



## VII

# Presidential Addresses





# Inaugural: American Society of Transplant Surgeons

THOMAS E. STARZL, 1974–75

From time to time, a news story appears about the birth of a husky, full-term baby, much to the amazement of the chagrined mother who had not realized that she was pregnant. Mother surgery seemed thus to have been caught by surprise when clinical transplantation burst upon the scene in the early 1960s. Then last October 21, 1974, at the American College of Surgeons meeting in Miami Beach, another infant was delivered, again with minimal warning or fanfare. I am referring to our American Society of Transplant Surgeons, a group which is meeting officially for the first time today. As your first president, I want to look at the prognosis for survival of our new organization, to describe some ways of nourishing it, and to identify how *not* to poison it during its defenseless early years.

Before exploring these matters, it behooves us to recall the immediacy of the total modern history of transplantation. For example, the clear beginnings of an understanding of the mechanisms and significance of homograft rejection are only 30 years old. Most of the investigators who probed these mysteries in animals still are alive and vigorous, including the incomparable Sir Peter Medawar and his first coworkers, Thomas Gibson, Rupert Billingham, and Leslie Brent.

Unequivocal successes after clinical renal homotransplantation under immunosuppression were not recorded until 1958 and 1959 when, first in Boston and then in Paris, homografts were taken from fraternal twin donors and started on their long survival in irradiated recipients. The presently employed multiple-agent techniques of immunosuppression were not evolved until 1962 and 1963, just about 12 years ago. Liver, heart, lung, and pancreas transplantation with extended recipient survival was not achieved in man until 1967 and 1968. Of the leading figures in the complete panorama of clinical organ transplantation, only David Hume is no longer with us and even his death in May 1973 was tragically precocious from a traumatic accident.

The brief duration of our clinical specialty does not connote a lack of substance. Instead, I believe that the scientific commitment of a decade ago to transplantation



represented the greatest interdisciplinary effort ever mounted in clinical medicine up to that time. Small wonder then, the amazing harvest of new facts and concepts that poured forth.

It has been common within universities to appoint department chairpersons or division leaders on the basis of an expertise in new and broadly significant areas of development. The consequence has been that general, neurologic, thoracic, vascular, and cardiac surgeons have come in waves across the academic beaches. Transplantation has been no exception. In the U.S., 11 chairmanships have been filled from our ranks (Table 1), as well as numerous division chiefships, exclusive of those divisions

Name	School
F. Belzer	Wisconsin
R. Egdahl	Boston University
D. Hume	Virginia Commonwealth
S. Kountz	New York Downstate
J. Mannick	Boston University
J. Najarian	Minnesota
K. Reemtsma	Columbia
P. Russell	Harvard
N. Shumway	Stanford
T. Starzl	Colorado
J. Turcotte	Michigan

*\*The list is a gross understatement. Some of the chairmen who were originators of transplantation such as William P. Longmire (UCLA) and Francis D. Moore (Harvard) have been omitted because they are best known for work in other areas. An incomplete list of other part-time transplanters who have made major contributions includes James D. Hardy (Mississippi), Vallee Willman (St. Louis University), Michael E. DeBakey (Baylor), J. Bradley Aust (Texas) and Lloyd D. MacLean (Magill).*

that were created solely for transplantation. A similar pattern has occurred in foreign schools too numerous to list.

The fact that transplanters would yield in droves to these administrative offerings does not necessarily speak well for their intelligence or character. (One of the notable resisters has been Joseph Murray at Harvard.) But it does suggest the extent to which transplantation has been accepted as a leading discipline in university surgical circles and the degree to which its practitioners have contributed to the mainstream of academic life. In addition, many from the modern crop of transplantation surgeons have served as presidents of the Society of University Surgeons (Richard Egdahl 1970; Samuel Kountz 1974) and the Association for Academic Surgery (John Najarian 1968; Thomas L. Marchioro 1974).

Why mention such details? It is to indicate that our new society already con-

tains the most important determinant for its own success. The work we do has the fiber and the depth to justify the organization. Without this intrinsic worth our prognosis would be hopeless, no matter how cleverly we conducted our affairs. With it, our failure to thrive can be explicable only by errors in our perception of our objectives or by miscalculations in the pursuit of these goals.

Granting this, you cannot shrink from a clear enunciation of our first priorities. My own bias is simple. I think that we exist mainly for the development and exchange of accurate information and informed opinion. By definition, our principal objectives are, therefore, intellectual and professional, and this must be reflected in the programs that we develop annually. We have made a great start in this our first meeting, but I hope in the final analysis that this year's program will be judged to have been the weakest when compared to those coming in the years ahead.



The incentives are there, leaving aside any collective instinct for organization self-preservation. An outlet for rapid publication of our program papers has been arranged through one of the finest of today's journals. *Surgery*. This alone should ensure the submission of new and outstanding work only, since the articles will be reviewed and edited closely. The conditions of publication are analogous to those for the prestigious Society of University Surgeons or the Society for Vascular Surgery. If we fail to respond to the challenge, this opportunity could be lost.

The outlet in the journal *Surgery* has some interesting implications that are worth dwelling upon for a moment. So far, the field of clinical transplantation has grown up in what might be termed a giant interdisciplinary matrix. The explanation and need for, as well as the advantages of, this hybrid state have been obvious. So has been at least one possible disadvantage, which is the potential disconnection of our specialty from a traditional base. The arrangement to publish our proceedings in a surgical journal will remind us of our origins in surgery and well may affect our choice of presentations. It also should systematically place a concentration of our work before our less specialized surgical peers, something that has not been done before, except by the mechanisms of the *Surgical Forum*.

These new conditions will strengthen our surgical heritage, but they cannot be used as an excuse to limit our interests. The name "Society of Transplant Surgeons" is all-inclusive. It would be both tragic and inexcusable if we functioned as a society for kidney transplantation. I look forward to hearing here of research and progress about the liver, heart, lung, pancreas, bone marrow, and other organs.

Until now, essentially all of the immunosuppressive techniques have been worked out on the kidney model. It would not surprise me in the future if generally applicable improvements in care came from work with the extrarenal organs and were reflected back to the kidney. By being inclusive, no possible avenues will be blocked. The society will be assured of breadth as well as depth. The society deliberations should be a mixture of basic articles and clinical ones in the best tradition of modern surgical science.

At the same time, another great organization, the international Transplantation Society, to which most of us belong, must be kept strong. Every two years the international Transplantation Society formally brings together a heterogeneous collection of basic investigators and clinicians. The exposure of each group to the unfamiliar ideas and points of view of the other can create the kind of climate from which progress stems. The American Society of Transplant Surgeons and the Transplantation Society are not competitive but are complementary. One is sectarian, the other catholic.

If we can accept that the major objectives of the American Society of Transplant Surgeons are those I have just described, you will now take very seriously certain other justifications for our new organization which I have heard cited. The most degrading misconception reported to me has been that we are a lobbying group designed to influence the language and the intent of federal legislation and to affect the implementation of laws already enacted. Were this to be the purpose of our new society, my advice would be to go home now. A sandcastle doomed by the first tide would have been built by your Council.

Nor should our organization become an instrument for the negotiation and



establishment of financial matters, including professional fees. We conduct our affairs these days in a cynical social climate, leavened by occasional ennobling acts of which organ donation is a prototype. If it became perceived or imagined by the public that hypocrisy and greed were central to our transplantation programs, cadaver donors would become unavailable and all the other punitive side effects that you can easily imagine would follow. Ours is the medical specialty most founded on public trust and personal altruism. The corollary is that it is the most fragile.

I do not imply that we should not talk to those who solicit our assistance for health planning and other purposes. Subcommittees of our society will have to begin work promptly in several vital areas that have needed attention for some time. The most pressing requirement is to define the relationship of established or proposed kidney transplantation programs to the government, particularly because of the major effect that Public Law 92-603 already has had upon our medical and administrative practices. Data should be developed to help in deciding how many renal transplantation centers should be set up, where they would best be located, and how they can be run most efficiently for the citizens of those specific regions.

I now am confident that there also will be a real justification for cardiac and hepatic transplantation centers within five years from now. These are not necessarily going to be in the same places as kidney programs. As all of you undoubtedly know, another bill, the Beall-Health Manpower Act, currently before Congress, would be a giant step toward the concept of regionalization of health care. Since it is tied up so heavily in government financing, transplantation of all kinds is certain to become involved in government experimentation with such planning.

In the same connection, you should be looking within our own ranks to see how the demands being made upon us fit the numbers of our membership. Are we training enough transplant surgeons to catch up with the need, and if so, when will a superfluity of trainees be a problem, as it has become in a number of other specialties? What constitutes adequate training? If we work at these questions, maybe we can avoid some of the mistakes that other groups with interests in special fields of surgery have made.

Finally, we also will have to involve ourselves in setting up and maintaining professional standards. It would be a great pity if the lessons of the last decade were not applied wisely and had to be relearned by new groups (or established ones for that matter) at the price of human suffering. At the same time, the trap must be avoided of freezing immunosuppressive treatment in its present mold, which, we all agree, still has too great a morbidity and mortality rate to be completely acceptable.

And so in closing, let me return again to the beginning and to the emphasis that I placed on the role in scientific development which our new organization must play if it is to fulfill its destiny. T. S. Kuhn<sup>1</sup> the distinguished scientist and historian, has shown how progress consists of a series of great and small revolutions against authority. A great advance necessitates the overthrow of an established dogma, and when that occurs the advance itself becomes the new dogma to which advocates flock. It is natural for those disciplines to become protectors instead of improvers of the status quo, guardians of the past instead of seekers of the future. To make matters formal,

they might even consider creating a society that, if unaware of the dangers, could be the means by which the next stage of improvement were blocked.

We know this hazard, ladies and gentlemen of the American Society of Transplant Surgeons, and if you avoid it, we should take our place beside the other great professional societies of this country.

## **Reference**

1. Kuhn, TS: *The structure of scientific revolutions*, Chicago, 1962, University of Chicago Press.







## ASTS: A Precocious 2-Year-Old

FOLKERT O. BELZER, 1975–76

**M**embers of the American Society of Transplant Surgeons and Guests: First, it has been a great honor indeed to serve the past year as the president of ASTS. Tradition now calls for a Presidential Address. I must admit I have had great difficulty in finding something appropriate to say. Perhaps it would be a good idea if the presidents did more and talked less. Last year, Tom Starzl compared the birth of ASTS with that of a child. His task was easier than mine. When a child is born, one can talk about one's hopes and wishes for the future, and can always say something nice about the parents. Indeed, Tom showed us some nice and interesting pictures of some of the parents of ASTS. But what can one say about a child who is 2 years old? The parents have changed little, and it is difficult to expect that in this short period the child would have made significant contributions.

I will talk today, therefore, about my own personal feelings about this society, what I believe we have to do, not only to keep it viable, but to make it grow so that it may achieve the same stature as some of our other surgical organizations. Because these are my personal views, I would rather talk as a member of the society than as your president, and for this reason I will not submit this address for publication. Thus, I can always deny what I have said.

First, let's reevaluate why ASTS or any society should exist. Basically, the goals are:

1. to stimulate progress in a particular field
2. to make known this progress through publications and to teach new information to fellow specialists
3. to stimulate young physicians to enter the specialized field and to make contributions to it
4. to provide leadership in securing financially sound and optimal patient care

When we mention dissemination of information and publications, it might seem that ASTS is not really needed. A sufficient number of surgical societies accept outstanding contributions in transplantation. If ASTS is to be the outlet for papers not accepted by the Society of University Surgeons, the American Surgical Association, or other estab-



lished societies, then we are doomed from the beginning. And yet, I do believe there is a place for a transplantation publication. Material that may not be revolutionary, or general enough to be of interest to surgeons outside our field, still could be of great interest to transplanters. Also, daily matters in the care of transplant patients may not by themselves, perhaps, be striking enough to warrant publication in an established surgical journal, but would be appropriate for our own publication. For example, how does one prevent lymphoceles after renal transplantation; or, are brush biopsies sufficient to establish the diagnosis of pneumocystitis, or does one need to do an open-lung biopsy? We as members should decide if there should be panel discussions at future meetings regarding these perhaps not-very-scientific-but-very-important matters in patient care. Perhaps we could find a balance between the highest quality of paper for publication and interesting general information about patient care.

To what extent should ASTS become involved in training transplant surgeons? Should we define what adequate training is? Should we establish guidelines for what is to be considered adequate training? And, how and where should this training take place? Should every transplant service that has a hospital administrator generous enough to provide \$16,000 have a transplant fellowship? How many transplants should a transplant service be doing to provide a good fellowship? Should every transplant surgeon be primarily involved in research, or is there a place for the clinical transplant surgeon? How can we make transplantation more attractive so we can attract the best and brightest young surgeons to enter this fascinating field for their careers?

We have already taken the first steps by listing in our program booklet some of the fellowships presently available. I confess I have no direct answers to these questions, but perhaps a task force made up of ASTS members could come up with some solutions.

The role of ASTS in the delivery of health care in the field of transplantation needs to be addressed. As you know, some have suggested that this society was born to be a strong opposition voice against a well-organized nephrology group. In traveling around and talking to transplant surgeons, I hear the complaint that nephrologists keep patients away from us because doing so is more financially rewarding for them. But one must not throw stones if one lives in a glass house. Before any one of us casts aspersions on our nephrology colleagues, let us at least make an honest appraisal.

What have our nephrology friends done in the last decade? Ten years ago, dialysis was only available in a few institutions. Patients died because of the unavailability of what is now considered appropriate health care. In the past 10 years, nephrologists have trained enough other nephrologists to provide dialysis to probably everyone that now needs it in the U.S. They have introduced innovative ideas such as limited-care facilities and home dialysis. The mortality—which was high initially—has decreased to an extremely reasonable level, even though patient selection has become more and more liberal, with many high-risk and older patients. In addition to providing health care, nephrologists are constantly involved in research efforts to further improve the art of chronic dialysis. At meetings that most surgeons do not go to, such as American Society for Artificial Internal Organs (ASAIO) and Kidney Foundation meetings, a



great amount of work is done to improve dialysis membranes, the size of molecules to filter, and related concerns. There have been financial rewards to these physicians, and in some cases the financial rewards have perhaps exceeded the individual's input.

But what have we, the transplanters, done? We have not greatly increased the number of transplants each year. As a matter of fact, this year, the number of renal transplants has actually decreased. We still have long lists of patients, including many young people, waiting months and even years for an appropriate cadaver kidney.

We still have unacceptable mortality figures of 20% to 40% in the first year post-transplant. Complications of iatrogenic Cushing's disease continue to plague us. There has been limited leadership in the field of organ procurement; probably the most innovative and productive approach was actually started by two nephrologists in Kansas City. If tomorrow one of the members of ASTS should publish a method to allow cadaver renal transplants with a 90% success rate, it would probably take us another decade before we had enough kidneys to meet the demand.

I certainly believe in some federal legislation approaches. Mel Williams and I suggested in the national guidelines, which to my knowledge still are not published, that every patient on dialysis with end-stage renal disease should be seen within six months by a transplant surgeon. But before we criticize our nephrology colleagues, it is much more important that we first improve our own results and provide better, more readily available, and less expensive health care. I sincerely believe that most nephrologists are honorable, dedicated physicians who would send their patients to us if optimal health care would be provided. Rather than deepening the cleft between transplant surgeons and nephrologists, maybe we should improve our relationship. I would like to see one or two transplant surgeons on the Executive Board of the Kidney Foundation. I hope we would not always be too busy to go to either government or local meetings. Gastroenterologists seem to work quite well with general surgeons as do cardiologists with cardiac surgeons.

Those of us who are in renal transplantation must work with our nephrology associates on the basis of mutual respect and optimal patient care. The Program Committee this year selected several excellent papers *not* in the field of renal transplantation. Our society is called the American Society of Transplant Surgeons, and I hope that we can continue to discuss scientific progress in all the fields of transplantation. If not, we might as well call ourselves the American Society of *Renal* Transplant Surgeons, comparable to our medical confreres who call themselves the Renal Physicians Association.

Finally, a word about another important aspect of professional societies: the ability to talk with one another and meet one another. I believe again that we owe our gratitude to Fred Merkel and his committee for organizing this meeting plus the evening that is to follow. The Program Committee wisely allowed enough time between presentations for open and free discussion which, as all of us know, can be more important than the actual paper. I would urge the more junior members of ASTS to get to know the more senior members. If there are any specific problems, ask them for advice. I hope we will never grow so big that we will not know each other on a personal basis.

Some may think I have been too critical of our shortcomings and perhaps have not emphasized the positive things we have done. Yet, just as with a 2-year-old child, our future is still uncertain and at times shaky. Only with firm guidance and a clear perspective of our goals will ASTS continue to prosper and improve, and I hope that we will all work for this particular goal.





# Our Heritage and Our Destiny

THOMAS L. MARCHIORO, 1976–77

Today, we begin our third full year as the American Society of Transplant Surgeons. The husky baby that Tom Starzl spoke of in his Inaugural Address has matured rapidly. The quality of the program, the vigor of the membership, and our acceptance by other surgical and medical organizations are clear witness to our growth and health.

It would give me great personal pleasure to repay the honor of being president by recounting past glories and confidently predicting more to come. Unfortunately, as always in the history of mankind, we, like everyone else, face an uncertain future. In the past few years the number and variety of apocalyptic books, editorials, and speeches has increased beyond all bounds. So much so that they have lost all power to shock, amaze, titillate, or stimulate. All they do is confuse.

I do not speak of imminent doom—nor of ultimate doom. Rather, I would like to review some of the problems, real and fancied, with which we are confronted and offer a remedy. While it may not cure every ill, it will certainly permit us not only to survive, but also to grow and fulfill that destiny toward which we were directed at our beginnings.

Our destiny is to increase the store of knowledge, principally medical, but in other areas as well, and to apply it in consonance with those ancient but ever new principles that have always guided the physician.

Progress in transplantation will go on. But we cannot placidly assume that we will be responsible for its advance. We are constantly being tested. If we are found wanting, others will take our place and we shall be consigned to the dustbin of history.

What then are some of the problems? I prefer to group them into “transplantation” problems and “transplanted” problems. The former remain much as they have for several years. More specific immunosuppression, induction of specific tolerance or enhancement, more effective and longer term organ preservation, an increase in the number and quality of organs—these are the questions to which our scientific programs are, and I trust will be, addressed. Past success has provided at least partial solutions to what at times seemed total enigmas.



How were these victories gained? To the uninitiated and uninformed, it might appear we were the beneficiaries of some marvelous “breakthrough.” Yet we all know that such is not the case. Every victory was tempered by defeat, every gain by loss. Progress has been achieved only by unremitting hard work, countless experiments, dashed hopes, and above all the courage to fail. It is out of such trials that organ transplantation occupies an honored place in the treatment of human illness. And it will only be out of such trials that tomorrow will find it further advanced than today.

I need not tell you these things. You have lived them. My words are but a pale reflection of the efforts of many distinguished surgeons gathered here today. My purpose in recounting, even briefly, what steps it took to bring us to where we are is to focus attention on those essential qualities that you exemplify. For it is those same qualities that must be applied to the problems I have earlier called “transplanted.”

We are so intent on transplantation as a means of doing good that sometimes we may not realize that some transplants may not be desirable. I refer now to that massive body of socioeconomic, philosophic, comic, tragic nonsense that finds its way into virtually every journal, newspaper, legislative hearing and, yes, medical curriculum. The profession is buffeted on all sides by self-proclaimed experts regarding our responsibilities for health care delivery, cost-effectiveness, unnecessary operations, excessive specialization. The list seems endless. We are the victims of a schizophrenic desire for Utopia in an Arcadian world. We have all been affected by these insane demands.

Why have I called these “transplanted” problems? Because they are social problems, many of them unreal, which have been transplanted to our vineyard. Unlike the grafts with which we daily deal, these are like weeds and will grow as such, ultimately choking out the good seed—unless we do something about them.

What solutions are available? Must we face the choice of Hamlet who asked

“Whether ‘tis nobler in the mind to suffer the slings and arrows of outrageous fortune or,  
Taking arms, oppose and so end them?”

There are sentiments for both courses. The desire to “oppose and so end them” seems to be especially strong. This is particularly true regarding the never-ending regulations for treatment of end-stage renal disease and the serious abuses fostered by some nephrologists.

With respect to this last, I would urge you to reconsider the profound remarks that Fred Belzer made in a plea for cooperation with our nephrology colleagues. As he was at great pains to point out, most nephrologists are hard-working, honest, and sincerely interested in better care for their patients—a goal we share.

