Judgment is difficult.

He also said: It is hazardous to prognosticate.

Taken from a historical view, the success of all forms of transplants has been steadily improving and is now quite respectable. Without providing a boring litany of results tissue by tissue, I call your attention to the following slide from the National Scientific Registry of the United Network for Organ Sharing.

SLIDE

It shows the six month graft survival for all cadaver donor kidney, heart, liver, and pancreas allografts performed in the United States between October 1, 1987 and September 30, 1988. These results are remarkable for kidneys and hearts. The ultimate patient survival with liver transplants is improved by about 15 percent by retransplantation. Allografts of bone marrow, bone, and cornea, provide comparable and, in some instances, better results.

Yet, although current success rates are spectacular for the short term (2-5 years); they are considerably less spectacular for the long term (10-15 years).

SLIDE

This slide from Terasaki's last book illustrates the gradual loss of cadaver donor kidneys over time. This phenomenon, that is the gradual loss of grafts with time, is common to most allografts.

It can be useful to think of transplant patients as falling into three categories. One group has a successful graft and is returned to normal health. This group is expanding and such grafts will usually function for years; nevertheless, the graft survival gradually declines through a 10-15 year period. These are the true winners, although they are not returned to a normal life expectancy. One group has an early failure for one of several reasons. They have substantial expense, but the issue is settled quickly. The third group may be the most unfortunate in that they receive grafts which, for one of several reasons, never function quite normally or do so for only a short time. Their grafts sustain life, but do not restore them to normal health. They have short graft survival times; 1-3 years, they are chronically ill, have repeated complications and hospitalizations costing large sums of money. It is the patients in this group which appear in statistics as successful for 2-5 years that have great expense and commonly do not ultimately benefit as much as they expected. Future improvements will shift more and more patients from groups 2 and 3 to group 1.

Equally important is the need for transplants to be more

durable. Today's situation is one in which grafts are placed and retained under cover of substantial immunosuppression. However, there is continuing antigenic stimulation by the graft and a constant attempt by the host to extrude or reject it. This balance ordinarily tips toward rejection sooner or later. In order to produce permanent acceptance some form of specific immunologic tolerance is likely to be required; i.e. the body must be convinced to receive and treat the organ as part of itself.

The theoretically bright prospect of inducing a specific state of tolerance through immunologic manipulation has not yet materialized some 40 years after the biologic phenomenon was demonstrated; however, several promising avenues toward this end are now being followed. Some clinical trials are underway and more will soon follow. This will be essential for transplantation to be reliable, predictable, and durable therapy. It will have a major impact not only on graft durability, but also on expense and prevention of organ wastage.

We should realize that clinical transplantation has always been ahead of our understanding of the biology of transplantation. This progress has been made possible primarily by pharmacologic innovations associated with the determination of clinicians. The use of Azathioprin and steroids followed by the introduction of anti-thymocyte globulin, and more recently Cyclosporine and monoclonal antibody therapy, have been key innovations which permitted better and better success rates in more and more complex transplants. The new experimental drug FK-506 may cause yet another pharmacologic revolution. Recent short term results appear

brilliant. It is, of course, possible that more precise and powerful immunosuppressive agents alone could induce tolerance.

A method to preserve whole organs for weeks or months, as is possible now for many tissues, would be revolutionary. It would allow electively planned transplants and also prevent the wastage of organs for which no recipient is immediately available. However, unlike the induction of tolerance for which the concepts are understood but the tools are lacking, prolonged organ preservation requires discovery of new concepts. Such insights in science are unpredictable; while they might occur tomorrow, they might not occur for another 100 years, and they cannot be purchased.

The need for improved surgical technology is commonly overlooked, but is substantive. Today's complex transplantations in many areas are beyond the skills of many surgeons and at times beyond the skills of the very best, since these technical requirements are at times at or beyond the limits of current technology. Periodically I feel as though I am practicing a medieval art. Every day, while some of my colleagues are using combined computers to clarify wanted images and screen out others, ultrasound to see heart valves, video cameras to magnify small tubes, I stand at the operating table and like all my brothers, clamp and tie one vessel at a time, or sew together bowel or blood vessels one stitch after another not unlike an experienced tailor, using essentially the same technology developed by the great pioneer surgeons of the last half of the 19th century. The only real innovations in surgical technology in the last 100 years have

been in better instruments, improved suture material, and the introduction of automatic stapling devices. This technology will not suffice for the 21st century. We have not expended enough resources in this area and this needs to change. If necessity is truly the mother of invention, we will see these innovations.

Organ Availability

Will the supply of organs and tissues ever met the demand? There certainly is no reason for the supply of bone, or skin, or corneas, or bone marrow to be insufficient. Proper organization and delivery systems can meet these demands and will do so with sufficient effort.

Theoretically there might be sufficient kidneys to meet demand, but if the indications for heart transplantation are liberalized as most expect, there will never be an adequate supply, and same is probably true for liver and lung. Presumably, if pancreatic islets could be retrieved with sufficient efficiency, they could be retrieved from non-heart beating cadavers and stored frozen. Perhaps islet cells can be expanded by culture prior to freezing. Barriers to the solution of these problems are largely technical and should yield to sufficient effort. If transplantation is to have a serious impact on diabetes, it seems unlikely that the supply of whole pancreas will ever meet the enormous demand. Thus, it may be wise to invest more research funds in islet transplantation than whole organ pancreatic grafting.

At present the only way to increase the donor supply is by increasing the donor pool. It is estimated that 20,000-25,000

citizens die a neurologic death annually in the United States and, while 75-80% of the population agrees that organ donation should occur, only 40-50% is willing to personally donate, but only 20-25 % of donor organs are actually being retrieved. These figures must change. Ultimately the rightness of organ donation must become embedded within the mores of our culture. This will take a very long time, but certainly it will occur since it is the right, the moral, the human thing to do. This requires constant reinforcement by continued public and professional education.