Why then is there such dissatisfaction with the current regulations for end-stage renal disease and such disenchantment with our medical colleagues? It is largely a matter of ignorance rather than cupidity. Many nephrologists are simply unaware of the medical, social, psychological, and economic benefits of transplantation. It is our job to educate them, as well as the public and the government. It is also our job to con-



tinue working to improve our results. Only in this way can we resolve the current impasse that exists in many, if not most, parts of the country.

On the other hand, it seems to me there is a tendency to passively accept certain forms of legislation, the main effect of which will be restriction of our opportunities to do meaningful clinical research. This is not to say that we are above the law and morality. It is meant to challenge the assumptions, tacit or otherwise, that the true welfare of patients can best be determined by those who are least equipped by training or experience in these matters. Of all the professions, medicine is universally recognized as the most humanistic. It would be tragic if we were to abandon our heritage as advocates of the sick to those much less qualified or not qualified at all.

The traditional duties of an academic surgical society and its members are teaching, research, and patient care. As an academic society, we are working to improve organ transplantation through research, and by this means, as well as others, to provide optimal care for patients.

But are we working as effectively as we can to teach? Our constituency is much broader than medical students, residents, or even “health care professionals,” whatever that term may mean. It includes the general public as well as the medical profession, legislators as well as learned societies, teachers as well as students, and ourselves as well as others. It is our solemn obligation not only to teach others, but to learn from them as well.

This society has the expertise, the energy, and the esprit necessary to bring order out of the chaos currently facing us. Where shall we begin? First, to reiterate, it will require all those qualities of heart and mind that were needed to prove that organ transplantation was possible. Without them, any venture is foredoomed to failure. With them, we have a fighting chance—a chance to convince the general public as well as legislators and bureaucrats at local, state, and national levels of the value of our work as cost-effective, health care delivery provided by experts; a chance to see that research and training continue; and above all, a chance to bring the benefits of our labors to those who appreciate it most: our patients. Second, we need to state our goals. Without a clear idea of what we want, it will be impossible to get a hearing. A corollary of precise goals is a realistic appraisal of what we have to offer and what our limitations are. Third, we must have organization. Undisciplined, undecided, unorganized, we are not likely to affect the legislative or regulatory process except to our own detriment.

Right now we have the first requirement. Our goals, like ourselves, are straightforward—to bring the benefits of organ transplantation to those patients for whom it is the best form of treatment and to continue our research and training.

As to organization, I would like to propose that we actively support two of the original ASTS committees, the Advisory Committee and the Education Committee. Among our members are many internationally known figures. With their help, working through these committees, it should be relatively simple to obtain audiences with the various professional and government groups that, by force of custom or law, exert such profound influence over our daily activities. Armed with hard facts, backed up by the good will of our patients and medical colleagues, we can hardly fail to make a

favorable impression. Free discussion and knowledge are required for effective persuasion. And persuasion, not confrontation, is the key to political action.

Our obligation as clinical surgeons is to those patients we care for here and now. As scientists, we are in the service of not only the present but also the future. Our problem is not only to maintain today's standards, no matter how excellent, but to exceed them. Each person, each society, has gone forward because of commitment to a goal. It will require similar commitments for us to advance, individually and collectively, and, along with us, all of humanity.

The hope for the future lies in our present efforts, not in some legislative panacea, improbable social or scientific revolution, or cowardly retreat into a poorly remembered past.

I promised you a remedy for our present problems: I refer to that simple four-letter word that Sir William Osler called the Magic Word in Medicine—Work. It still retains its magical quality. But, although it is magical, it is limited in its effectiveness. The conflict between the ideal and the real will never be resolved. Nor should it be. All that we can realistically hope for is that our efforts of today will find us further than yesterday.

As Theodore Roosevelt said, "It is not the critic who counts; not the man who points out how the strong man stumbled, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs and comes short again and again; who knows the great enthusiasms, the great devotions; who spends himself in a worthy cause; who, at the best, knows in the end the triumph of high achievement, and who, at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those timid souls who know neither victory nor defeat."





# The Importance of Formal Training for Transplant Surgeons

JOHN S. NAJARIAN, 1977–78

I served as the fourth president of the American Society of Transplant Surgeons from June 1977 to June 1978. My Presidential Address focused on the importance of education as a foundation for the emerging clinical field of organ transplantation. Before this time, transplant surgeons were trained in a variety of ways—primarily on the job. I felt strongly that a formal training program, as we had developed at the University of Minnesota, would be important for our discipline's growth in quantity and quality.

Dick Simmons and I had established a formal fellowship training program in transplantation at the University of Minnesota in 1969. Initially, our program involved six months of training of what we called a donor doctor; responsibilities included placing all the access lines and shunts as well as doing all the donor operations (both cadaver and living related). During the second six months of our training program, the fellow would be responsible for the renal recipient, and would perform or first assist on all the transplant procedures.

In my Presidential Address, I stressed the importance of this kind of formal training for individuals who had completed their surgical training and had qualified for the American Board of Surgery. Because multiple-organ transplantation was coming on the clinical scene (primarily liver, pancreas, and kidney), I also stressed that comprehensive general surgical training should be the prerequisite for a transplant fellowship. I felt that candidates for the American Society of Transplant Surgeons should have completed a minimum of one year of a formal transplant fellowship, along with their Boards (preferably in general surgery, but urology was also acceptable given the prevalence of renal transplantation at that time).

Two years later, in his 1980 Presidential Address, Dr. James Cerilli reemphasized the importance of training that I had suggested in my address. He placed on my shoulders the responsibility for developing quality programs that would become the standard in this country. Specifically, he appointed me chairman of the newly formed

Education Committee and put me in charge of evaluating and approving training programs at institutions involved in clinical transplantation. Only approved institutions would be listed in the annual American Society of Transplantation Surgeons program book. Completion of training at an approved institution, along with the Boards in general surgery or urology, would be required for membership in the American Society of Transplant Surgeons.

My 1978 Presidential Address also suggested inviting basic scientists in immunology to give a lecture to the society each year—in keeping with my theme of improving education for transplant surgeons. The selection of this honored lecturer would be the prerogative of the president. My choice to be the first honored lecturer was Sir Peter Medawar, the 1960 Nobel laureate and “Father of Transplantation,” whose presentation was entitled “The Wider Implications of Transplantation Surgery.” The following year, Dr. Frederick Merkel as president chose another world-renowned transplant immunologist, Dr. Robert Good, to be the honored lecturer. This tradition has continued to the present. Five years ago, it became apparent that a more extensive means of continuing education was needed. Hence, the postgraduate course in transplantation was begun: on the Saturday after the annual meeting, invited lecturers give overviews of relevant subjects in immunology and clinical transplantation. The papers from that day are published annually in *Clinical Transplantation*.





# Reassessment and Reevaluation

FREDERICK K. MERKEL, 1978–79

**M**y Dear Colleagues,

It has been a privilege to serve as ASTS president for the past year. In the beginning, our society emerged as an outgrowth of several ad hoc meetings some of us had with the Social Security Administration and U.S. Department of Health, Education, and Welfare (HEW) agencies during the development of the end-stage renal disease program. Initially, we maintained a low profile and concerned ourselves primarily with scientific matters. In this respect, we were quite successful. Tom Starzl, Fred Belzer, Tom Marchioro, and John Najarian, previous presidents, aided by Tony Monaco's unstinting support as program chairman, provided us with a record of annual scientific meetings of ever-increasing merit. Although our society has, in this way, grown steadily, I believe we must now firm up our position on a number of burning issues and perhaps make some changes in our direction. This is a critical period for us.

The following five points seem most crucial: 1) the function of our society in relation to all organ systems, not just the kidney; 2) the relationship of our society and its members with other specialists, such as nephrologists; 3) how our society and its members can help provide better delivery of health care; 4) the interaction of our society and its members with the government; and 5) structural changes in our society that would make it more effective.

First, ASTS is a society of all transplant surgeons. Although papers dealing with liver, pancreas, heart, lung, and parathyroid have been presented at our meetings, we must encourage and direct our Program Committee to select more papers dealing with other organs, even if it means increasing the length of the meeting or decreasing the kidney-oriented papers. We must attract all transplant specialists if we wish to further enhance our programs and provide the cross-fertilization at our meetings that specialists in different subfields can provide. We must clearly let transplanters of other organs besides the kidney understand that they have an equal place. Our organization can benefit them, not only in terms of information they gain from the kidney program, but also because we have much in common with one another. The clinical kid-



ney program, as the only federally funded catastrophic health care program now in existence, will certainly serve as a model for future federal health care delivery systems involving other organs.

Second, it is clear that our individual relationships with neurologists have often been less than ideal. Although many nephrologists and transplant surgeons get along well together, significant numbers of nephrologists throughout the country are dialyzing large numbers of patients who should be referred to surgeons for kidney transplantation. On the surface, the problem appears to be caused by economic considerations. However, transplantation as a treatment is not foolproof; so it does not take much for nephrologists to convince themselves that dialysis is just as good and that they are doing patients a service by avoiding a supposedly dangerous and unnecessary operation. It becomes easy for nephrologists to take the position that, from the standpoint of survival, transplantation is inferior to dialysis. This is not true. Recent studies indicate that, when transplantation is feasible, it is superior to dialysis from the standpoint of long-term success in reversing renal failure, enhancing the patient's general medical well-being, and rehabilitating the patient's self-esteem.

Unfortunately, we as transplanters are not in the driver's seat. These patients are referred to us by nephrologists if, and only when, they decide to do so. Furthermore, because of the dependent type of relationship with their nephrologists, patients often won't stimulate a request for a transplant themselves. We become a passive bystander. Rules and regulations have been developed, and more rules and more regulations will come and go. But as such, they can and probably will always be circumvented by some. Enforcement will always be a difficult issue, especially since we are far outnumbered by our nephrology colleagues. To solve this problem, we need to look to our own problems in health care delivery and to our own relations with the government.

Third, more than 35,000 patients are now undergoing chronic hemodialysis in the U.S. Although many of these patients may not be suitable transplant candidates, certainly 20,000 of these patients could be. Unfortunately, never, during the past four or five years, has the rate of transplantation in the U.S. gone above 4,000 per year. Last year, only 3,700 patients underwent kidney transplants. To this end, we are not doing our job. It is critical that we markedly increase the availability of cadaver organs. We must encourage the growth and development of existing transplant programs and initiate new programs when needed.

At present, an argument often quoted by those seeking to minimize the growth of transplantation is the shortage of donor kidneys. By concentrating on organ procurement, we can make the kidneys available so that this argument cannot be used. I believe organ procurement is one of the most difficult and sensitive aspects of kidney transplantation. It requires a personal interaction between the donor team members, including the transplant surgeons and the staff of community hospitals throughout the U.S. Personal contacts and relationships must be developed even superior to those one normally uses in building a clinical practice of surgery. Programs such as the one developed in the Centers for Disease Control (CDC) office of organ procurement should be used to determine the donor potential of hospitals throughout the country and to then achieve the potential for organ procurement. Again, as long as kidneys are



in short demand, we are not doing our part. ASTS must help its members by providing consultations, education, and site visits for new and developing programs so that we may eventually have the finest possible nationwide organ procurement program.

Directly tied to this is the need for enhanced sharing of kidneys. Although some programs claim they transplant all the kidneys they are able to get, many times local situations make it impossible to use kidneys at exactly the moment they become available. This may be because of inadequate facilities or personnel. It is important to see that kidneys removed and not used locally can be used by other programs. We have demonstrated that kidneys can be preserved for up to 67 hours without adversely affecting short- and long-term results. Yet, loss rates of 30% are not unusual today. The kidneys lost are good organs that simply have not been placed successfully for transplant. Just by using all available kidneys, we could increase the number of transplants per year to 5,000. As more kidneys are procured, sharing is going to become more complex. The South Eastern Organ Procurement Foundation (SEOPF) and United Network for Organ Sharing (UNOS) are reasonably successful approaches toward organizing kidney distribution. However, it seems to me that, since ASTS is a society for all transplant surgeons in the country, perhaps we could do a better job.

One approach might include one or more central crossmatching labs where lymph nodes could be sent the moment a kidney is harvested. Then when it appears that one of the kidneys will be available, crossmatches could be done at that lab and thus minimize the transportation of multiple specimens here, there, and everywhere in an attempt to find a home for the unused kidney. For example, such a center could be developed at the O'Hare Airport, which has accessibility to all parts of the U.S. A well-functioning professional kidney distribution organization under the aegis of our society could speed the exchange of organs and minimize our loss.

ASTS must encourage and help develop our many transplant programs. I do not think we should be trying to shut down small programs. Instead, we should stimulate small programs to grow larger and inferior programs to become better. Because transplantation is a relatively new therapy, just making itself felt in the medical world, we can't afford to close small programs and eliminate their transplant surgeons. No one will be left to do the work that needs to be done. We must support and enlarge our field. Our society can do this by offering help to programs having difficulty.

Various potential solutions to local problems can be offered. While some large programs have a seemingly limitless capacity, most transplant programs in the country are limited either by space or personnel. If we are to achieve our objectives of superior delivery of health care, we need every person and program we can get.

Fourth, the symposium preceding our scientific meeting represents the first major attempt of our society and its members to meet, and develop a dialogue with, the various agencies of the federal government. It is important that this dialogue be continued and enlarged, so ASTS can improve relations with the government agencies both for scientific reasons and for health care delivery. Our Scientific Studies Committee has begun by developing a cooperative study of donor pretreatment. This is only a beginning. We can also push for increased funds for transplantation research, and this means increased funds not only to the big and successful programs, but also

to other smaller programs as well. Less than 2% of the funds expended for kidney transplantation are spent on research. We must have more support. ASTS can provide advice to young investigators and small programs as to how they can best go about getting research monies.

We can also follow the lead of our advisory committee in discussing the many aspects of health care delivery with HCFA, covering such areas as quality and financing of health care.

Fifth, it may be time for ASTS to make some structural changes so that we can better help our members and patients. A logical extension of the work begun by our advisory committee is to obtain the services of a permanent liaison with the federal government, a lobbyist if you will. Only by having direct contact with what is going on in Washington can we be fully aware of the legislative and political events that will affect transplantation. Furthermore, it is important that ASTS and its individual members get better feedback on what's going on. To accomplish this, we must, at some point, establish a permanent office with a staff whose job it would be to carry out these activities. I realize there are many problems in developing a staff office for societies, but the issues today and in the future are important enough to warrant the ongoing support that only a permanent office can provide. To inform our members, we need a quarterly newsletter that will provide us with up-to-the minute information. The permanent office could communicate with the medical information system, which so far has been very ineffective in providing us with needed information on the successes and failures of our transplant programs. We need a registry, which could be a part of our permanent office.

Finally, we must all get more involved in the functioning of our society. Jim Cerilli has done a tremendous job in initiating meetings with the government. Let's all pitch in and work together!





# Transplantation: A Maturing Surgical Discipline

JEREMIAH G. TURCOTTE, 1979–80

The art of modern transplantation can be dated from the technical contributions of Alexis Carrel in the early 1900s or from the initial effort of Dr. Lawler in Chicago, who transplanted a kidney into a human in 1950. The science of transplantation, on the other hand, can be dated from the pioneering work of Drs. Medawar, Brent, Hume, Hamburger, and Starzl in England, Boston, Paris, and Denver in the 1940s and early 1950s. Since that time, renal, cardiac, and bone marrow transplants have become accepted treatment for selected patients with end-stage organ failure. Although these modalities of treatment are now accepted by the scientific medical community, the practice of transplantation surgery is still—even in the mid-1990s—in the early stages of being incorporated into our traditional systems of medical education, organization, and quality assurance. The 1950s and 1960s gave birth to our science; the 1970s have been our adolescence; and the 1980s taught us to prosper and reproduce. ASTS now finds itself in a unique position. We should accept the mantle of responsibility to provide leadership not only for scientific advancement, but also for the maturation and full incorporation of transplantation surgery into American medicine.

First, a few words about the status and future of our science, especially as it relates to histocompatibility testing and immunosuppression. While the HLA system of major histocompatibility antigens was being defined by Dausset, Terasaki, Van Rood, Cepellini, and many others, a logical goal of many transplant centers and histocompatibility laboratories was to seek the best matches between donor and recipient. This endeavor has an obvious solid experimental basis and rationale. Unfortunately, the goal has not proved to be practical and its pursuit is perhaps illusionary when dealing with an outbred population. At times, our typing results do help us select a two-haplotype match rather than a one-haplotype match familial donor, but more often we do not have that choice and feel fortunate to have available a willing related volunteer of at least a two-antigen match. With cadaver transplantation, the probabilities of find-

ing a well-matched donor are so slim and the logistics and practicalities so complicated that only a small fraction of cadaver transplants in the U.S. are between HLA-compatible donors and recipients. Some have even proposed that we abandon tissue typing for cadaver transplants. Our federal government even recently suggested that, since there is no definite proof that tissue typing benefits cadaver transplantation, Medicare should stop reimbursing for such testing. I am convinced that those who would dismiss tissue typing as irrelevant in cadaver transplantation are both premature and perhaps misdirected in their goals. Rather than continue to seek ever more compatible matches, I would recommend more investigative effort in histocompatibility testing in these areas:

1. Develop histocompatibility tests to rule our donor-recipient combinations in which we know the results will be poor. Certainly a positive crossmatch is one test that already contraindicates transplantation. A mixed lymphocyte culture with a high index of any stimulation also appears promising to rule our poor donor-recipient combinations with related transplants.
2. Identify those antigens to which an individual recipient is unable to mount an active immune response. Matching for nonstimulating antigens seems more logistically feasible than continuing to seek matches on the basis of identical antigens.
3. Recognize the enhanced significance of antigenic matching as immunosuppression improves. If immunosuppression were perfect, then rejection would not be a problem even in the face of great antigenic disparity. On the other hand, when the match is perfect such as with identical twins, no immunosuppression is needed. It is only when we are in the intermediate area of this interdependent continuum that the effect of tissue typing becomes apparent. Thus, as our immunosuppression becomes more effective, rejection will be prevented in a greater proportion of the antigenic disparities encountered and the significance of selecting for better matches may be unmasked.
4. Finally, tissue typing will be of obvious importance to identify the profile of antigens in a particular recipient or donor when our science advances to the point where we can engineer tolerance or enhancement for specific antigens in a given donor-recipient pair.

I would submit, then, that the science of histocompatibility testing remains promising and that its clinical applications are in their infancy.

A few words about a second scientific problem, that is, the status of our art of immunosuppression. Many continue to use the same two agents introduced in the early 1960s, that is, azathioprine and steroids, to prevent or reverse rejection. There is no convincing evidence that the addition of other drugs, the use of radiotherapy, or a course of antilymphocyte globulin has improved the overall or long-term results of renal transplantation. Programs using only the simplest of immunosuppressive regimens report equally good results as those using a more complicated regimen, including adjunctive operations such as splenectomy and recipient nephrectomy. Differences in results between programs are just as readily explained by differences in



selection, differences in population pools, or perhaps by differences in experience and administrative organization.

I believe the only immunosuppressive adjunct for which there is convincing evidence of benefit is the use of pretransplant multiple blood transfusions. Unfortunately, even here we do not understand the mechanism of action. The time has come that we as a scientific community insist that any studies of new immunosuppressants or adjuncts to immunosuppression be both prospective and randomized. The argument that having a concomitant, control series in which the experimental treatment is withheld is unethical simply does not hold up under close inspection when we are talking about potential improvements of the 20% to 30% range.

What is the role of ASTS in all of this? Certainly we can continue to encourage investigation and provide a forum for presentation of outstanding scientific contributions. Our Scientific Studies Committee, chaired by Richard Simmons, has already taken the lead in encouraging and organizing cooperative randomized studies. This effort is expanding and, in my experience, is a unique undertaking of American scientific surgical organizations.

ASTS is also rapidly assuming another and equally important role in the field of transplantation. We are one of the few organizations—perhaps the only representative organization—to which American surgery, the educational community, the government, and others can turn for advice and counsel on issues related to transplant surgery. This role will and should occupy much of our time during the forthcoming years. We do have some unresolved problems and we do have some tasks we need to complete if transplantation is to pass through and assume its proper place in the American surgical community: (1) Many medical students and residents are never exposed to the principles of transplantation; there are probably too few well-qualified candidates entering the field today. (2) The outcomes of transplantation vary widely from center to center and cannot be fully explained simply by differences in patient selection. Programs with poor results and high mortalities reflect badly on our entire discipline, and the public is no longer content with superficial explanations for these differences. (3) The so-called waste rates of cadaver kidneys also vary too widely. Rates as low as 5% and as high as 35% have been reported, with no adequate explanation for the differences. Transplantation has not had adequate input or representation within the National Institutes of Health (NIH) or within the Social Security Administration. NIH research monies allocated for transplantation are small. Many regard the federal guidelines as they relate to reimbursement and network governance as actually discouraging the clinical application of this discipline.

So much for the problems. Many tasks need to be completed. Work has already begun on many of them, especially through the Advisory Committee on Issues chaired by president-elect Jim Cerilli. We need to define the essentials of what should constitute adequate training and education of transplant surgeons. We owe, to the public as well as our medical colleagues, some mechanism to identify individuals who are qualified to engage in transplant surgery. If we follow the traditional norms, there should be a certifying mechanism for transplant surgeons either under one of the existing boards or as a separate board. We need to develop standards to serve as guide-

lines for quality assurance to help hospitals and others evaluate transplant and organ procurement programs. If we complete these tasks, many of our problems will be solved and a system will have evolved that is appropriate for the proper maturation of a professional discipline such as transplantation.

I can think of no better organized or more representative group to deal with these problems than ASTS. Certainly we will and should remain primarily a scientific organization, but we should also accept the responsibility and mantle of leadership to maintain the quality of transplantation surgery and to assure that transplantation is incorporated into the mainstream of American medicine.

It has been my very special privilege to serve on your Council and for this past year as your president, working on these tasks with you. Yes, it has also been my very special pleasure and good fortune to be assisted by such able fellow officers and Council members. It has also been my special blessing to have the support of my family and my wife, Claire, who is with me today. Thank you all for the privilege of serving as your president during the past year.





# Role of Kidney Transplantation and its Implementation

JAMES CERILLI, 1980–81

Today I wish to present to you my views of transplantation, discussing some of its problems emphasizing those that this society can help alleviate. Thus, the major thrust of this talk will be to present how I feel this society can and should impact on certain current problems in transplantation.

Transplantation, like most surgical disciplines, began as a highly research-oriented clinical program. The initial results in the few centers that performed transplantation in the early and mid-1960s, if one reviews those results today, were extremely encouraging. Living related donor graft survivals were 60% to 70%, cadaver graft survivals approximately 40%, and technical complications quite reasonable. The number of surgeons performing transplantation was limited and each had extensive experience in the dog laboratory. Without doubt, the major problem with transplantation at this time was an unacceptably high mortality rate.

Research efforts during the 1960s were very productive in solving some problems, but with others failed dismally. We must recognize these failures, and ask ourselves why we were so ineffective in solving some very important questions. For example, efforts in organ preservation remarkably improved the management of patients with end-stage renal disease by making cadaver transplantation logistically more efficient and more convenient. Certainly, the ability to preserve kidneys for 24 to 36 hours took cadaver transplantation from the rare and unusual into a more routine form of care. In contrast, however, our efforts in other directions were not so productive. Is it not disappointing that despite 20 years of investigation into antilymphocyte globulin, we still have not been able to standardize this product and to determine the best method of production and administration. Certainly, 20 years of investigation of such an important agent should have compiled more information than is currently available. Is it possible that, had this society been the catalyst for large, cooperative, carefully directed studies, such a question might have been answered? There is little question that this society must play a major role in stimulating cooperative studies of this type;



this responsibility becomes more important as the delivery of transplantation services becomes increasingly fragmented.

As transplantation evolved, it developed within a limited number of research-oriented institutions and its applicability was limited by the lack of funding. The passage of the HR-1 legislation in 1972 changed that very dramatically, and unquestionably we are still feeling its impact. Now, for the first time, patients could be cared for literally without regard to cost, and, because of this, the number of centers performing transplantation rapidly exploded. Many transplant surgeons have commented that during the mid-1970s transplantation results appeared to deteriorate. This was attributed to many causes; however, it is my belief that one of the fundamental causes of this deterioration was the rapid increase in the number of transplantation units that often were directed by surgeons with little or no background or formal training in transplantation. Directors of many units were physicians whose background in administering immunosuppression was limited and whose technical training was meager. Individuals established transplantation programs simply by beginning to do transplants, and this clearly was one of the major reasons that transplantation results deteriorated. For this reason, as well as others, I have for several years had a major interest in the formalization and certification of transplant training programs and during the past year have tried to bring this objective to fruition. The significance of these attempts will be discussed later in this address.

Unquestionably, during the past three to four years, results in transplantation have improved. Primarily owing to the contributions of several of the members of this society, there has been a significant decrease in patient mortality. We must all very clearly understand that without this decrease in mortality, transplantation as a clinical tool for end-stage renal disease was clearly in jeopardy. However, the fact that not all centers have achieved this decrease in mortality not only affects patients receiving care in specific centers, but is detrimental to the entire discipline of transplantation: such results are widely quoted by our colleagues who question the role of transplantation.

There are many factors that contribute to an unacceptable mortality, morbidity, and graft survival, but I wish to mention a few of the more obvious. There are still centers that do not use mixed lymphocyte cultures to evaluate living related donors. The value of mixed lymphocyte culture for living related donor transplantation in my mind has been proven beyond any question, and to perform living related donor transplantation without mixed lymphocyte culture analysis is clearly wrong. Second, many centers still routinely perform bilateral nephrectomy when there is little documentation that this is of value and patients who reject their grafts are left with the disabilities of severe anemia and anuria. Third, immunosuppression is still used much too aggressively in many centers. Fourth, the technical complications in many centers are inexcusably high and inexperienced individuals often perform this procedure under poor supervision. While clearly we must train individuals to carry on this discipline, inadequate supervision of poorly trained personnel must be condemned. This is true not only for the transplant operation itself but also for the donor. Improper procurement of cadaver grafts leads to increased patient morbidity and mortality. This is not a procedure to be delegated to an unsupervised surgical resident.



Inadequate training also affects cost, a third and major issue in the management of patients with end-stage renal disease. With the emphasis now placed on maximum cost-effectiveness in all federal programs, a close look is being taken at the relative benefits of transplantation and dialysis. Without question, the cost-effectiveness of transplantation is significantly superior to that of dialysis. This fact needs to be publicized, defended, supported, and brought to the attention of responsible persons in federal and local government. Transplantation is cost-effective, however, only when performed properly and accompanied by low mortality and low morbidity. Properly performed, the cost of 100 transplants followed for 10 years, even assuming that only 60% of the grafts functioned and attributing all dialysis costs of rejected grafts to transplantation, would yield a savings of over \$15 million over the cost of center dialysis for 10 years on the same 100 patients. That is an enormous cost benefit. However, the cost/benefit advantage can even be heightened by the elimination of technical errors in the operating room, loss of kidneys from irreversible acute tubular necrosis because of poor donor procurement programs, high mortality rates because of over-aggressive use of immunosuppression, and the management of patients by relatively inexperienced, poorly trained people.

Now these issues define certain problems that should be addressed at this time and can be solved with the help of this society. First, transplantation is not as yet identified as a discrete surgical discipline. Second, the results of transplantation are, unfortunately, still inconsistent. Third, organ supply is inadequate. Fourth, end-stage renal disease expenditures are excessive.

Transplantation must develop into an identifiable discipline. This is difficult when many nephrologists have a valid complaint that many transplant surgeons refuse to see patients preoperatively, or that patients are seen by a fellow or by a transplant surgeon who has other clinical interests with a higher priority. Transplantation surgery will not gain identity as a discrete discipline as long as referring physicians have this very valid complaint.

Second, transplantation will never become an identifiable discipline until training programs with established standards are certified. I attempted to establish with the American Board of Surgery, the American College of Surgeons, and the Residency Review Committee of the American Medical Association (AMA) the formal review and recognition of transplantation training programs. I have endeavored to work through these historical and established administrative channels to accomplish formal recognition of transplantation training programs. However, it is clear that the administrative systems for review of training programs is too rigid and will not encompass the discipline of transplantation under their supervisory umbrella at any time in the foreseeable future. Therefore, it is necessary and mandatory that this society assume responsibility for the quality of transplantation postgraduate education. I have endeavored to establish this concept during the past year and believe that we must have certification of transplantation surgical training programs with periodic review of these programs. Many centers have applied for certification through ASTS and will probably be certified. However, I have asked the Education Committee to



establish high standards, and it is possible that some centers will not be approved until the quality of their training programs is improved.

In addition to assessing the quality of transplant programs, there must be some assessment as to their proper quantity. The number of transplant surgeons in the country must meet the clinical and research needs of the country, yet not exceed these needs so that skills cannot be maintained and also improved. According to present estimates, approximately 6,000 transplants should be performed per year. About 4,000 are now being performed and about 150 transplant surgeons easily meet this clinical responsibility. Clearly, about 10 to 15 well-trained surgeons per year should be adequate to meet future clinical needs. These surgeons must be highly trained in the technical aspects of transplantation and must also have a knowledge of transplantation immunology so that they can continue to advance the field and improve results. I repeat, the society must assume a role of leadership in ensuring quality education.

Another serious problem to which I have already alluded is that of inconsistent results. Two years ago, I appointed a standards committee to evaluate what should be reasonable clinical results in 1980. As you know, seven centers believed to be adequately staffed with trained personnel were reviewed. At these centers, cadaver transplantation is being performed with a one-year graft survival of approximately 55% to 60%; living related donor graft survival of approximately 78%, and mortality in both groups of approximately 5 to 10%. Our recent experience at Ohio State since 1977 shows that cadaver graft transplantation has been performed with a mortality rate of 3% and a one-year graft survival rate of 65%. Certainly, transplant centers whose results are not at least as good as those obtained in the American Society of Transplant Surgeons survey must rapidly reassess and change their methodology or cease offering transplant services. The only exception to this should be centers evaluating new techniques and methodology that may incur short-term poor results.

I recently spent a day discussing the current status of transplantation with some members of Congress, their staffs, and representatives of the Rand Corporation who frequently serve as their consultants. It was discouraging to hear their concepts of the role of transplantation relative to dialysis in the care of patients with end-stage renal disease. Their data are 5 to 6 years outdated. Nevertheless, they accurately indicate that many transplantation centers have poor results. That this assessment is accurate is demonstrated by the fact that in the recent survey to which most of you responded of 81 centers, the overall one-year mortality rate for cadaver transplants was 18%. Thus, it is clear that centers whose programs do not meet previously described standards need to reevaluate their methods and to cease performing transplants until clinical results can be improved. Uniform results must be achieved rapidly if we are to maintain transplantation surgery as a discipline and if we are to meet our moral and medical obligations to patients with end-stage renal disease. Now the question arises as to whether or not there is an optimal system to maximize the possibility of administering the best possible quality care to patients with end-stage renal disease. It is my view that one of the important requirements for the delivery of medical and cost-effective transplant services is encouragement of the concept of regionalization of transplant services. Unlike dialysis, geographic proximity of the patient in



the transplant centers is not an important factor in the development of optimal transplant services. It is very difficult for small units to maintain skilled personnel and facilities of the same quality as large units doing open-heart surgery and other complicated forms of surgery. It has also been demonstrated by a screening of more than 80 transplant centers in this country (unpublished observations) encompassing over 3,000 transplants, that centers performing fewer than 15 transplants per year had a 40% to 100% higher mortality rate depending on donor source than centers performing more than 30 transplants per year. Thus, it is my view that it is difficult to maintain the skills of medical and paramedical personnel necessary to maintain quality transplantation in centers performing fewer than 30 to 40 transplants per year.

This is an important issue and clearly must be definitively established or refuted for the discipline of transplantation in this country. The Health Care Financing Administration is in the process of evaluating the relationship between the size of the transplantation or dialysis units and cost and medical effectiveness. I have pledged the cooperation of this society and all its members to this study.

I am sure you are all aware of the close interrelationship between the federal government and our ability to deliver transplant services because of the Medicare legislation. However, new legislation, if enacted, will have an equal but unfortunately deleterious effect on us now. Our goals of maintaining outstanding research and training programs, quality care, and cost containment in transplantation are being threatened by current efforts toward deregulation that is being supported by the Reagan administration. The administration's current goal is to remove the health planning agencies that have been ineffective in regulating end-stage renal disease and to eliminate the networks that have been reasonably effective in some areas. The goal is to relinquish regulatory powers to the states. In some states, this may prove to be successful, but in most states it will be disastrous. There is no financial motivation for most states to be cost-effective, unless the source of the end-stage renal disease dollars is transferred from the federal government to the state government. Therefore, when an application for a dialysis unit or a transplantation unit is reviewed by the state, the political aspects will supersede the medical or cost-effective aspects. The federal government will continue to pay the bill through Medicare, while the states will be deciding the size of that bill. Therefore, costs will escalate, dialysis and transplantation units will proliferate, and quality of care will suffer because of fragmentation of services.

An additional consequence will be, I firmly believe, a worsening of the problem of the sequestration of patients on dialysis because small dialysis units in small communities are marginally cost-effective. To improve cost-effectiveness, they must increase their pool of center dialysis patients. To accomplish this, they must decrease the flow of patients into transplantation, chronic ambulatory peritoneal dialysis, and home dialysis. Therefore, in my view, deregulation of end-stage renal disease programs will encourage proliferation of units which will inhibit proper use of transplantation services.

Regrettably, the regulatory process of the network system has not met expectations. The system is responsible for a too small geographic area, often making objective decisions difficult. Its roles and authority in relation to the health systems agen-



cies and state regulatory agencies have never been defined. The network system's medical review boards are of questionable effectiveness. However, in most states, the networks are currently the only group of well-informed individuals about end-stage renal disease. Their elimination without a concurrent increase in the authority or staffing of the Health Care Financing Administration regional offices, in my view, will be detrimental to patients with end-stage renal disease for the reasons outlined. Although in conflict with the Reagan administration position, both the subcommittees on health of the House Ways and Means Committee and the Senate Finance Committee have retained in their proposals the network concept. I hope that the members of ASTS will communicate to both subcommittees as well as their local Congressional representatives, recommending the preservation of meaningful controls at the federal level to avoid the inescapable problems of costly duplication and inappropriate patient therapy.

Pressures leading to uncontrolled proliferation of transplantation units come not only from the federal government but also from the AMA. The AMA recently passed a resolution that transplant services be delivered in all hospitals capable of providing the necessary medical support. No mention was made of costly duplication or the effect of fragmentation on quality care, education, or research. I have responded to the AMA position on behalf of ASTS, and I suggest that those of you who are members of the AMA who disagree with the position express your disagreement. The AMA position does influence those who determine federal policies toward the end-stage renal disease program.

Still another issue with which ASTS should be involved is the quantity and quality of cadaver kidneys. As the number of hospitals from which we procure kidneys increases, the difficulty of quality control in organ procurement escalates. Our wish to continue a relationship with a community hospital often conflicts with maintaining adequate standards for kidney procurement. Nevertheless, it behooves each of us to recognize that kidney waste is very expensive and that the use of marginal kidneys is clinically unjustified. This society, through its standards and preservation committees, should establish guidelines for organ procurement and utilization with the goal of increasing the efficiency of procurement and decreasing the cost.

The problem of organ procurement extends beyond the relatively narrow problem of the quality of individual kidneys. It is my impression that the whole concept of organ procurement rests on a tenuous and unstable base, requiring continuing and maximum effort by each transplant center to maintain a supply that remains inadequate. Any proposed solution to this problem must not increase the cost of organ procurement, since this is clearly not the time to approach Congress with suggestions that would increase the costs of the end-stage renal disease program. For this reason, I have been working with the staff of Representative Philip M. Crane of the subcommittee on health of the House Ways and Means Committee to introduce a bill in the summer that would provide credits to donors of cadaver kidneys.

The advantages of this bill are clear: (1) The patient receiving the kidney would obviously benefit by receiving an optimal and recommended form of therapy. (2) The donor's family would benefit from the financial sequelae of a tax credit. (3) The gov-



ernment would benefit because the patient receiving the kidney would be removed from dialysis, which costs \$28,000 per year and offers minimal hope of rehabilitation.

In short, if this bill is passed, everybody benefits. The bill obviously does not meet all needs but it is an important beginning to improving, through legislation, the problem of inadequate organ supply. However, to assure passage of the bill, your help is needed. I request and I urge that each of you when you return home to write to the members of the Senate and House subcommittee on health and send copies to Representative Philip Crane and your local representative and senator and ask for support of any reasonable bill that would increase the supply of kidneys. With an outpouring of support, this bill has an excellent chance of passing. Without it, it is doomed to failure. Congress must be convinced that this bill fills a need and only you can establish the need.

Another approach to augment the supply of cadaver kidneys would be to establish the concept in this country of a "presumed consent" rather than an approved consent by specific request. In 13 countries, presumed consent is accepted and kidneys can be removed from a donor unless the donor had at some time specifically objected. I have asked our consultants at Health Policy Alternatives to review the effectiveness of this legislation. This will be a long-term goal and program, but it is the type of activity that I believe ASTS should support.

Clearly, therefore, many problems exist in transplantation that can be addressed by ASTS through cooperation among its members. I have presented several specific examples of activities that should be addressed by the members of the Society that would favorably affect transplantation. They are: (1) support a bill for tax credits for kidney donation; (2) help maintain effective regulation of the end-stage renal disease program; (3) strengthen cooperative research studies; (4) cooperate with the programs to evaluate the relationship between the size of a transplant unit and its quality of care; and (5) support the effort establishing accreditation of training programs by ASTS. I hope you will work together to realize these objectives. Your support, effort, and cooperation are essential if ASTS is to be a meaningful force in these programs that will ultimately improve patient care, which after all is our major responsibility.







# Academic Surgeons and Surgery— Who, What, When, Where, Why and How?

RICHARD L. SIMMONS, 1981-82

**A**cademic surgeons are, as a rule, a frustrated lot—frustrated by what they chronically see as a group failure of performance and, simultaneously, by the failure of their entrenched basic scientific community to recognize our real accomplishments and our special needs.

If academic surgery as we once dreamed of it is dead—a fact widely acknowledged by those of you who have recently applied for NIH grants—let’s see if we can’t determine what the function of academic surgery was and what the function of the academic surgeon is supposed to be.

I think it is to create and disseminate knowledge relative to the surgeon and his or her patients. In other words, does the surgeon teach? Clearly, the control of rejection, both before it occurs and after, is an important area of study in transplant surgery. This needs to be taught to patients as well as other transplant surgeons.

Let’s look at this generic Presidential Address once more and recognize that, unfortunately, we strive for excellence at all times and in all things, and try to do what we thought our heroes had done—and their accomplishments are frequently exaggerated. I think, herein lies our failure. Too much is expected of us and we expect too much of ourselves. In other words, we may know what our functions are, but we really don’t know who we are.

What is expected of us? First of all, we must be great surgeons. That is, we must operate successfully. People expect surgeons to operate with great skill and quickly, with lots of personality, charm, and good humor. To gain this skill, we must first become general surgeons, that is, dedicate five or more years (unfortunately, at the peak of sexual maturity) to a residency. During this period, we spend as much time as possible in the operating room, assisting at and performing as great a variety of operations as we can, so that we can have a very wide experience with as many difficult sit-

uations as possible, so that we can be prepared for any eventuality in any subspecialty. Everybody agrees that this is an essential requirement for being an academic surgeon. A broad experience is necessary.

During this period of surgical residency, we were taught to concentrate on what we are doing. In fact, concentration may be the characteristic that most often distinguishes the exceptional from the average surgeon. The surgeon who constantly banters about jogging, or, more important for this discussion, about laboratory research, does not get the job done. This is not the time to contemplate molecular interactions. We always advise our academic surgical trainees to shut up and operate.

What else is expected of us? In addition to being great surgeons, we must be experts in complex clinical care. We are expected to be capable of taking care of our patients' needs in cardiac, respiratory, and circulatory physiology, and have a smattering of gastrointestinal endocrinology, nutrition, transplantation, urology, neurology, pharmacology, pathology, gynecology, trauma, and intensive care. The Boards are happy to oblige by insisting that we become head and neck surgeons, even though we cannot visualize the larynx with a mirror, and that we compete with our gastroenterologists by passing a colonoscope through the splenic flexure. And, now that we have to pass a basic science test, clearly, the surgical resident becomes the very model of a modern major general, replete with information (animal, vegetable, and mineral), however superficial that information may be.