In the short term I favor implied consent legislation. That is, organs may be removed unless there is known objection. This seems strategically right to me since it forces the public to take the initiative should they wish to take the immoral course, while it places the law in the morally correct position. I expect this to happen in the next few decades. Such legislation should greatly expand donor supply, not only because organs and tissues can be retrieved from unidentified individuals who are neurologically dead, but also because it is likely that many relatives will not take the initiative to refuse donation if it were considered the natural and right course in our society. It should help imbed the concept into society's mores. Further, many additional organs could be salvaged by the simple expediency of placing patients with sudden, unexpected cardiac death on percutaneous femoral-femoral bypass for rapid induction of whole body hypothermia and asanguinous perfusion. Techniques for this are simple, rather inexpensive, and readily available. They are rarely used today for fear of litigation. Potentially, such approaches could be used

with some clarifying legislation in the absence of an implied consent law, but would be more productive with it.

The demand for organs and public opinion will ultimately produce this change in mores. Thus, the supply of organs and tissues will increase, but it is unlikely to ever be adequate to make the replacement of some organs a routine, elective process.

Many organs remain unused because they are in a questionable state of health when obtained. When Belzer introduced perfusion preservation, he initially thought that perfusion might be used to improve the health of an organ. Little has been published on this subject possibly because of the absence of a good way to establish the health of a specific organ at a specific time other than to reimplant it. Nevertheless, this seems attainable and might greatly expand the number of available organs.

I should not fail to mention the needs for artificial organs to sustain people with non-functioning organs such as the liver, lung, or heart for days or weeks to both sustain life, as well as improve the physical condition.

Ultimately it will be necessary to produce human organs in some artificial way, and some scientific philosophers, if not scientists, are beginning to discuss this possibility. The development of transgenic animals has accelerated these speculations. This technology of inducing an animal to incorporate xenogeneic genes into its germ line is in its infancy, but has stimulated great interest as a research tool of great promise. Since the phenomenon is established, it is not pure science fiction to consider the requirements to induce some animal, for example the

pig, to produce some human organs, for example a heart. The complexities of organogenesis, the number of genes involved, the sequencing of activation and deactivation, and many other barriers seem at present to be overwhelming. Yet, these issues are not known to be unsolvable by available technology and these avenues will undoubtedly be explored in a logarithmic way.

There are many other issues in transplantation that are parascientific. Cost is most commonly emphasized and at times we seem almost ready to abandon some efforts because we cannot afford them. The federal and some state governments have been exceedingly slow to support clinical transplants. This is very short-sighted for many reasons, but I only want to emphasize one. The cost of all transplants will be greatly reduced in time. Today enormous expense is encumbered in donor acquisition. This is because of high fixed minimal cost to operate organ procurement agencies and a low yield of organs even in the best of agencies. The yield in whole organs is only 20-25 percent of those available, even using very conservative estimates. If all organs and tissues were retrieved, the organs recovered would go up at least 4 or 5-fold at an increase of expenses of perhaps two-fold, thus, cutting the cost of organs by half. As the skills and technology to perform transplants is diffused more widely, it will no longer be necessary for teams of people to be flying up and down the country in chartered jet aircraft to retrieve hearts, livers, pancreases, etc. Rather, each OPO will retrieve all organs and tissues and send them by commercial airlines. This alone will save as much as $5000-$6000 per organ. Finally, when transplant outcome is more

predictable and more durable, they will be much less costly. Complications will be fewer and repeat grafts rarely necessary. Transplants will never be as inexpensive as appendectomies, but a reduction to one-third current cost is not an unrealistic guess.

A great threat to transplantation is the AID's epidemic. No one knows the number of people infected with this virus and this plague must be conquered to salvage the lives of the people afflicted. I do not want by subsequent remarks to sound insensitive to that desperate need, but a byproduct of HTLV-III infection is the reduction in organ donors. In my home state of Louisiana during the past year approximately 10 percent of all potential donors were refused because they were in the high risk groups which might bear the virus. I am told that the percentage has reached over 20 percent in some areas of the country.

We must not let the public forget that the transplantation of whole organs other than the kidney, as well as the transplantation of many tissues is not available to perhaps as many as 100,000,000 Americans for lack of money. THis is absolutely unacceptable. I often wonder how many poor people would be more anxious to donate organs had they friends or family who had received organs.

A still darker side is the possible exploitation of the weak by the powerful, the poor by the rich, to obtain life-saving organs for the "more valuable" members of the human race. This spectre, that is the brokerage of human organs, is already on the horizon and must be dealt with while in its infancy.

The senario I have drawn is almost certainly wrong in its blueprint, but not necessarily in concept. For example, diabetes

may be more likely to be eliminated by elimination of the genetic susceptability or the autoimmune trigger than by transplantation. Bioengineers may make a successful artificial heart, and on and on.

Transplantation is only one avenue to the correction of the end stage of many diseases, but this route can be successful. Had someone told me 30 years ago while I was a surgical resident that death from uremic coma would disappear, that many people in liver coma or terminal heart failure could be restored to perfect health, that leukemia could be cured, hips and joints replaced, I would have thought him overly optimistic, to say the least. Changes in the next 30 years will certainly be much more spectacular, not necessarily in concept, but in practicality, reproducibility, availability, since the information base has been expanding logarithmically and many more intellects are involved in the adventure.

Thus to summarize, if we perservere, if we stay on a moral, humanistic course, we can reasonably expect reliable and durable transplantation of most tissues and organs for a progressively larger number of people at reasonable cost. These shining goals are almost within our grasp.