So now, all age 32 and Board-certified, we are broadly educated general surgeons and we can disseminate the folklore taught during residency to future generations. We have, in fact, become highly qualified to explain the intricacies of any procedure, operative or otherwise, using the inevitable phrase indicating deep intellectual understanding: "I always do it this way and I never get into trouble."

But a broad education leading to rote performance is not enough. As academic surgeons, we are expected to subspecialize so that we can understand a problem in depth. For this, we need a fellowship. Happily, each of the subspecialties of the past has devised a way to immortalize their knowledge. They have created centers of excellence judged to be capable of teaching the errors of the past. For teaching the errors of the past really well, such programs become qualified to issue certificates of special competence.

I like this statement, written to John Najarian, to address what a certificate of special competence is: "I am really grateful to have had the opportunity to work here and see so many interesting complications."

That is all very good. Now, we are 35 years old and several million brain cells are dying every day. We still cannot call ourselves academic surgeons just because we are skilled at operations and complex patient care, and have special competence in the errors of the past. We must now dedicate ourselves to correcting those errors through deeper understanding. We must become scholars.

We must, in fact, do research, and this also requires training somewhere along the way. This is eminently reasonable. So we apprentice ourselves to someone reputed to be an expert in research, or, by chance, to someone who *is* an expert in research. After a year or two, we have presented abstracts at six meetings of the distinguished surgical



societies, like this one, each of which demands that we publish our manuscript in the society journal, reviewed, of course, by our surgical peers, like this one. Now it is time we get a job.

To get a job, as everyone knows, one has to fill a slot. A slot means certain defined duties. Some of them we have to do in the operating room: we operate, perform pre- and postop care. And, of course, there are teaching duties in the OR, on the ward, specifically designed for residents, medical students, and other research fellows. There are also administrative duties: organizing clinics, organizing educational programs, organizing patient referral systems, and organizing follow-up systems. We all have to serve on committees. We have to join societies like this one and become an officer.

Now, we get to the important stuff: we have to make some money. We have to not only practice, but also fill out and sign charts to prove that we are taking care of the patients we are actually taking care of. We have to operate. If we don't have time to operate, we have to at least sign operative notes to justify our salary or to participate fully in incentive plans. Clearly, the incentive is not research-oriented. And, finally, we have to get grants.

Please note that we have hardly mentioned research. Research cannot fit itself on the slot list. Instead, on this list of items defining our slots, it has been replaced by the means and not the end. This is the essence of our frustration: we have let ourselves be judged—and in the end we are judged and we judge ourselves—as successes and failures in academic surgery by our ability to get these grants.

Grants are a good thing. They allow us to do very good research. They allow us to do research that we could not otherwise get money for. They allow us to fool around in the laboratory and maybe discover something. They give us prestige among our peers, as exemplified by the commonly overheard conversation: "What does he do?" "I don't know, but he gets a lot of grants."

In addition, we must respond to pressures from the department head to justify his or her faith in our performance. In fact, in a modern surgery department, it is the only way we can get judged in an esoteric field. An external review committee must tell our boss why he should promote us or why he should pay us more or why he should have hired us in the first place. This is why we get the grants.

Only grants can justify the use of resources—residents and secretaries—because, in fact, grants have become the most important source of overhead for the university. In turn, it's a mechanism for us to gain the attributes of power and prestige exemplified by more space.

Surgeons do not get lots of grants, and we suffer, at least in our own eyes. Surgeons don't get a lot of grants, but they don't apply very frequently either. Applications are seen as poor. Surgeons need better training; the application systems are cumbersome and time-consuming.

Solutions to these problems have been suggested: attract better students, get more training grants, use clinical monies to seed research, develop systems to help prepare for grant applications, lobby the NIH to eliminate antisurgical biases by having surgical applications go to surgeons for peer review. But, these are generally thought to be superficial solutions, like Band-Aids.



The problem, really, is inadequate training. We do not attract students interested in investigation. I think it's our fault. If we were really interested in research, we would attract a different breed of student. Our last major recruiting effort takes place when we try to attract into the internship year. It's worthwhile looking at the criteria we use for this.

First of all, to get investigators, we take graduates from medical school, clearly a bad choice. They have to be tall and thin, play ball, go to Princeton or some other effete institution. They are clean-cut, have no facial hair, are predominantly male, and, of course, get good grades on their clinical rotations. Good grades on surgical rotations, which is why we hire "trained surgical investigators," means they have to come first to the ward in the morning. They leave last. They look eager. They talk about how great it is to be part of the team to really cure people instead of just talk about it. And, of course, how they like to use their fingers—I always suggest they take a knitting class—and they say, "Yes, sir" and "No, sir."

We were selected and we, in turn, continue to select our trainees in academic surgery using people who provide safe service and who will never embarrass their preceptors, their heroes—who, in striving for excellence always, want to avoid embarrassment absolutely the most.

We, in fact, select students who are trainable in the errors of the past, that is, in doing it this way and never getting into trouble. We train surgeons the way we train soldiers: originality of thought is eliminated as a component of the clinical response, and an environment is established in which rethinking is disparaged.

Here is my concept of some of the mistakes made in training academic surgeons.

1. We don't know what we want from academic surgeons, and we have no point of view in training them.
2. We generally choose the wrong people. We do not know whether we want teachers, performers, administrators, or investigators. If we want investigators, we certainly choose the wrong people, because we choose and are chosen by the individuals who are clinically adept and not intellectually curious.
3. We reward the trained response, not the curious or original one.
4. We train them in the incorrect sequence. That is, they are taken from the middle of their residency at which time they are low priced—and that's the principal reason—and they are introduced to research, become competent, sometimes even authoritative. As a reward, they are returned to the residency, which they view as a reward, so that when they emerge, they can no longer capitalize on their expertise and have to begin again.
5. And, finally, as a rule, at least in research and administration, we give them poor training.

Good training consists of working for an established, competent investigator who is productive and publishes in basic sciences, as well as clinical journals, and recognizes that the important thing about peer review is that it is critical in every sense of the word, that is, essential for improvement. The preceptor, I think, should present the student with very big questions—Why do wounds heal? Why do infections occur?



Why do grafts reject? Why do patients die?—and help them focus on achievable answers.

A good laboratory is one in which there is a continuity of approach. That is, the laboratory's been dedicated for a long time to a single question or group of questions that are related to one another and that are adequately supported by funds, so that research and teaching can take place in a comfortable environment. There is usually a critical mass of collaborators involved, so that many ideas are heard.

I think it's important to provide a suitable problem to the student with critical research training in which ready data can be obtained early, so that there is some kind of satisfaction, postponing the big questions for the very difficult solutions until later.

But instead, very frequently what we do in our laboratories is introduce students to a new problem that we would like to have solved. It's merely an impossible job. By the time they have solved it, it's time to leave. Surgical training tends to have an inadequate time period, a year or two with mandatory middle-of-the-residency training. There is no opportunity to cut it short if one is no good, or to lengthen it if one is talented. This inflexible schedule and set of guidelines is enforced by the Boards. The Boards, for example, will only permit a certain number of residents to be trained per year. If fewer are trained one year, picking up more the next is not allowed.

In addition, there are all those slots to fill during the residency. The preceptor is generally a surgeon who is generally behind the cutting edge of raw biomedical research, generally poorly funded, and preoccupied with other duties. Much time is spent on obtaining funds and less on doing the research. There may very well be big questions, but the projects are frequently out of focus.

The investigators tend to be isolated, by and large, from the basic science investigators from the same school or from biological leaders in the same community. Rarely is there continuity for a number of reasons, one of which is that each resident wants his or her own project. Therefore, one does not learn from errors in the past.

Nonetheless, surgeons have, in fact, made enormous contributions. These areas of achievement are listed as the Top 4 of the last decade:

1. Organ transplantation
2. Parenteral nutrition
3. Cardiopulmonary bypass and the whole field of cardiac surgery
4. Vascular reconstruction

There is nothing here to be ashamed of. These are very great surgical advances, indeed. But they are of a certain type. Such surgical advances, by and large, emerged in the minds of the surgeons without grants. They just did it. The problems were self-evident. The solutions were technical. The biological rationale came as an after-thought, or somebody else think it.

If this is true, our academic colleagues see us for what we are. We are a kind of necessary, temporary, soon-to-be-obsolete weapon platform against disease, like an aircraft carrier, full of high-tech apparatus, but rather dysfunctional when it comes down to winning a war. We are susceptible, in fact, to the next generation of missile design.



Scientists know full well that a truer technology will naturally follow a clearer basic understanding. All they need to do, in fact, is to keep us literate, so we are able to adapt new principles to the engineering task at hand. There is a bigger problem. With our focus on false technology, our very mode of thinking is foreign to that necessary for good science. If the essence of science is to garner the necessary information to prove a hypothesis, the essence of surgical judgment is to guess right with minimal information. We teach this day and night. In other words, in the eyes of the grant givers, we really do not qualify as grant getters, except when a practical solution to a clinical problem is in view.

Thus, we are not rewarded or appreciated by our clinical colleagues, whose reward system consists of big operational lists and big money.

We do not really have to live up to the criteria of other people. The grant givers properly have to set the priorities in grant getting. Our priority is, like engineers, to adapt the knowledge they create for more practical goals, and to stay literate in what they are doing so we can make the appropriate adaptations. Our mistake and our frustration is to assume that the grant getting is the measure of our work, while really it is only the means to a certain end.

Most surgical contributions have been and are made by surgeons without grants and, in fact, without suitable training for grant getting. Well-funded research is a full-time job. We are lucky to be doing part-time Ph.D. work for full-time surgical wages.

I have proposed a tentative list of individual solutions for individual people who are interested in individually competing with basic scientists for the appropriate grants. To this end, I suggest we take another look at selling the Boards and the residency review committees on a special track for academic surgical training that would eliminate the middle year, the G-3 year, of clinical training. The third year is generally a waste. There is not much new material and there is no new responsibility. We have to encourage at least 2 to 3 years of full-time research, because it takes that long to get started and develop real independence. We have to be much more careful about the proper choice of research preceptor. We have to provide, through junior faculty positions, research continuity in career training. This is the critical point in my mind. Whatever time has been spent in research training is frequently lost in the middle of residency, because so much time intervenes between the research training and the assumption of an academic job. Everyone needs time to get back in it. The most common frustration for young surgical investigators who have been very successful is that the project they started in the residency years has already been completed by the time they are ready to take a faculty job.

One of our serious mistakes is to have a cottage industry approach to research. In other words, we think in terms of bench research only. Very few of us have developed or taken on or understand the problem of clinical trial planning, data management, computer use, ethics, and statistics related to surgery. Recently, I was struck by the fact that I had ignored, my entire life, the major work of individuals like Bernard Fisher and his group, who revolutionized cancer research simply by sitting in their offices and developing clinical trials. We very seldom participated. We have to encourage and reward multiinstitutional trials in surgery.



ASTS made a good start in this regard several years ago in forming a Scientific Studies Committee designed to foster collaborative research. But it is just the beginning. A few worthwhile cooperative multicenter projects emerged. The scientific studies committee of a society should be designed to foster collaborative research. Necessary travel must be funded by ASTS, the committee made to stand yearlong, and its members kept in office for at least five years. Its progress should be periodically read, not as part of the membership meeting, but as part of the scientific program.

It is important to take the Band-Aids seriously. We should lobby for three things: reinstitution of the NIH academic training grants in surgery, creation of a studies section to review only grants from surgeons, and NIH support programs for prospective cooperative trials in surgery and for data management centers for certain disease states. Unfortunately, this does not draw a lot of publications to support the grants and, therefore, has not been supported. In fact, the cooperative clinical trial is always in trouble.

Throughout this polemic, I have tried to suggest that surgery faces some inherent problems. In addition, I think we have trained too long and too broad. Really, who needs to defend so much turf all at once? Our everyday tasks do not require scientific thinking. In fact, scientific thinking is generally discouraged in the urgency of clinical care. Our scientific training and exposure tends to be meager.

I think we distrust science. Ours is a very ambivalent discipline. While loving new techniques, we distrust basic research deep down. We feel that any improvement might well lead to our obliteration. Think about the dissolution of gallstones. Lithotripsy has recently come of age. What would happen to us? What resistance have you seen in your own practice to percutaneous drainage of abscesses or angioplasty? What if, God forbid, one could prevent atherosclerosis someday?

I believe that there is a deep-seated fear that such fundamental advances will put surgeons out of business. If research is ultimately going to put us out of business, we really have to pay it only lip service.

This distrust is echoed by the surgical establishment: the residency review committees, the Boards, and the American College of Surgeons. All of them are ideologically committed. They allocate their resources to education and to the errors of the past and to the current standards of practice—a practice which is largely folkloric—supported by the experience of our heroes and, by and large, weakly supported by scientific study.

We justify our failure to restudy our favorite habits on the basis of ethical concerns for patient welfare. But just look back a few years. Pick up an old journal and see how often good ethics of the past are now equated with discarded operations and indications.

Just as international organizations raise standards—the Olympics led gradually to improved athletic performance—a reorganization of the surgical establishment, a real slight one, might well lead to better science performed by surgeons.

A very thoughtful pamphlet has been published by an “add hope” committee that addresses all of my concerns and more. This “add hope” organization deserves a permanent place in the surgical establishment, obviously, as part of the American College

of Surgeons. There it can serve, not only as a clearinghouse (on grants and contracts from public and private agencies, on joint ventures with industry, on multiinstitutional research projects) but also as an educational center (on clinical research, statistics, and grant preparation). Based within the college and nowhere else, it would have visibility, prominence, and access to vast communication resources. Of most importance, with a permanent staff on behalf of surgical research, it would serve as a constant reminder to this principally educational and economic body that everything we teach will soon be history, whether surgeons participate or not.

Such a powerful influence could constantly provide a focus for the training of surgical investigators. It could lobby for sufficient flexibility on the part of the Boards for an academic track within surgical residencies. An academic track would counteract tendencies to further broaden surgical training and, instead, encourage a deeper understanding of biology in surgery.





# The Status of the American Society of Transplant Surgeons on its 10th Anniversary

OSCAR SALVATIERRA, JR., 1983–84

**I**t is a privilege and a pleasure to stand before you today as the tenth president of the American Society of Transplant Surgeons. This meeting not only commemorates the 10 years of existence of our society, but—more than that—it provides me with the opportunity to review and chronicle some of the many achievements our society has made during the past decade. At the conclusion of my presentation, I know you will join with me in agreeing that our society has established itself as the central forum for discussion of organ transplantation—it has been strong, vigorous, and credible in directing the course of transplantation in the U.S. This achievement is primarily due to three factors: first, our society has always had a scientific orientation; second, our society's scientific orientation has always been balanced with equally important humanitarian goals; and third, our society's scientific and humanitarian achievements have only been made possible by the intense interest and cooperative efforts of our society's membership itself. Herein lies the strength of our society—our scientific orientation, our humanitarian goals, and our members. These are the specific subjects I would like to address today.

Our society's commitment to the advancement of the science of transplantation has provided a yearly forum for the exchange and critical evaluation of clinical and basic scientific research in the field. One has only to review how the quality of the scientific program has improved with each advancing year to recognize what we have been able to accomplish. The scientific program this year probably represents the best such program—and I expect that the program next year will be a further improvement.

This year's activities have also produced several new efforts for the advancement of transplantation science. One important innovation in our usual program is the introduction of a panel to discuss a timely issue in transplantation—and its practical

significance as we make this therapy available to our patients. In this inaugural year of the panel, we have chosen to address the impact of cyclosporine on renal transplantation as well as the relevance of pretransplant blood transfusions and tissue typing. This year's multidisciplinary panel earlier this afternoon was well-received. I would like to acknowledge that it was made possible through the cooperative efforts of our transplant nephrology colleagues. Also important in the advancement of transplantation science have been the many programs sponsored by our Scientific Studies Committee. This year's Biometrics Program, under the chairmanship of Everett Spees, was no exception—and, additionally, it enjoyed the cosponsorship of the American Society of Transplant Physicians.

Other innovations this year include an award for outstanding research by a transplant resident or fellow. This award has been made possible through the generous support of the Upjohn Company. Likewise, this year we are pleased to announce an ongoing funded transplantation fellowship that will encourage the training of transplant surgeons skilled, not only in the clinical aspects of transplantation, but also in the immunobiology of transplantation. Each training grant will be for \$25,000 per year for a two-year period, and it will be awarded each year commencing in 1985. However, in 1985 two awards will be made, one of which will be a one-year award given on a onetime basis, to allow for subsequent yearly staggering of the two-year awards. Our extreme gratitude is extended to the Sandoz Corporation for its generosity in making these awards possible and for the commitment they share with us to advance the training of well-qualified transplant surgeons.

Another extremely important activity during the past year has been the well-coordinated, cooperative effort by members of our Standards Committee on Organ Preservation and Sharing, under the chairmanship of Nick Feduska, and the NIH, under the direction of Ken Sells, to advance the concept of, and develop standards for, multiple-organ procurement.

In addressing the scientific advancement of transplantation, special acknowledgment should also be made to two individuals. Anthony Monaco deserves mention for his efforts in developing a special yearly issue of *Transplantation* that provides for the publication and dissemination of scientific papers presented at our annual meeting. John Najarian, through his Education Committee, has provided standards for, and an ongoing means for certification of, graduate education programs in transplantation surgery. This training not only includes surgery itself, but also provides instruction in the basic sciences as they relate to the physiology, pathology, and immunobiology of transplantation.

I have briefly enumerated our society's commitment and progress in advancing the science of transplantation. Equally important, however, has been our society's commitment to making this therapy more accessible to patients who can benefit from transplantation. The recent advancements in the technology and performance of human organ transplantation have been rapid and dramatic in their results, and as a society, we are extremely gratified by the improved success of transplant procedures. But because we recognize that an increased number of patients can now be restored to productive and fulfilling lives, our society is striving for a major humanitarian goal: to



make the benefits of this therapy more accessible to patients requiring transplantation. During the past year we have identified certain problem areas that have made transplantation less than optimally accessible to patients. We have sought political assistance in resolving these difficulties, by sponsoring and supporting legislation that provides solutions to some of these problems—legislation that is truly patient-helping legislation.

We have particularly addressed six areas, which are now well familiar to you: (1) organ shortage and the need for assistance for local organ procurement; (2) the need for an improved nationwide transplantation network that would more effectively deal with national placement of organs that cannot be used in the region of procurement—and, in addition, provide for regional pooling of sera of hyperimmunized patients, so as to optimize the opportunity of those patients to be matched with compatible crossmatch-negative organs; (3) the need for a scientific registry for all organs; (4) the need to modify the current reimbursement system, which has proved to be a disincentive to transplantation; (5) the problem of purchase and sale of organs; and (6) a means for further assessment of the problems faced in transplantation. Our efforts to help our patients thus far have been quite effective: most of the areas mentioned have been embodied in the Gore bill before the House of Representatives, and some have also been included in the Hatch bill before the Senate. These bills as developed, therefore, are truly patient-oriented bills.

I would now like briefly to address one of the areas mentioned—that is, hospital and drug reimbursement. We have been particularly disturbed by the inequitable access of patients to transplantation of organs for which appropriate reimbursement mechanisms do not exist. In these cases, transplantation has often become dependent on public fundraising campaigns that favor the patient with media appeal. We have also been disturbed by the difficulty some patients have had in obtaining better drug therapy—more specifically, cyclosporine—because they are unable to afford it. As surgeons dedicated to helping and providing optimal therapy to all patients in need of transplantation, it has been difficult for us to be forced to apply an economic means test before a transplant, to ascertain whether a patient could receive the better drug therapy, cyclosporine.

We all recognize that cost-effectiveness of medical care is a central health care issue today. In the specific case of end-stage kidney disease, kidney transplants are a more economical therapy and afford a greater potential for rehabilitation than long-term dialysis. The number of kidney transplants performed each year could be realistically increased from 5,000 to 8,000—and perhaps even to 10,000. Just maintaining this greater transplant level yearly, with the current improved rate of success of cadaver grafts with cyclosporine, would ultimately produce enormous savings, and many more patients would be returned to normal productive lives. The case for heart and liver transplants may be even more impressive. Not only do they have the potential to provide a cost saving when compared with the alternative treatment and (the care these patients must receive until they die), but it is the only therapy that makes possible the survival and rehabilitation of these patients. Unfortunately, the present reimbursement system has, for the most part, made it easier for potential heart and liver



recipients to be maintained in a costly, critically ill state until death than to be restored to normal life by transplantation.

I am pleased to announce that a cyclosporine provision has been reinstated into the Gore bill. However, the provision to provide reimbursement for nonrenal organ transplants has been deleted for the present. Nevertheless, through our society's articulation of the needs of these patients, and their inequitable access to transplantation, we have aroused the conscience of the nation, so that a number of commercial insurance carriers and Medicaid programs are now opting to provide some reimbursement for nonrenal organ transplants—therapies that are life-saving and cost-effective when compared with costly alternative medical care, which can only maintain patients until death, but which is already fully reimbursable. What we have attempted during the past year is well known to all of you, because we have interacted with Congress to provide solutions to many of these problems. I have tried to keep you informed through timely communications about the progress we were making in the legislative process. We, as transplant surgeons, have looked at these issues, not according to whether they were Republican or Democratic issues, but purely on their merits. We are particularly pleased at the time of this meeting to realize the nearly successful culmination of our efforts. As indicated earlier today, the National Organ Transplant Act now before Congress appears almost to be a reality. Presently the Senate and House are about to meet in conference committee to resolve some of the differences between the legislative measures before them.

Certainly the problems facing organ transplantation are not solely the responsibility of the federal government. The most important contribution of federal legislation in this area has been to provide leadership that can result in a more effective public and private partnership. We must make every effort to assure that the technology that has made this country the world leader in the field of organ transplantation is available to those citizens for whom it is appropriate therapy. This is the humanitarian goal that complements the scientific direction taken by our society.

As we review the scientific accomplishments and humanitarian achievements of our society, not only during this past year but in previous years, we must acknowledge that attainment of each has been possible only because we have developed an effective organization, based upon the cooperation and unselfish efforts of our membership. The response of members of our society to my requests for intercessions and letters to members of Congress in support of patient-helping legislation was perhaps the most instrumental activity resulting in the favorable progress of our legislative efforts. In addition, I must particularly acknowledge a number of our members who never hesitated to respond and participate in Congressional testimony when requested. I can only list the last names alphabetically, because they have all made important contributions. We are extremely grateful, therefore, to: Nancy Ascher, Ben Barnes, Fred Belzer, Tom Berne, Nick Feduska, Ronald Ferguson, Barry Kahan, Robert Mendez, Anthony Monaco, Norman Shumway, Tom Starzl, and Mel Williams. Also critical to the success of our efforts have been the members of our Board of Directors, who were extremely helpful in offering good judgment and counsel as we approached many important issues during the past year.



Our past presidents in particular must be individually acknowledged. They deserve an immense amount of credit and debt of gratitude for their continued efforts on behalf of the society. It is unique that, in addition to the work and effort expended by each when president of the society, they have continued to provide support and counsel in a way that foster the continued growth and strength of our society. Tom Starzl was our first president and was responsible for the initial organization of our society. Despite his other time-consuming activities, Tom has been particularly and unselfishly helpful to me during the past year with counsel—and, in addition, on the numerous occasions when he has accompanied me to provide Congressional testimony in Washington. Fred Belzer, Jim Cerilli, John Najarian, and Mel Williams, as well as Jerry Turcotte, Richard Simmons, Tom Marchioro, and Fred Merkel, have also made themselves available to provide important counsel and support during the past year. In addition, Jerry Turcotte has recently chaired an ad hoc committee that developed guidelines for the newly established competitive fellowship award.

As is clearly evident, our society has established itself as a pillar among professional organizations. Most important, it serves as the focus and center for scientific advancements in the field, and has maintained concurrent humanitarian sensitivity to the needs of all patients requiring organ transplantation. These achievements, as mentioned before, have only been made possible by the genuine interest, commitment, and cooperative efforts of the members themselves.

But now that we have examined where we have been, and where we are, it is time to look also at what we must do in the future. Certainly our principal objective must be to continue to support the scientific and humanitarian goals that I have addressed. This will provide the principal basis for the continued growth and effectiveness of our society. On a more specific level, though, there are four areas that will require our special attention during the coming year.

1. The cyclosporine amendment as drafted, if passed into law, places tremendous responsibility on transplant surgeons. The federal government will be responsible for purchasing cyclosporine directly from the manufacturer and then distributing it to transplant centers. Transplant centers, in turn, will be responsible for determining which patients shall receive the drug and in what amounts. The only requirement for transplant centers is that they do not charge for this drug. This is a somewhat unusual approach, but we are faced with an unusual problem that has required considerable compromise to make cyclosporine available to those who cannot afford it. In fact, the present legislative measure is better than the previously written provision. The previously written provision provided outpatient reimbursement only for Medicare recipients, whether they needed financial assistance or not. Instead, the present provision provides distribution of the drug only to those unable to pay for it, whether Medicare-eligible or not, and whether kidney, heart, heart-lung, liver, or pancreas recipients. There is limited regulation with the measure, so this immunosuppressive drug program, as stated by Albert Gore earlier today, will place a great deal of responsibility on transplant surgeons. We must ensure equitable distribution of cyclosporine to all patients needing the drug. There are centers in which a large percentage of the patients have co-insurance, and therefore have little need for the drug; whereas at



other centers, the great majority of patients have no means of payment. The drug must be redistributed so that it will reach all patients not able to afford it. Because we have strongly interceded for the reinclusion of a cyclosporine measure, after an initial defeat by the House Ways and Means Committee, the reputation and credibility of our society is at stake in assuring this equity, but I am confident that Gore will act responsibly in this effort. This, in turn, can only further enhance our stature and credibility with the federal government and the medical community in future interactions. To help our centers in recognizing where the drug is most needed, and to assure equitable distribution to needy patients, I am forming an Ad Hoc Committee on Cyclosporine Distribution to assist in this area, and to be activated on passage of this legislation. I am asking Nick Tilney to be chairman of this committee. Other members of the committee will include Tom Berne, Clive Callender, Ron Ferguson, Barry Kahan, and Joshua Miller.

2. As we have approached patient-helping legislation with vigor and zeal, I believe we must also approach research funding in a similar manner. Our society has achieved a stature whereby the new leadership should include this effort as a top priority. Our intercessions for a National Organ Transplant Act have only made people in government and the NIH more aware of the needs in our field. The background has been established—the time is fertile for active intercession by our society in this area.

3. The National Organ Transplant Act, if it becomes law, will name a task force that will further evaluate the needs and problems in transplantation, with recommendations to be issued at the completion of the task force's term. Several members of our society will be asked to participate on this task force. I am hopeful that those asked to participate on the task force will maintain communication with our Board of Directors, as well as our advisory committee composed of our past presidents, so as to best provide organized input into the important recommendations that might be made by this task force regarding transplantation. The issues to be covered by this task force are multiple, from organ shortage to reimbursement problems.

4. Lastly, it will be important for our advisory committee and for our new leadership to keep abreast of DRGs as they are implemented. As you are aware, the DRG for transplantation is all-inclusive for the procedure, regardless of whether the transplant is cadaver or living related, or whether the recipient is nondiabetic, diabetic, low-risk, or high-risk. Initially, organ procurement was included in this global DRG, but our society managed to intervene about 10 months ago to achieve rightful separation of patient care from organ procurement reimbursement, so that the latter will continue to be reimbursed at cost. This separation was important, because it became apparent that it would be difficult to separate necessary funding for organ procurement from that which would be used for patient care. However, the principal problem remains that the transplantation hospitalization DRG is essentially a single-reimbursement package, without regard to the type of transplant performed or the type of patient receiving the transplant. The real danger in this area is that transplantation may be rationed to patient and transplant categories in which the cost would be least, potentially depriving many patients, such as diabetics, of this most important therapy. Our



input is extremely important and urgent in achieving equitable change before full implementation of the DRG process.

These suggestions for our society's direction during the coming year are only a further extension of the goals and tradition already embodied in the American Society of Transplant Surgeons—that is, we are primarily a scientific organization with equally important humanitarian goals. We are committed to making this life-enhancing and lifesaving therapy accessible to all patients requiring organ transplantation—whether it be kidney, heart, heart-lung, liver, or pancreas—and we have the best means to accomplish the goals enumerated, a committed membership. These are the ingredients of the strength and vitality of our society.

As I conclude my presentation this afternoon, I acknowledge that there are many persons whom I did not have time to thank by name for their important contributions during this year and past years. Their efforts deserve equal and utmost recognition. Yet there are several other persons who, at this time, I must personally acknowledge, for during the course of the year they have facilitated my interactions on behalf of the society. I would be remiss if I did not mention my colleagues at my own institution, who believed in and supported what I have tried to accomplish on behalf of the society and our patients. Despite the volume of activity at my own institution, they provided extra coverage and support when needed. I am, therefore, especially grateful to surgeons Nick Feduska and Julie Melzer and nephrologists William Amend and Flavio Vincenti for their support and assistance during the past year. I must also, at this time, render a special expression of gratitude to Fred Belzer, who has been an inspiration to me and is most responsible for my being a transplant surgeon.

In conclusion, the American Society of Transplant Surgeons has proved to be an ever increasingly effective organization that can only continue to grow. It is a society that has acquired strength and stature because of its goals, both scientific and humanitarian, and because of its strongly committed membership. It is not a society representing a few, but it is a society representing all transplant surgeons and the transplantation of all organs. This society belongs to all of us, as is evident from my mention of the numerous persons involved in the many activities of our society. The future of this society is very bright, and we will approach it with confidence and purpose. I personally have the faith and conviction that our society will meet all new challenges in the future—vigorously, courageously, and with great sensitivity to the needs of our patients. I myself, therefore, am extremely proud to be a member of this society and, in addition, to have had the honor and privilege to serve you as your president, during our 10th anniversary year.







## Problems in Transplantation— Ethics, Education, and Expansion

A. P. MONACO, 1985-86

First, let me begin by expressing my gratitude to you, the membership, for the honor and privilege to serve as your president this past year. I also want to say thanks to all who have helped me discharge this duty, especially all the past presidents and members of the Council—and particularly to Oscar Salvatierra, H.M. Lee, and Robb Corry for their wise and generous advice on some difficult problems, as well as Barry Kahan, Bruce Reitz, and Andy Novick. Special thanks go to Wes Alexander and John McDonald who worked so hard at the ever-increasing job of secretary and treasurer in spite of their demanding academic and clinical duties. I know I speak for all of you when I express my gratitude to Jerry Rosenberg and his committee for the beautiful job they have done in preparing this meeting's program. Likewise, we are all indebted to the local organizing committee, especially its chairperson Olga Jonasson, for the magnificent job they have done in organizing this meeting—and this at a time when Olga has had so many obligations with the National Task Force. Time does not permit me to publicly thank all of the committee chairmen and their members individually for their work; I have tried to express my personal gratitude at their meetings yesterday. Finally, I would like to acknowledge the thoughtful, professional, and expert work of Janet Wright and her organization in handling the day-to-day affairs of the society and our annual meeting. We are lucky to have them.

I had hoped to talk to you today about a scientific subject—namely, the use of donor antigen to modulate the allograft response, an area of long-term interest to me, and one that I think should and will be the next application of clinical immunosuppression. This subject I will leave for a later talk because I want to focus today on three problems I see facing the transplantation community in general, and the American Society of Transplant Surgeons in particular. These are the general concept of ethical practice in transplantation, the education of the transplant surgeon, and the expansion of the clinical practice of organ transplantation.

### *Ethics in Organ Transplantation*

First, I will discuss at some length certain ethical considerations in transplantation. You are no doubt aware of the recent significant negative publicity generated in the public media concerning access to organ transplantation, exportation of organs, preferential treatment of certain recipients, and other equally disquieting matters. As your representative, I was repeatedly asked (and sometimes verbally assaulted by the media, including all the networks and most major papers) for ASTS's stand on this or that issue relative to ethics or practice. I had to state that for many of the issues raised there was no official stand that I could articulate for the society. I had my opinions, but they were just my own. Frankly, I did not feel the urgency to elaborate Society guidelines. I thought then, as I do now, that the overwhelming majority of our members act ethically with the welfare of their patients as their foremost consideration. Furthermore, a law had been passed making a felony of the purchase and sale of organs, and the international Transplantation Society had already dealt with a number of important ethical issues and published their guidelines. Likewise, the task force was at work and it was going to address access to organ transplantation. I also thought that media attention, particularly that as motivated by sensationalism as this was, would abate—and it did. But the incident that identified to me an urgent need for an ASTS statement of guidelines came one day in a phone call from one of our members. He told me that his university president wanted to contract to do cadaver transplantation for a significant number of foreign nationals and that he, the transplant surgeon, was under great pressure to cooperate in this for “the good of the university.” The transplant surgeon wanted help in the form of the official stance of ASTS in this matter, and unfortunately there really was none. Incidentally, this university was not in a city with a major league baseball or football club. It seemed to me that, if academic, institutional, or administrative pressures could be brought to bear on transplant surgeons in areas of ethical consideration, ASTS should provide some shield of protection.

### *Guidelines for Organ Transplantation*

Accordingly, your Council at its mid-winter meeting discussed in detail the need for written guidelines on certain aspects of transplantation practice. A set of guidelines was elaborated, for the most part through the enormous efforts of Jim Cerilli, chairman of the Ethics Committee; they were discussed and eventually approved by the Council and mailed to the membership for vote. We have 331 members in ASTS, and 192 replied, an excellent reply rate for a mail ballot; there were 183 affirmative votes and only 7 dissenting votes (2 abstentions). Thus, 95% were in favor of these guidelines. I want to review these guidelines briefly and identify what I think is the particular significance of each one, fully acknowledging that this is an imperfect document.

*1. The supply of transplantable organs is a national resource and procurement is almost exclusively fiscally supported through federal funding. Therefore, the distribution and assignment of organs to patients must be determined by medical criteria and cannot be*



*influenced by other considerations, such as political influence, monetary exchange, or center favoritism.*

The first guideline identifies cadaver organs as a national medical resource that should be dispensed only on the basis of medical criteria without political, financial, or other potentially corrupting influences. Although some quibbled over describing cadaver organs as a national resource, all agreed that the basic tenet of this guideline was correct and something we could live with.

*2. There must be no shipment of transplantable organs to foreign countries by an organ procurement organization or individual unless there is verifiable evidence that a concerted attempt has been made to place these organs somewhere in the U.S. Such evidence must include the referral of the organ to a national center for organ distribution if regional patients are not available for its utilization.*

The second guideline clearly affirms ASTS's opposition to exportation of cadaver organs from the U.S.—regardless of a profit or nonprofit motive—unless verifiable efforts to use the organ in the U.S. have been made. This is current practice in both our national sharing networks and will be standard practice when the national network is established under the Organ Procurement and Transplantation Act—which it soon will be. There were no significant objections to this.

*3. The active recruitment or encouragement of foreign nationals for the sole purpose of transplantation in the U.S. is inappropriate and unacceptable to the American Society of Transplant Surgeons.*

The third guideline was designed to address the problem I identified initially. Specific contracting of groups of foreign patients by individual centers could clearly lead to disadvantages to the regional patients of the center or the national patient pool, by sheer numbers or by the financial pressure that a single large patient referral source can exert, as it does in so many areas of medicine. The guideline also renders unacceptable advertising and guaranteeing of cadaver organs within certain lengths of time, which have encouraged foreign nationals to seek organs in the U.S. in the past. No one had trouble with this guideline.

*4. Organs made available for transplantation in the U.S. should be preferentially transplanted into citizens of this country, individuals residing permanently in the U.S., and foreign nationals under specifically defined conditions. The transplantation of any organ into an individual who comes to the U.S. for the express purpose of receiving a transplant is acceptable for humanitarian reasons, providing such transplants constitute a very small percentage of organs transplanted at a given center. This percentage must not exceed, on average, 5% per year of the organs transplanted at any single center.*

*Foreign nationals who are on the transplant waiting list of a center in the U.S. must reflect the religious, ethnic, and economic profile of their country of origin. The patient or the*



*responsible financing agency must be charged for transplantation services on the same basis as citizens of the U.S.*

The first half of the fourth guideline definitely states citizens of this country should receive cadaver organs procured in the U.S. preferentially. It does not exclude cadaver organ transplantation for foreign nationals categorically—as some of our members wanted—for a number of reasons, including the realizations that a human being is a human being, that many countries do not yet have complete transplant capabilities, that many foreign nationals have been treated in the hospitals of the transplant center for years for the very disease that now brings them to require transplantation, that foreigners donate organs when they die in the U.S.—and for numerous other reasons reasonably described as humanitarian. The Council realized that, practically, these transplants should constitute a small percentage of any center's activity. One could have endless ethical discussions pro and con about the concept of identifying a specific numerical limitation (here 5%) for foreign nationals. Nevertheless, identifying a numerical limitation acknowledges preference for citizens of the U.S., restores flagging public trust in the transplant community, and provides you, the society and its Council and Ethics Committee, with a reasonable monitoring mechanism and a behavioral yardstick. I might add that the recently completed task force report addressed this problem and similarly recommended a numerical limitation of 10% for foreign cadaver kidney transplants and heart and liver transplants only if no recipients were identifiable in the U.S.

The second half of the fourth guideline shown here attempted to ensure that foreign nationals who were accepted at a center would not be restricted to the wealthy and privileged of a country. It was a naive attempt, difficult to interpret, and clearly in retrospect undefinable and uninterpretable. This statement requiring transplanted foreign nations to reflect the religious, ethnic, and economic profile of their country might be the first part of the guidelines to be modified by future Ethics Committees. On the other hand, the requirement that everyone should be charged the same is appropriate and important, and again reinforces the public trust that financial inducements for foreign transplants have been removed or minimized.

*5. The use of living related donors is currently accepted because of the shortage of cadaver organs, and because current long-term results with living related donors are better than with cadaver organs. The use of living related donors must assure (A) proper informed consent with adequate documentation, (B) proper donor psychological and medical follow-up, (C) absence of financial profit by the donor, and (D) no known coercion of the donor or family.*

The fifth guideline identifies standard practice for living related kidney transplantation. It was included because some members expressed concern that with the current good results of cadaver transplantation, living related transplantation might be considered unnecessary, obsolete, and not peer practice by people not acquainted with the field. Clearly it still is peer practice; obviously we all eagerly await the day when use of living related donors will not be necessary.



6. *The use of living, nonrelated donors is acceptable only under specifically defined circumstances that include a documented “emotional relationship” between donor and recipient and a medical situation necessitating prompt transplantation. When living, nonrelated donors are used, there must be documented informed consent, lack of monetary exchange in excess of reasonable donor costs, and an assurance of proper donor medical and psychological follow-up. Because, at this time, the overall clinical results and benefits of using living, nonrelated donors are still unknown, such transplantation must be conducted with the approval of the respective center’s Committee on Human Experimentation.*

*The American Society of Transplant Surgeons, while recognizing the occasional appropriateness of living, nonrelated donor utilization and the current justification for the use of living related donors, is committed to the goal of an adequate supply of cadaver organs with a graft success equivalent to that of living related donors, thus ultimately eliminating the need to use healthy living donors.*

The first part of the sixth guideline affirms that nonrelated living donors—whether the transplant is done with DST, cyclosporine, or something else—may be an acceptable alternative to cadaver kidney transplantation. It requires that a documented emotional relationship between donor and recipient and a special medical need be conditions for use, and it sets up barriers to the mere buying of organs from external sources. This guideline is designed to oppose opening the flood gates to use of living nonrelated kidneys from donors whose motives are less than altruistic or whose circumstances, economic or otherwise, might force them to donate their organs against their will. However, the guideline has been discussed for at least a year, and several members honestly object to the description of this procedure as experimental and the requirement for Human Studies Committee participation. With new and more complete experience, this objection seems valid and the Ethics Committee might consider modifying or deleting the statement that nonrelated living donor kidney transplantation should be conducted with approval of the institution’s Human Experimentation Committee.

The second half of this guideline restates the ASTS commitment to develop cadaver transplantation to such a level that living nonrelated donors would not be required, a noble and noncontroversial goal.

7. *The Ethics Committee of the American Society of Transplant Surgeons will review complaints against individual surgeons and/or centers regarding alleged breaches of ethical practice. The Ethics Committee will present its findings to the Council of the American Society of Transplant Surgeons who will decide upon appropriate disciplinary action, which may include censure by or expulsion from the American Society of Transplant Surgeons if violations of ethical practice are confirmed. The governing board of the facility utilized by the offending member for the purpose of transplantation will be notified in writing if such disciplinary action is taken.*



The seventh guideline squarely states that ASTS will concern itself with alleged breaches of ethical practice. It identifies the role of the Ethics Committee in investigating these alleged breaches, confirms the right of ASTS to exercise disciplinary action, and asserts its intention to inform appropriate institutional administration of any disciplinary actions it has taken.

I emphasize that these guidelines are not perfect, but they are certainly a starting point from which a great scientific society can fulfill its professional responsibilities. They should be reviewed and changed as scientific progress and clinical practice mandate modification. Indeed, if organs become plentiful, some guidelines may be rendered obsolete and others strengthened. I think that if we follow them and take adherence to them seriously, our ethical problems and public concern and distrust will be things of the past.

### *Education of the Transplant Surgeon*

The education of the transplant surgeon is another area of concern. Please note I said *education*, not *training*. It implies that the individual is taught or trained to react in a defined way or to do things only in a defined manner. It connotes a shade of anti-intellectualism that some people attribute to certain areas of surgery in general. Certainly in the beginning, transplant surgeons were the opposite of this concept in every way. They were the eggheads of surgery—talking about genetics, immunobiology, inbred strains, tolerance, enhancement, haplotypes, public antigens, private antigens—and more recently, lymphocyte subsets, killer cells, suppressor cells, helper cells, lymphokines, IL-1, IL-2, interferon, and so on. In the early days a young resident surgeon invariably went off to a basic science laboratory, frequently not related to a surgical department, to study some aspect of immunobiology, and only after that experience would he or she take up clinical transplantation studies and activities. With the increased success of all organ transplants, especially with the use of new, more effective immunosuppressive agents, many young residents bypass the basic science year and plunge into clinical organ transplantation. Whatever basic immunology they learn is picked up along the way. The chance to immerse themselves in immunologic studies is missed along with the many lifelong good habits of sophisticated scientific experimentation that they could apply to their clinical studies throughout their professional careers. Basic science immunologic preparation combined with surgical skills invariably made the transplant surgeon the leader of the transplant unit. I am concerned that, as we get away from basic immunologic education requirements, the transplant surgeon can become the “sewer-in” of the organ and not the unit leader and contributor. I remind you that in other countries where it has not been the frequent practice for the surgeon to be prepared in immunobiology, the leader of the transplant unit is frequently a nonsurgeon who has prepared in immunology. My admonition is clear; as clinical organ transplantation expands and our young people go into it, we should emphasize and reinforce—and even require—a basic science investigational experience as part of the transplant surgeon’s education. This could be obtained in a basic science department or as part of a qualifying research-clinical



transplant fellowship in one of the many leadership laboratories of our major clinical transplant centers.

The expansion and success of organ transplantation brings into focus another problem in the education of the transplant surgeon. Institutions are putting together transplant teams for nonrenal organ transplants in which the surgeon's role is strictly technical. This surgeon has had no experience in such subjects as immunobiology, immunogenetics, or management of immunosuppression, and cannot function in a leadership role. ASTS must review and redefine appropriate clinical transplant education to designate the qualified transplant surgeon and what fellowship programs are qualified to achieve this. My own preference is that qualified fellowships include a year of investigational experience and a year of expanded clinical experience in kidney transplantation, as well as in transplantation of one other extrarenal organ. No matter what type of transplantation the fellow intends to pursue, this implies a minimum of two years' laboratory-clinical experience. I further advise that all our fellowship programs be rereviewed by our Education Committee for recertification, and that they be reviewed regularly every two years thereafter once our qualifications are defined.

#### *Expansion of Clinical Organ Transplantation*

Elaboration of these more stringent requirements for qualifying as a transplant surgeon leads me to discuss the third problem: proliferation of clinical organ transplant activities. The impetus for transplant center proliferation is multifactorial but includes (1) the obvious success of all organ transplants; (2) the misconceptions that the problems of immunosuppression are over—just sew the organ in and give cyclosporine—and that transplantation is strictly a technical problem that any good surgeon can handle; (3) the decrease in all surgery and the desire, frequently generated by hospital administrations, to get what is euphemistically called the market share of new patients; and (4) the need for many surgeons, even academic ones, to expand into clinical transplantation as their own particular field of interest diminishes in scope and importance. I am amazed at how many GI surgeons propose to transplant the small bowel or pancreas, let alone the liver, without the slightest previous interest or experience in transplantation. In the short term, to stem the tide of proliferation, ASTS should take a forceful role in defining and enforcing what it perceives as appropriate criteria for description of qualified centers, including supporting or expanding the recommendations of the National Task Force for Center Qualification. In the long run, proliferation can only be controlled by enforcing two demanding requirements: that the transplant surgeon in a center must be a graduate of a qualified fellowship program under the expanded requirements I described above, and that no extrarenal organ program can be undertaken in an institution without a qualified kidney transplant program under the direction of a qualified transplant surgeon.

Finally, in a little less serious vein, I would like to mention the *gift of transplantation*. The phrase can mean many things—to the recipient, it is the gift of being saved from morbidity and mortality; to the donor, the chance to give a gift of life to someone; and to the transplant surgeon, the gift of being able to help the patient. To me it

also means another gift to the transplant surgeon. This was brought home to me a couple of years ago when I attended the 50th birthday party of my college roommate who was a successful internist right here in Chicago.

He was bored, disillusioned, and unhappy with his profession, and he announced his semi-retirement. I could not believe it. I felt as if I were just getting started and he was ready to quit. How could two people who started out at the same time in the same profession end up so differently? I concluded it was the particular work I was doing. Transplantation is a vibrant, vital field, ever-changing, ever-challenging, ever-stimulating, ever-accomplishing, with many limitless possibilities to affect all aspects of medicine and surgery—as it already has done and will continue to do. So this is another gift of transplantation, the opportunity it gives us to be continually creative, innovative, and productive. To you younger members, I emphasize this wonderful vitality of transplantation, which is like an unirradiated mixed lymphocyte culture, a two-way reaction. You get from it and you give to it, depending on your hard work and contributions. To you older members who have already contributed so much, I remind you of this continued opportunity, of which I know you will all continue to avail yourselves, perhaps best expressed by a medieval cleric, Bishop Richard Cumberland: “It is better to wear out than to rust out.”





## Recommendations Regarding Issues Facing Organ Transplantation

ROBERT J. CORRY, 1986–87

Many previous presidential addresses of ASTS and the Transplantation Society have been concerned with various political and ethical issues facing the transplantation community and the public. My distinguished immediate predecessor stated last year in his Presidential Address that he had hoped to discuss the use of donor antigen to modulate allograft response, but he elected instead to delay this important immunologic topic to respond to the timely political and ethical issues facing transplantation. Perhaps we can look forward to the scientific topic as the subject of his next Presidential Address in Australia. Until a few weeks ago, I had planned to discuss the accumulating evidence that pancreas transplantation stabilizes and prevents some of the secondary complications of diabetes. However, I too have succumbed to the discussion of the pressing issues affecting transplantation currently. While some issues have been at least partially resolved, others have become more diverse and complex and await final solution. Many of these current problems would be simpler had we continued to perform the same number of renal and other organ transplants that were being performed a decade ago or even five years ago. Fortunately, for the patients and transplantation science, results have improved dramatically, and the volume of clinical transplantation has increased substantially. As a result, organ transplantation has been extended in a number of well-known centers to include at least two of the three other primarily vascularized organs—and, in a few institutions, all four organ transplants are being performed.

With the increase in clinical organ transplantation, the continued short supply of organs has become one of the most vital issues facing transplantation today. The short supply is compounded by the fact that success rates have increased by approximately 30% for the kidney, liver, heart, and even the pancreas; this has rendered kidney transplantation the best option for treatment of end-stage renal disease and has removed the other organs from experimental status.

Several measures have already been undertaken to improve the supply of donor



organs for transplantation. Excellent public and professional education programs and audiovisuals have been developed by several organizations. In addition, federal legislation has been passed that requires, by October 1, 1987, as a condition of participation in Medicare and Medicaid programs, the establishment of protocols and procedures for encouraging organ and tissue donation in hospitals, ensuring that families of possible organ donors are made aware of the option to donate. Furthermore, the potential donor hospital must notify the federally certified organ procurement agency. Also, the passage of required request laws has increased donor organ supply in certain areas of the country. All these measures have helped to increase public and professional awareness.

I would like to suggest that ASTS become more active in its support of organizations and associations engaged in professional education and public awareness programs. Heretofore, we have been only mildly supportive of these various efforts to increase donor awareness and acquisition. Our active support of these ongoing programs will lend legitimacy to these efforts. Obviously, in so doing, ASTS will be instrumental in determining which types of programs should be supported. I propose that the Council develop a mechanism to actively endorse effective public and professional education programs regarding organ donation. In addition, the Council should carefully evaluate the possibility of developing a well-organized strategy of professional education regarding donor identification and care.

A more complex issue is the question of which is the correct method of organ distribution and sharing, a discussion in which many of you participated yesterday. Should donor organs stay in local areas and regions, or should they be shared nationally? This issue is particularly sensitive in light of the fact that sharing on a broad scale has been recommended by the National Task Force on Organ Transplantation, as well as by other key individuals and groups. Should matching for kidneys—and, for that matter, other organs—be considered? While ischemic times for nonrenal organs are crucial, should prolonging ischemic times by a few additional hours be the major reason for not sharing kidneys if total ischemic times are below the critical limit? The answers to these questions are, of course, not clear, and evidence can be cited to support either side. For example, in some single-center analyses, the benefit of matching for renal transplants has become less evident—or, in fact, not present at all. Our own program has long advocated sharing, initially based on matching for haplotypes and more recently for DR specificities for cadaver kidney transplantation. Our two-year graft survival since the use of cyclosporine has been 85% for donor-recipient combinations matched for three or more antigens of a possible six, compared with 83% for donor-recipient pairs matched for two or fewer antigens. However, when one looks at far larger numbers, such as the Opelz multicenter data, the effect of matching is clear; six-antigen matches for first kidney transplants have success rates approaching 90%, while poorer matches are a little better than 70%. Also, a retrospective analysis from a single heart transplant center presented in Helsinki by Mr. Yacoub showed that the two-year survival for a 1 DR-matched pair was 84%, compared with a 68% two-year survival for a 2 DR-mismatch. The suggestion that well-matched heart transplants are less likely to develop coronary artery disease, usually associated with chronic vascular



rejection, may be a factor that should be considered in the future if longer storage times become possible.

For the present, it seems to be most logical that kidneys should stay in the local area first. Then, they could be distributed to the immediate region, based on some equitable point system that includes length of time on the waiting list, medical urgency, tissue match, and degree of sensitization. This will assure transplantation of patients within the region and will enhance local and regional education programs. An esprit de corps in these geographical areas will develop. It is unlikely that the same degree of initiative for increasing donor awareness would occur if a large number of kidneys were shipped out of local areas and regions to distant metropolitan areas with large populations. When recipients are not available in the region, kidneys should be shared nationally based on a similar point system. In addition, in the case of a six-antigen match, when all specificities are identified in both the donor and the recipient, we should give strong consideration to the concept of national sharing: results are superior, and the highly sensitized patients would be more likely to receive a transplant than if there is little or no national sharing. Adoption of a policy of sharing for totally compatible matches will require careful monitoring to ensure that the designated recipient actually receives the perfectly matched organ—and, if not, the reasons for choosing another recipient should be documented. If national sharing is adopted, analysis of the data should be performed at least at six-month intervals to determine whether this strategy of sharing based on matching should be continued. For non-renal organs, local and regional allocation should occur in a like manner, based on a point system including the degree of medical urgency. I think a patient with extremely urgent status should receive an organ from the national pool, also with the proviso that a reputable accountability system is adopted. If organ donation were to double, it would be appropriate to institute a program more heavily weighted in the direction of national sharing. In that situation it might be likely that local initiatives would already be maximized and waiting lists would be reduced. In essence, a substantial increase in donor organ supply would lessen the sensitivity regarding whether a high percentage of organs should be kept in local regions or shared nationally. I am confident that the National Organ Procurement and Transplant Network—i.e., the United Network for Organ Sharing (UNOS)—will carry out this complicated task in a highly professional and fair manner.

Another issue is the question of center designation. Since donor supply is limited, it is crucial that every organ should be transplanted to a recipient at a qualified transplant center where good results have been documented. Until recently, there has been a well-established practice of initiating transplant services in comprehensive medical centers, more commonly university-based, where fundamental laboratory and clinical research fuels their development. In the past couple of years, we have had to answer the question of whether or not it is appropriate for the principles of marketplace economics to be a factor in determining the initiation of new transplant services. This trend of proliferation of renal and cardiac transplant services must be governed by a system that assures quality. It is apparent that UNOS has been given considerable authority to establish standards for transplantation programs, histo-



compatibility laboratories, and independent procurement organizations. In essence, UNOS will determine which centers can do which organ transplants, and they are charged with monitoring the results to ensure that these standards are met. By linking Medicare coverage to UNOS membership, there is the remarkable opportunity to ensure quality.

For example, the transplant program must use for its histocompatibility testing a laboratory that meets the standards of the American Society for Histocompatibility and Immunogenetics (ASHI). The clinical transplant program must have eight transplant surgeon on site with a minimum of one year of formal training and one year of experience in an ASTS-approved transplant fellowship program. This individual must be certified by the American Board of Surgery or Urology for kidney transplants, by the American Board of Surgery for liver and pancreas transplants, and by the American Board of Thoracic Surgery for heart and heart-lung transplants. In addition, each center must have on site a qualified transplant physician who is board-certified in internal medicine or pediatrics and has at least one year of specialized formal training in transplantation medicine or two years of experience. Although these criteria for membership adopted by UNOS are less stringent than the criteria recommended by the Task Force or the Ad Hoc Committee consisting of representatives from ASTS, ASTP, and ASHI that met a year ago, they do emphasize quality.

One of the most important tasks facing ASTS is the approval of programs for the training of surgeons in renal as well as extrarenal transplantation. These programs must meet the standards recently developed by the Education Committee led by John Najarian and Gil Diethelm. This committee should move very quickly to evaluate training programs within the next several months, by October 1 it is hoped. In this way ASTS becomes the unofficial credentialing body for approving the training of new transplant surgeons. I believe it is reprehensible today for a young surgeon who is not a graduate of a recognized ASTS-approved program to undertake the direction of a new transplant program. It is equally inappropriate for a surgeon to be performing organ transplants without his or her respective professional boards or their equivalents. I believe the new ASTS Governor of the American College of Surgeons, Oscar Salvatierra, should pursue this issue with the Board of Governors of the American College of Surgeons, and develop a policy statement that fellows of the American College of Surgeons should not perform organ transplants without appropriate credentials and education.

If only those programs that meet the UNOS criteria can perform organ transplants, and the official transplant surgeon at each center is a graduate in good standing of an ASTS-approved program, quality will be assured and inappropriate proliferation of centers will be controlled.

I think it is vital that ASTS and its members remain in a very strong advisory position to UNOS. Many of the officers and leaders of our society are also in leadership roles in UNOS. It is up to them to see that UNOS functions properly and efficiently in this incipient stage of its development. I hope that the members of ASTS, as well as members of ASTP, will continue to play as strong a role in the development and implementation of the policies of UNOS as they do now.



It is important that the surgeons and physicians in this country providing transplantation services to patients continue to be the prime determiners of policies that affect the delivery of this complex branch of medicine. In this regard, it is worthwhile to note that even prior to the implementation of any laws or significant regulation, the physicians entrusted with the care of these patients traditionally offered their best judgment and carried out their duties in a highly professional, successful, and ethically correct fashion—and, as a result, the field has been allowed to develop very rapidly. I know we are all opposed to overzealous federal and state regulation that might stifle appropriate growth and development of transplantation science and clinical advances. However, now that some regulation is here, we must strive to arrive at a partnership with federal and state governments, as well as the other purchasers of these services, to provide the kind of balance that supports high-quality, affordable, and accessible care that permits the same degree of innovation. Even though such a partnership should develop, members of ASTS should provide the leadership and make appropriate and sound recommendations. In essence, we should, in fact, be the policymakers and not the followers in this partnership.

In the process of these changes, most of which are for the public good, ASTS should unite its membership rather than be tempted to form subgroups to work behind the scenes on one controversial issue or another. The leadership in this organization must be made aware of problems as they arise so that they can speak for you, the membership, in a way that is appropriate.

I know there is not one quick and easy answer to these problems. Obviously, many of these issues are controversial enough that it will be difficult for all of us to agree totally on one approach or the other. Nevertheless, I've tried to suggest a few recommendations that I think would be worthy of your consideration for some of these controversial issues. However, I'm sure we all agree on two points: everything should be accomplished in the best interest of the patient, and scientific progress and involvement in clinical care should not be hampered by regulatory measures.

Finally, I'd like to thank all of you who have helped me in the past year in my attempt to discharge my responsibilities. I'd like to particularly include the members of the Council and many of the past presidents. Also, I'm most appreciative of the support and help of my family during the past and previous years.







# History, Irony, and Perception

JOHN C. MCDONALD, 1987–88

In preparing this address, I was determined not to fall victim to nostalgia and reminiscence since such tendencies are signal signs of senility. Nevertheless, one is not president of the American Society of Transplant Surgeons often. Certainly, such an occasion is cause for some reflection. I recall that previous presidents have expressed gratitude to their teachers, usually at the end of their addresses. I choose to pay these respects at the beginning rather than the end.

I thank my surgical teacher and professor, Dr. John D. Stewart, for interesting me in transplantation, which he did in quite a subtle way. While a chief resident, I asked him for a place on his full-time faculty. He asked what area of surgery I wished to study. Since I had previously spent a year in the laboratory studying liver metabolism, I suggested this field. He replied that he had faculty studying that subject and didn't think the department needed anyone else. So, ever the bright student, I asked him what he thought I should study, whereupon he suggested transplantation. I accepted his suggestion, and he accepted me on his faculty.

I thank my immunology teacher and professor, Dr. Felix Milgrom, for introducing me into the wonders of his discipline. July 1 will mark 25 years since I entered his laboratories. In 1963 Dr. Milgrom accepted two research fellows who had just completed their surgical training, Dr. Loren Humphrey and me. I don't believe he has ever done this again. Being a classic European professor, he was not accustomed, I might say even unprepared, for fellows who would actually argue, who debated their ideas with vigor, and did not automatically accept his opinions or direction. Those two years were a great learning experience for all of us, including Dr. Milgrom. They were happy and productive times. Since then I have gained immeasurable pleasure from being a foot soldier in the small army that has taken organ transplantation from the realm of science fiction to common therapy in about 30 years.

This historic achievement is unique in medical history. Most medical achievements can be attributed to one or a few individuals: antisepsis to Lister, anesthesia to Morton and/or Wells, open-heart surgery to Gibbon. A litany of many such associations can be recalled. This cannot be done fairly in transplantation. It has truly been a



many-disciplined international effort. Its progress can be looked upon as a tribute to scientific cooperation and rapid communication. Many, many contributions provided by many different people, each building upon the other, account for this revolution. I hope that historians who write definitive papers about this era will capture this unique aspect of clinical transplantation.

Although this scholarly effort has included many disciplines and a substantial number of people, the number has remained small enough for most of the participants to know each other, at least on a national level. This camaraderie has not only been another source of pleasure, but also has been a major factor in successful national cooperation. I remind you once again that the transplantation movement has, like the limb of a tree, developed a branch. The primary limb is the study of the science of transplantation. The new sprout is the provision of the service of transplantation to the population. Like it or not, we are immersed in this latter problem.

My primary ambition has always been to make scientific contributions to the field of transplantation, and it continues to be so. Nevertheless, it is my perception that the primary reason I was elected to your presidency relates to the role I have played in multiinstitutional collaboration in transplantation.

This seems to me quite ironic. While I think about questions and participate in research daily, I became involved in national planning and interinstitutional collaboration almost as an aside. It is not unlike giving to the United Fund, something you do as a duty, but certainly not a primary aim or goal.

Nevertheless, events have conspired to put me in the center of this caldron for about five years and at the epicenter for two. I have performed these responsibilities to the best of my ability, working always with the patient's best interest in mind.

In general, to paraphrase a former secretary of defense, what is best for the patient should be best for the profession and what is best for the profession will usually be best for the patient. This is not always true and does not apply uniformly to individual members of the profession. So in thinking of the national transplant network, we must think broadly as statesmen, not narrowly as individuals.

I do not wish to catalogue the successes and failures of the OPTN (Organ Procurement and Transplantation Network), but rather I wish to relate some of my perceptions acquired while working with these issues the past few years. Of course, it is necessary to relate my own perception. Wise men have commonly counseled caution in relying upon personal perception. It is true that when one looks at a problem one gains a certain picture; when one takes two steps to the right, the perception changes. That is, take two steps from your original position and truth changes. A corollary would be that wisdom is related to one's ability to look at a problem from several viewpoints. One of the lessons I have learned in approaching these complex problems is the truth of this simple concept. The problems related to delivering the service of transplantation are seen very differently by the patients, the government, the immunogeneticists, the physicians, philanthropic organizations, and surgeons. The truth does not lie within any one view but emerges only after the entire composition has been viewed.

The network developed primarily as the initiative of this society. Because we took



the initiative, we have had more influence in its evolution than others. This was neither unfair nor unexpected; nevertheless, clinical transplantation is neither the preserve of transplant surgeons nor, more particularly, of abdominal transplant surgeons. Other groups wish more influence in this larger effort. Thus, I expect that influence in the network will diffuse to include this broader constituency. This is as it should be, and this society needs to participate in the process in a positive way.

I originally viewed the explosion of clinical transplantation procedures with considerable fear. It was clearly the great increase in demand for transplantable organs that created the crisis in confidence between the population and the profession. Yet, I have been surprised and proud of the way the profession has responded. One reason for this is the camaraderie that already existed on a national level. This knowledge of the players and their strengths and weaknesses was invaluable.

I believe, however, that a much simpler process accounted for our ability to adapt to change positively. While I hope this does not sound naive or incurably romantic, the basic virtue exhibited by the discipline has been one of altruism. This probably relates to the youth of the discipline. Most of the original students of the field are still active and are in leadership roles. It is obvious to me that anyone who has been in transplantation for over ten years has not been in it for personal gain, financial or otherwise. Thus, the group has been able to approach the problems in a statesmanlike way. I know this is true. After two years leading UNOS (United Network for Organ Sharing—OPTN contractor), I have yet to encounter any individual who failed to perform any requested task—all requests have been accepted and carried out cheerfully and honestly. Further, when any conflict has arisen, it has been my custom to get all concerned parties in the same room and insist that they resolve the issue. They have never failed to enter the debate, nor have they yet failed to resolve the issue on principle. I submit this as remarkable testimony to the integrity and altruism of our membership.

The network is healthy and growing in strength and respectability. Congress and the federal bureaucracy are still not quite convinced that the professionals can be expected to regulate themselves. They are correct when they refer to a bad track record in other areas, but I perceive that they are becoming more comfortable as time passes. Bureaucracies in particular are finding that we can be more effective than they and can relieve them of substantial “heat,” when controversy arises. The network should be considered as an evolving system. It and its board have been accused of being inconsistent, which is true. Nevertheless, only politicians and the press seem to demand foolish consistency. Wise people change course when they find they are drifting away from their goals.

There are many issues that will demand attention in the future. I will only mention two. The cornerstone of the foundation of UNOS is its ability to establish criteria for transplant centers. These criteria are not yet firmly established. The federal government has now accepted, or at least acquiesced to, our criteria. In order to gain this acceptance, it was necessary to establish a provisional membership for centers that had previously performed some transplants but did not meet standards. This was a wise move. It defused the issue. It removed the Health Care Finance Administration



from an intolerable position. All provisional members tacitly accepted the criteria by accepting provisional membership. Thus, UNOS attorneys are now confident that the standards can be successfully defended if litigation arises. Nevertheless, the matter will probably not be settled until the issue has been adjudicated.

Further, mandated systems for organ distribution are not firmly established and are not symmetric, although remarkable progress has been made. This is another problem in perception. The public seems to believe that for every organ there is a single preferred recipient. Even if this were theoretically possible, they do not understand that the scientific capability of recognizing this recipient is not available. In addition, many lay organizations seem to expect a degree of centralization that is both unwise and impractical. These groups need a broader perspective that they can only gain by a good working relationship with the professionals of the discipline. We as surgeons suffer from an image that has been described as “a group of lone rangers” working under the thesis that the organs we procure are owned by us and are ours to distribute as we see fit. Some see this as an outright conflict of interest. Like most caricatures, it contains an element of truth. This image is not in our best interest and can be eradicated by more responsive approaches toward this scarce national resource.

The Scientific Registry will ultimately provide a data base unparalleled in the history of medicine and probably will serve as a prototype for other fields of complex health care. Further, this data will provide the basis for reaching consensus on effective national policies.

The network can be said to have been developed as a means of standardization and regulation of the movement. If it fulfills its promise, within a few years we will have sufficient unity and strength to represent the discipline almost monolithically. It will be stronger in affairs relating to transplantation than either the American College of Surgeons or the American Board of Surgery is to surgical affairs. There is no parallel to it in American medicine.

This power is to me an awesome responsibility. It is easy to be dogmatic and loud when what you say has no consequence. It is another matter entirely when your policies have the effect of law. It is our responsibility to see to it that this remarkable organization, which is basically representative of the discipline and empowered as a semi-official government agency, continues to flourish.

The American Society of Transplant Surgeons is primarily a scholarly organization and should not be diverted from its principal mission, which it has come perilously close to doing in recent years. UNOS will be a much more effective political force than ASTS, and we should funnel our political activities primarily through that organization.

Finally, I thank you for the opportunity to serve in a leadership role. I have particularly enjoyed becoming thoroughly acquainted with so many of our members. Certainly, serving as your president has been a signal honor in my career—but, more important, you have honored my department and my university.





## The Cutting Edge

### A LOOK TO THE FUTURE IN TRANSPLANTATION

J. WESLEY ALEXANDER, 1988–89

The American Society of Transplant Surgeons has seen remarkable evolution and progress during its brief 15 years of existence. It has served as a scientific bond for a group of pioneers and their followers who have developed and applied the most exciting and dramatic new method of therapy ever achieved—restoration of life by replacement of a diseased vital organ. Remarkably, almost all these pioneers are still actively practicing and continue to make meaningful contributions both scientifically and at a societal level.

The phenomenal success of solid organ transplantation has led directly to, or served as a catalyst for, major advances in numerous other fields, such as basic immunology, infection, nephrology, hepatology, cardiology, and pharmacology. The field of transplantation and the society are truly at the cutting edge of scientific advances in medicine—hence the title of this talk. But what about the future and the problems this rapid progress has already created? A cutting edge can be jagged and rough when greatly magnified and dangerous to those not skilled in its use.

The doomsday call is often heard reverberating from within our ranks, reinforced by the suffocating specter of malpractice, the depressing restriction of funds for research, the increasingly oppressive effects of bureaucratic controls and interventions, and a waning of interest from the public that has already seen the miracles of our handiwork and is ready to move on to bigger and more exciting miracles. Undoubtedly, there are some of us who will succumb to these pressures and retreat, as others have, to a more comfortable and less hectic life at one of the many hernia clinics of America. What about the rest of us and the future of transplantation and this sentinel society during the next 15 years, a period when nearly all of the pioneers will have retired?

I would like to begin with a review of where we have been during the last 15 years for four specific organs—the heart, liver, pancreas, and kidney—in order to address some of the current problems and to project what I think will come in the next 15

years so that we, as a society, can begin to plan for the inevitable and sometimes dramatic changes.

Cardiac transplantation had a dramatic but dismal start in the U.S. in 1968, dismal because most of the procedures at that time were done by technically adept cardiac surgeons who were ill prepared to deal with the immunosuppressive problems encountered in these difficult patients. As a result, only 15 heart transplants were performed in 1974 with a success rate, judged by one-year graft survival, of less than 50%. However, pioneering work with regard to patient management, largely at Stanford, and the commercial introduction of cyclosporine in 1983 made a difference in both the number performed and the success rate. More than 100 times as many heart transplants were done in 1988 as in 1974, and the success rate almost doubled, to 81% one-year graft survival, for those transplants being performed in 1987.

Liver transplantation has developed in this country primarily because of the efforts of a single individual, Dr. Tom Starzl, to whom the society is greatly indebted also for being its first president. With fewer than 20 transplants per year before 1980, the number performed lagged behind the number of heart transplants until 1988 when 1680 were performed like the heart transplants, the biological acceptance of the technically successful liver transplant which increased appreciably with the introduction and routine use of cyclosporine, which was available to Starzl before commercialization.

Transplantation of the pancreas has considerably lagged behind the transplantation of the heart, liver, and kidney, at least in numbers, because of the relatively poor technical success rate, limited ability to detect early rejection, and lack of convincing evidence that it prevented the ongoing progression of secondary complications associated with diabetes mellitus. Although first performed in the late 1960s, pancreas transplant activity was virtually nonexistent during the first few years of the society, but it reached nearly 200 in 1988 with a projected success rate of greater than 60% for the country as a whole.

ASTS was formed only a year after the initiation of the ESRD program that provided federal funding for kidney transplantation. A total of 3190 renal transplants were performed in 1974. There was a progressively rapid increase in the number of transplants until 1986, but thereafter both the number and success rate stabilized. It is noteworthy that the one-year graft survival did not improve between 1985 and 1987. Also of interest is the fact that the growth in kidney transplants has come largely from increased numbers of cadaver transplants. There have always been fewer than 2000 living donor renal transplants performed in the U.S. each year. This is of importance because the one-year graft failure rate has consistently been more than twice as high in recipients of cadaver organs, with approximately 1 in 4 organs of primary cadaver grafts currently being lost by the end of the first year. Since the survival trend has actually decreased during the last three years, it is unlikely that improvements in survival will occur without major changes in immunosuppression.

The ESRD program has seen an almost linear increase in the number of enrollees since its inception. Currently, there are more than 1,200,000 patients on dialysis in the U.S. with an annual increase of 9% per year. The cost of the ESRD program has risen



proportionately, although there has been little increase in cost during the 1980s when adjusted for inflation. The real dollar amounts per patient have been continuously eroded, by more than 50% since 1974, because of the insidious effects of inflation. It is appropriate to ask how this influences patient care.

The number of patients entering the waiting list for cadaver renal transplant has risen more sharply than the entry of dialysis patients, by approximately 14% per year. Currently, more than 16,000 patients are on the UNOS list for cadaver organs.

With all solid vital organs, there is an ever-growing discrepancy between the number of organs transplanted and the number of patients who could benefit from transplantation. It should be clear that the number of transplants that are being performed today is strictly limited by the availability of donor organs. Last year, there were only 4,083 donors of solid organs in the U.S., and the first quarter of this year appears to be down by approximately 10%. There may be several reasons for the lack of increase in suitable cadaver organ donors in the last three years: (1) improved care of the trauma patient, especially patients with neurosurgical trauma, because of advances in the field and the development of trauma centers; (2) a reduction in the incidence of deaths from motor vehicle accidents because of the increased use of passive restraint devices and tougher laws for driving under the influence of alcohol or drugs; (3) exclusion of many potential donors because of routine testing for hepatitis and HIV (this exclusion will become worse with testing for hepatitis C—it is noteworthy that the leveling off of cadaver donors in this country coincided roughly with the introduction of routine testing of donors for HIV); (4) exclusion of donors who might be in a high-risk category for the development of HIV infection; (5) possible resistance to organ donation because of required request legislation. I do not believe this to be an important factor, but there are insufficient data to make a meaningful conclusion.

It is probable, although not certain, that the number of potential donors in the U.S. who are suitable for organ donation is actually decreasing. If so, the percentage of suitable donors actually used for transplantation may be increasing. At the same time, it is clear that the organ procurement effort could be greatly improved and that ASTS should expend a major effort in this direction. In my opinion, a substantial increase in cadaver organ donation will not come from public education alone. Difficult ethical issues must be addressed and new ideas thoughtfully explored such as variants of implied consent, required referral, the use of living nonrelated donors, and the use of higher primates. Most of all, the public's trust and support must be rigorously maintained.

Renal transplants from living related donors clearly give the best results, but less than 2,000 are performed each year. This number could be increased significantly with better family counseling and by removing the disincentives for donation. As a cost-effective measure, a living donor should be guaranteed that he or she would not lose income because of donation, and full disability insurance should be provided for the extremely unlikely possibility that the donor would be unable to return to gainful employment. Both the pressure for the need for organs and the clearly superior results



of living related donor transplants will result in a reassessment of the use of living donors for transplantation including nonrelated donors.

Another way to improve organ availability is, in simple terms, to improve the results. A 15% increase in one-year graft survival would mean that 15% more organs would be available for transplantation during that year and perhaps even more during the ensuing years. Some ethical questions will arise in addressing this issue; as an example, with the current failure rates, should we be transplanting the highly sensitized patient who has had prior loss of a kidney from rejection in the first six months knowing that the failure rate will be 10% to 15% worse than for a nonsensitized patient? However, continued incisive and productive research is obviously the key to achieving better graft acceptance. It is here that this organization can make one of its greatest impacts. I believe that near-perfect graft survival will be a reality in the very near future, but achievement of this goal will require increased involvement of the federal government by means of substantial support for relevant research. It will be one of the major roles of ASTS to convince the funding agencies, and perhaps more importantly Congress, that research in transplantation is cost-effective, using specific data derived from UNOS, the Renal Disease Data System, and HCFA. With aggressive investigation, tolerance induction with minimal or no immunosuppression after the first year should be possible within the next five years. This will be achieved by antigen presentation with or possibly even without lymphocyte reduction coupled to the administration of multimodality immunosuppressive therapy, based primarily upon the use of cyclosporine. Even small changes can make an impact on outcome. As an example, simply starting cyclosporine therapy 24 hours before transplant can result in a 53% reduction of the occurrence of any rejection episode in the first year after a living related donor renal transplant.

Within the next 15 years, active induction of suppressor networks as well as anti-idiotypic regulation will be possible in man prior to transplant. It will also be possible to perform *ex vivo* manipulation of regulatory networks with introduction of "educated" cells back into the patient. Posteducation driving of suppressor networks may be done with the use of certain agents such as prostaglandin E<sub>2</sub>, prostacyclin and/or their analogues, or perhaps more important, by suppressor mediators produced in large quantity by recombinant technology. Monoclonal toxin-linked antibodies will be developed that can be used to treat rejection or delete selected subsets of cells, a technique that will be useful for preparation of a graft by reduction of antigen-presenting cells as well as for treatment of the recipient in preparation for grafting. Hybrid antibodies, as we have already heard, will have several important purposes in tolerance induction and will be useful for providing improved agents for treatment of rejection. Toxin-linked lymphokines may also be useful for the highly selective depletion of certain types of cells. Successful clonal deletion by activation of antigen-reactive cells or networks followed by their deletion using cytotoxic agents or toxin-linked monoclonals and/or lymphokines should prepare the way for the successful transplantation of the highly sensitized patient and also for the use of xenografts.

One extremely promising therapeutic approach is the use of gene therapy in transplantation. The human genome will be sequenced in the next 15 years. Even



using current technology it will be possible to insert genes into somatic cells, especially the bone marrow, which will offer several exciting possibilities. Immunoregulatory genes could be inserted that may alter the ease of acceptance of a graft, as well as change resistance to tumor or disease. More obvious is the use of gene therapy for treatment of genetic or metabolic diseases, such as diabetes mellitus or severe combined immunodeficiency disease that can occur because of absence of a single enzyme. Indeed, fewer people may need transplantation once gene therapy is fully developed and applied to humans—as it will begin to be in the next 15 years. It is important that ASTS members be first-line sources of information for Congress, the NIH, and other government funding agencies to encourage and develop support for the basic clinical research needed to accomplish such goals. Emphasis needs to be placed on the enormous cost savings because of improved outcomes. ASTS should also play an active role in the development of NIH-sponsored multicenter studies for the evaluation of new therapeutic techniques via the Scientific Studies Committee.

The next 15 years will see several important social as well as scientific changes. There will be increased federal and societal regulation of our practices. The End-Stage Renal Disease Program will serve as a model for outcome analysis that will require the development of accurate data. In this regard the data base of UNOS and the Renal Disease data system will be most helpful to both the government and ASTS. There is an effort by some to release center-specific data for outcome, but I believe such efforts should be vigorously opposed until there is a mechanism that is uniformly predictable that will properly weigh and adjust for various risk factors. We will see escalating pressures in the field of transplantation because of an increasingly insufficient availability of organs to meet the needs for transplantation. Through a concerted effort, however, I believe that in about three years there will be a modest increase in the availability of cadaver organs that will reach a maximum of about 8,000 to 9,000 solid organ donors per year 10 years from now.

Weighing all these factors and others for the four major organs discussed before, I will accept the risk of being wrong and make projections for the next 15 years. By 2004, the one-year graft survival rate for heart transplants will improve to 95%, and approximately 3,200 transplants will be performed per year. Transplantation will remain the preferred form of cardiac replacement, although totally implantable artificial hearts may be developed by then. The one-year survival rate for liver transplants will rise to 90% with twice as many being done. However, the needs will not be met partly because liver transplantation will be extended to more patients with Laennec's cirrhosis and to patients with malignant tumors using adjuvant chemotherapy protocols. For pancreas transplants, there will be a progressive rise in the success rate to 90% within the next 5 years and to 95% by the end of 15 years. The number transplanted will grow remarkably greater on a yearly basis, rising to 400 or 500 per year within the next five years and doubling again within the subsequent five years. However, following this there will be a leveling off of pancreas transplants and maybe even a fall because of the possibility of prevention of the disease by genetic engineering, which will have its greatest effect later than 2004, and because of the successful use of islet transplants in about 8 to 10 years.



As a result of task-directed research, the success rate will steadily rise to achieve an overall one-year renal graft survival of approximately 95%: 98% for living-related kidneys, 92% for cadaver kidneys. These results will occur despite an enlarging proportion of transplant recipients with increased risk factors or severe complicating disease. There should be more living donor kidney transplants done during the next five years because this will remain clearly the best method of treatment, and there is little documented risk to the donor. By the year 2004, it may be possible to reach a steady state for kidneys where the supply is roughly equal to the demand. Heart-lung and lung transplantation likewise will become increasingly successful. Clinical transplantation by 2004 clearly will be extended to skin transplantation for reconstructive surgery, small bowel transplantation, and limb transplantation.

Where should ASTS put its primary efforts during the next 15 years? I believe the major effort should be placed on improving the science of transplantation and rapid application of the laboratory advances to patient care. Strengthening the relationship with other scientific societies will be an important tool for increasing our effectiveness in dealing with federal and administrative issues. Because of this, I have appointed a scientific liaison committee to improve the strength of our communications and the effectiveness of our voice. There is a continued need for interaction with Congress, the NIH, and the public at large with particular regard to continued and improved ability to provide quality research in this exciting era. As an obvious example, we must take the responsibility along with others for the continued availability of animal research.

In conclusion, ASTS has the opportunity to continue at the cutting edge of scientific investigation and its application to patient care for the cure of disease and improvement in human suffering. We are living in an age of wonderment and expectation—wonderment of the advances that have already been made in our field and expectation that even our wildest dreams will someday, and perhaps soon, be achievable.

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# Transplantation Timeline

## MANKIND'S THREE MILLENNIA— ONE MAVERICK'S THREE DECADES IN THE STRUGGLE AGAINST BIOCHEMICAL INDIVIDUALITY

BARRY D. KAHAN, 1989–90

### Mythic Timeline

In the transplantation timeline that spans three millennia, organ replacement begins as the medicine of mythology. How better treat a diseased or injured tissue or organ than replace it completely? Chimeric gods and heroes appear in a number of cultures. Probably the first and most famous is Ganesha, the god of wisdom and vanquisher of obstacles, a Kumar child upon whom the Hindu god Shiva xenografted an elephant head. This twelfth century B.C. Aryan legend in the *Rig-Veda* was written during the Western eras of the Hebrew Exodus from Egypt and the Trojan War. Six centuries later (just after the time of Homer and during the life of Confucius) Ezekiel in the Old Testament alluded to transplantation: "A new heart also will I give you, and a new spirit will I put within you; and I will take away the stony heart out of your flesh, and I will give you a heart of flesh." In addition to deities, legendary doctors performed transplants. Pien Ch'iao, who was born about 430 B.C., corresponding to the lifetime of Socrates, sought to replace superstition with a practice of medicine founded on rational principles. He used four methods of diagnosis—examining the face, listening to the respiration, taking the history, and checking the pulse. The writings of Lieh Tzu narrated that Pien Ch'iao treated Ch'i Ying, who displayed a strong spirit but a weak will, and Kung He, in whom the opposite was true, by an exchange of their hearts to cure the unbalanced equilibrium of the two men's energies. In the West in the fourth century A.D., at the time of the Byzantine era, the twin brothers Saints Cosmas and Damian traveled through Asia Minor healing without reward and eventually dying as martyrs during Diocletian's persecution of Christians. The classic *Leggenda Aurea* of

Jacopo da Varagine recalls the “miracle of the black leg” believed to have occurred in 348 A.D. The lower extremity of a recently buried Ethiopian Moor gladiator was retrieved from the Hill of St. Peter to replace the gangrenous limb of Deacon Justinian, the sacristan of the Roman basilica that was later dedicated to the saints. This is the first recorded use of cadaver donor tissue for transplantation.

## Surgery Timeline

The second century B.C. skill of the Indian surgeon Sushruta using skin autografts for rhinoplasty was rediscovered in the first century A.D. Greek text *De Medicina*. Gaspare Tagliacozzi, a sixteenth-century Italian surgeon who restored lost noses with autografts, seemed to be the first physician to appreciate biochemical individuality: “The singular character of the individual entirely dissuades us from attempting this work (tissue transplantation) on another person.” Three centuries later, John Converse reasoned that Tagliacozzi appreciated the barrier to allotransplantation. In contradistinction, John Hunter’s successful engraftment of a human tooth into a cock’s comb in the eighteenth century led him to believe that “transplantation is founded on a disposition in all living substances to unite when brought into contact with each other.” Although Baronio in 1804 claimed successful grafting of both autogenous and xenogeneic skin transplants in sheep, Paul Bert disputed this finding in his 1863 thesis “*De la Greffe Animale*,” which described his own animal experiments using skin and tissue, allo-, xeno-, and rat parabiont “Siamese” grafts.

The last quarter of the nineteenth century witnessed advances in suturing techniques by Jaboulay, Murphy, and Payr. In 1902, Emerich Ullman of Vienna autotransplanted a dog’s kidney to the nuchal vessels and attempted allografts as well as xenografts. Floresco in Bucharest successfully transplanted saline-perfused donor kidneys into nephrectomized hosts using ureteroureteral anastomoses. By 1910, Unger claimed over 100 successful experimental kidney transplants from fox terriers to boxer dogs; Zaaier reported long-term success in canine kidney autotransplants. Using unique vascular techniques, Jaboulay of Lyon tested pig and goat kidney transplants in man. One of his assistants, Alexis Carrel, collaborated with Guthrie to perfect the triangulation vascular anastomosis technique using continuous silk suture mounted on fine needles. On the one hand, Guthrie transplanted a complete dog head onto the neck of another dog. On the other hand, Carrel performed experimental transplants of vessels, kidneys, thyroid, parathyroid, heart, ovary, and limbs; developed the internal vascular shunt; reported aortic patching with inert foreign substances; and cultivated adult tissues and organs outside the body. In recognition of his multiple contributions, he won the 1912 Nobel Prize in Physiology and Medicine. As one century earlier Baron Boyer had boasted that all major problems in surgery had been solved, so did Carrel in 1914 suggest that little work remained to perfect transplantation techniques. Although short-term survivals of corneal transplants reported in 1872 by Power were followed by consistent success in the reports of Filatov in 1924 and Castroveijo in 1931, the first human cadaver donor kidney allograft by the Ukrainian surgeon Yu. Yu. Voronoy in 1933 was unsuccessful, as were his five subsequent attempts during the next 13 years.



In 1947 Hume achieved transient function of a human kidney allograft anastomosed *ex vivo* to the vessels of the arm of a woman, a procedure that had been a technical failure in the hands of Ullman. Fortunately she spontaneously recovered from postpartum acute renal failure. While an orthotopic cadaver kidney transplant into a woman with polycystic kidney disease was probably technically unsuccessful, the Parisian surgeons Kuss, Servelle, and Dubost developed successful heterotopic techniques. However, all of the allografts eventually failed due to the lack of immunosuppression, although one living related donor graft functioned 22 days. Joe Murray, an honorary member of this society, has reported nine cases in which the hemodialysis technique designed by Willem Kolff was performed under the direction of John Merrill for preoperative preparation of end-stage renal disease patients. But these—as well as similar attempts reported by surgeons from Cleveland, London, and Los Angeles—produced only temporary function.

Exploiting the scientific foundations laid by Little and Tyzzer and the success of Bauer with skin grafts, Joe Murray documented permanent survival of an identical twin donor kidney transplant in December 1954 as well as six more cases during the next four years; approximately 30 isografts had been done worldwide by fall 1963. Thereafter some of the greatest technical advances in twentieth-century surgery were described by members of our society, including transplantation of the heart by Lower and Shumway, lung by Hardy, liver by Starzl, pancreas by Lillehei, and heart-lung by Reitz. Even eight decades after Carrell's boasting, members of this society continue to explore technical challenges in transplantation. However, translation of these surgical feats to acceptable long-term clinical results demands methods to prevent graft rejection.

### Immunology Timeline

The oriental practice of variolation for prevention of smallpox originated about 1000 A.D. In 1798 Jenner rediscovered this technique for cowpox vaccination, initiating the modern era of immunology. By 1888, the year of the dedication of the Pasteur Institute, immunologists had reported major advances: identification of many human bacterial pathogens; development of Pasteur vaccination for chicken cholera, anthrax, and rabies; and formulation of Metchnikoff's phagocytic theory of host resistance. Nuttall's experiments on serum bactericidins and Roux and Yersin's on diphtheria toxin documented natural immunity to be mediated by antigen-antibody complexes. Ehrlich's postulate that natural antibodies represent shed cell surface receptors for important nutrients suggested that antigens were substances that mimicked nutrient ligands. In the productive final decade of the nineteenth century, Koch demonstrated hypersensitivity to the tubercle bacillus; his students von Behring and Kitasato, the therapeutic potential of antitoxins; Bordet and Gengou, complement activity; Pfeiffer and Kolle, immune bacteriolysis; Von Gruber and Durham, bacterial agglutination; Belfanti and Carbone, immune hemolysis; and Kraus, precipitin reactions.

At the turn of the twentieth century, immunologists continued their prolific output: in 1899 Metchnikoff reported the activity of antilymphocyte serum; in 1900



Landsteiner discovered the ABO blood groups; in 1902 Portier and Richet documented anaphylaxis; in 1903, the Arthus reaction; in 1904 Donath and Landsteiner, the first autoimmune disease; and in 1906 both Obermeyer and Pick, the immunologic specificity of reactions to chemically modified antigens, and Von Pirquet and Shick, serum sickness. Shortly thereafter, Landsteiner's classic study *The Specificity of Serological Reactions*, introduced the concept of hapten inhibition; Prausnitz and Kustner, the passive transfer of allergy by humoral antibody; and Dienes and Schoenheit, delayed hypersensitivity to simple proteins.

### Transplantation Immunology

Onto this stage of burgeoning knowledge came seminal developments in transplantation immunology. Little and Tyzzer used the methods of Mendelian genetics in Japanese Waltzing mice to document inheritance of factors eliciting host resistance. Subsequent elegant analyses by Snell utilized congenic techniques to document a codominant major histocompatibility gene complex that controls transplant survival between inbred mouse strains.

The mechanism by which these genetic differences caused graft rejection was uncertain. In 1903, Jensen suggested that active immunity destroyed foreign tumor grafts, a concept affirmed by Schone's term "transplantationsimmunitat" with which Lexer concurred. Both Bashford et al. in 1908 and Russell in 1912 observed accelerated rejection of murine skin grafts, providing a scientific basis for the immunity theory. Davis in 1917, Shawan in 1919, and Williamson in 1923 suggested that the biological incompatibility between donor and recipient was due to disparate blood groups. In 1924, Holman reported that the "anaphylactic hypersensitivity" induced by skin allografts was specifically directed toward repeat donor but not third-party tissue transplants.

An alternate hypothesis of local graft rejection emerged in contradistinction to the systemic immunity theory. Ehrlich's 1906 "athrepsia" theory used a nutritional basis to explain the results of zig-zag transplants between allogeneic and autologous hosts: after eight days of residence on an allogeneic host, grafts were only viable if transplanted back to their original donors. These findings were interpreted to document that after eight days grafts require a fresh nutrient supply only provided by the "self" environment. Because Leo Loeb failed to use the same donor for experiments testing the survival of repeat grafts, he never observed accelerated rejection and thus espoused a local rejection theory based upon "individuality differentials." A foreign host's chemistry failed to provide the proper "fit" (or nutrient environment) complementary to the unique template of donor tissue. Upon this stage of controversy came Peter Medawar's carefully designed, stringently controlled experiments. Kindled by Tom Gibson's observations that repeat donor skin grafts in humans were rejected more quickly than the initial ones, Medawar (89, 90) documented in rabbits that transplantation induces systemic, specific "active immunization."

Although as early as 1910 DaFano observed large numbers of lymphocytes in rejected allografts, in 1951 Arnold Rich could still say: "There are numerous



reasons . . . for believing that lymphocytes play a role of importance in acquired resistance, though the precise manner in which they act is still obscure, chiefly because so little is known about the function of these cells.” In contradistinction, rapid advances in the understanding of antibodies began with Woglom’s documentation of humoral mediators of tumor resistance in 1933, followed by chemical characterization of these unique serum constituents by Tiselius et al. Within two decades antibodies were quantitated by Coons’ fluorescence, and Kabat’s hapten inhibition methods. Porter and Edelman described the heavy- and light-chain structure of antibody molecules; Kunkel et al., their uniquely reactive sites, idiotypes; Jerne, idiotypic-anti-idiotypic immunoregulation; and Tonegawa and colleagues, gene arrangements producing immunoglobulin specificity. The importance of humoral components of the host response was underscored by Williams and Hume and their colleagues, as well as by Kissmeyer-Nielsen et al., who described the destructive effects of preformed cytotoxic antibodies on allografts. While crossmatching techniques to detect cytotoxic antibodies have significantly reduced the incidence of this most pernicious hyperacute rejection, humoral mediators of acute and chronic vascular injuries remain unclear.

In addition, molecular understanding of cell-mediated resistance, a prime mover in allorejection, remains incomplete. The transfer of delayed hypersensitivity by immune cells was demonstrated in 1945 by Chase, who recognized the need for inbred animals to avert allorejection of the adoptive effectors. Using similar methods, cells were shown to carry immunologic memory toward foreign tumor grafts by Mitchison and toward allografts by Billingham et al. The critical role of the thymus was described by J.F.A.P. Miller: thymectomy of newborn animals prevented the development of cellular immunity, and lymphocyte repopulation following irradiation required the presence of the thymus. Thus, the mediators of cellular resistance became known as T cells because of their mandatory maturation in the thymus.

Although distinctive surface antigens on different lymphocyte subpopulations were postulated to explain the inconsistent reactivities of polyclonal antilymphocyte sera, identification and isolation of T cell subsets required development of a panel of monoclonal antibodies by Kung et al., using Kohler and Milstein’s hybridoma technology. A physiologic relation between T cell subsets was proposed in the two-signal hypothesis of Lafferty and Cunningham: a first humoral signal generated by antigen-presenting elements to helper-inducer T cells is transduced as a second humoral signal from these cells to effector T (and B) elements. However, time has eroded an absolute correlation between CD4 or CD8 surface phenotype and T cell functional activities—namely, T and B cell collaboration, production of lymphokine humoral mediators, and direct target killing. Indeed, the mechanisms of T cell triggering, transducing, and effecting cellular resistance remain important current research objectives.

### **Molecular Basis of Alloimmunity**

*The histocompatibility antigens.* During the past three decades, chemical techniques have elucidated the molecular basis of biologic individuality. The human major histo-



compatibility complex (HLA), including class I, class II, and other ill-defined loci encoding antigenic products, spans 3.5 million DNA base pairs—2% of the genetic material in autosomal chromosome 6. Class I and class II glycoproteins serve as scaffolds for presentation of antigens in accord with the T cell restriction hypothesis of Zinkernagel and Doherty: T cells recognize foreign markers only when presented with histocompatibility antigen. This function explains the relation of these glycoproteins to immunoresponsiveness originally noted by McDevitt and Tyan. Second, and possibly coincident to their first function, these markers trigger alloimmunity. Initial hypotheses of a lipid or carbohydrate nature of the antigenic epitopes that determine transplantation polymorphism were disproved by the demonstration that the immunogenic materials extracted with sonic energy display the buoyant density of protein. Transplantation polymorphism is due to peptide sequence differences: glycoprotein antigens purified from histoincompatible hosts displayed distinctive amino acid compositions and unique peptides on two-dimensional maps.

Class I (HLA-A,B,C) genes encode polymorphic heavy peptide chains noncovalently bound to an invariant 99 amino acid  $\beta_2$  microglobulin stipulated by chromosome 15. Although class I products are normally expressed on all nucleated cells to present antigenic peptides to CD8 cells, thereby triggering cytotoxic activity, these antigens are not essential for survival. Transmembrane class I glycoprotein heavy chains include distinctive extracellular, intramembrane, and intracellular portions. In contradistinction to the regions of conserved amino acid sequences, namely the TcR binding sites of the  $\alpha_1$  and the CD8 coreceptor site of the  $\alpha_3$  domains, papain-extracted HLA-A2 antigens show polymorphic regions in the extracellular  $\alpha_1$  and  $\alpha_2$  domains. The  $\alpha_1$  residues 9-74 and  $\alpha_2$  residues 95-156 each display 8  $\alpha$ -helical turns and 4  $\beta$ -pleated sheets forming a peptide-binding cleft. Antigenic recognition pockets along the cleft bind side chains or ends of peptides at  $\alpha_1$  positions 74 (residues 74, 97, 116) and 45 (residues 24, 26, 34, 45, 67). Peptide binding "instructs" the class I histocompatibility antigen to fold into a conformation necessary to bind  $\beta_2$ m. Indeed most surface antigen bears bound peptide, even when it is a "self"-constituent—namely, modestly polymorphic products of an MHC-linked gene, or, more probably, incidental "stand-ins." Malinger and Bevan propose that the high frequency of alloreactive CD8-positive T cells includes immune elements recognizing transplantation polymorphism plus those reactive toward the associated cleft-borne, foreign- or self-peptide antigen. The allospecific polymorphism corresponds to the peptide binding sites of the  $\alpha_1$  and  $\alpha_2$  domains in a "boomerang" distribution—namely, running along the inner edges of the helices and subadjacent  $\beta$  sheets of a variety of class I A, B, and C markers, suggesting that this biochemical individuality confers species variation for the recognition of foreign peptides. Class II (HLA-DR, DP, DQ) and 13 molecular chains each bear one peptide-binding and one immunoglobulin domain in three-dimensional motifs similar to those of class I antigens. The  $\alpha_1$  and  $\beta_1$  domains on the outer surface and sides of the antigen-presenting cleft trigger CD4 cells, thereby inducing and amplifying the immune response.

The assembly of histocompatibility antigen-peptide complexes is vulnerable to chemical manipulation. Class I (and, to a lesser extent, class II) antigenic markers uti-



lize an endogenous assembly pathway. A chaperonin-like protein, possibly the heat-shock protein HSP70, transfers peptides, which have been either degraded within or experimentally introduced into the cytoplasm, to class I markers synthesized in the endoplasmic reticulum. Antigenic structure determines the efficiency of this process: Townsend found that influenza virus nucleoprotein molecules were assembled more readily after modification of the N-terminal amino acid. Detailed structure-function correlations have emerged from binding analyses using mutant HLA-A2 molecules with pure virus peptides. In the next step, class I peptide complexes are transported from the endoplasmic reticulum to the Golgi apparatus, a phase vulnerable to Brefeldin A. On the other hand, an exogenous assembly pathway links class II antigens to antigenic peptides generated after endocytosis and digestion of antigen in endosomes by cathepsins B and D, a process sensitive to weak bases such as chloroquine. The class II MHC markers synthesized intracellularly are associated with, but not inactivated by, an invariant chain, which is proteolytically cleaved after peptide association and before surface expression.

One strategy to avoid rejection seeks to match the polymorphic transplantation antigens present on donor and recipient. Human leukocyte antigen (HLA) typing defines these determinants with polyclonal antibodies. However, this system shows extensive crossreactivity attributed to the sharing by different antigens of “public” (modestly polymorphic) epitopes. In addition, modern chemical techniques reveal that even the purportedly distinctive HLA antigens display micropolymorphism—for example, six subtypes are easily distinguished among patients bearing HLA-B27. Thus recipients of “the same” HLA-type as the allograft donor are not identical matches, but only part of an antigenic family, the members of which can discriminate foreign epitopes within common determinants on each other’s tissues. Thus the HLA system oversimplifies biochemical individuality. The statement by Fuller et al. that “matching in organ transplantation tells us little about the true degree of compatibility” has been amply confirmed in clinical practice. Although monoclonal antibodies and DNA sequencing techniques may permit “epitope matching” of HLA subgroups, the tremendous polymorphism makes “perfect matches” even more unlikely, as Medawar concluded three decades ago. Of greater social concern is the likelihood that a shift to epitope matching will aggravate the Caucasian preference of the present system, since subgroups of the HLA markers commonly represented in minority groups are poorly understood. Alternatively, the failure of the existent HLA system to assure transplant success may be due to the contribution(s) of at least some of the other 35 genes in the major histocompatibility complex, including HLA-E, F, and G.

*The T cell receptor, the second major component.* The two forms of TcR include  $\alpha/\beta$  dimers on the majority of mature peripheral blood T cells, and  $\gamma/\delta$  dimers on a smaller number of lymphocytes, many of which do not appear to be classical T cells. The  $\alpha\beta\gamma\delta$  polypeptide chains share similar 110 amino acid sequences that are characteristic of the immunoglobulin superfamily and intrinsically complementary to HLA antigens. The chains bear extracellular membrane-distal variable, and membrane-proximal constant, domains that are anchored via transmembrane portions to short cytoplasmic tails. TcR diversity is generated by three mechanisms: germline variation,



somatic mutation, and a strictly regulated, site-specific, recombination process that links distinct variable, diversity, and joining gene segments. A single, shared recombinase, which is found only in immature B and T cells, assembles unique structures by randomly rearranging TcR variable region genes. The recombinase complex performs three steps: cleaving a gene segment flanked by a specific recognition sequence using a site-specific endonucleolytic mechanism, catalyzing nucleotide addition or removal at the DNA ends, and ligating the modified segments.

The binding of peptide-histocompatibility antigen assembly to clonotypic TcR is solidified by three sets of independent, accessory receptor/ligand interactions: CD8 markers to class I or CD4 to class II MHC molecules; leukocyte function associated antigen-1 (LFA-1) to intercellular adhesion molecules ICAM-1 or ICAM-2, two members of the immunoglobulin supergene family; and CD2 (LFA-2), the sheep erythrocyte receptor, to LFA-3.

*Alloimmune signal transduction.* There is only fragmentary biochemical knowledge concerning the cytoplasmic pathways that transduce the membrane signal. Foreign transplantation antigen binding to host TcR induces CD3 complex perturbation via noncovalent salt bridges. The CD3 complex, which contains five ( $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\eta$ ,  $\zeta$ ) peptide products of duplicated immunoglobulin genes, displays two motifs, each linked to a distinct T lymphocyte activation pathway: 90% as  $\gamma$ ,  $\delta$ ,  $\epsilon$  chains with  $\zeta$ ,  $\zeta$  homodimers; the rest as  $\gamma$ ,  $\delta$ ,  $\epsilon$  chains with  $\eta$ - $\zeta$  heterodimers. Ligand-occupied  $\eta$ - $\zeta$  receptors trigger a GTP-dependent protein that activates phosphoinositol phospholipase C. This enzyme catalyzes hydrolysis of phospho-inositol-diphosphate ( $\text{PIP}_2$ ) to inositol 1, 4, 5-triphosphate, which releases  $\text{Ca}^{2+}$  from intracellular endoplasmic reticulum storage sites (in the fashion of calcium ionophores), and to diacylglycerol (DAG), which activates protein kinase C (PKC), in the fashion of phorbol esters. This pathway, which may be affected by the CD-5 surface marker, produces multiple secondary effects: generating arachidonic acid as a lipoxygenase substrate, opening voltage-insensitive  $\text{Ca}^{2+}$  channels, and activating PKC catalysis of phosphorylation, including CD3  $\lambda$  and  $\delta$  chains.

In contrast,  $\zeta$ - $\zeta$  homodimers couple membrane events to the T cell-specific, tyrosine protein kinase, isozyme pp56<sup>lck</sup>. Once the CD4 or CD8 coreceptor crosslinks to invariant  $\alpha 3$  domains of histocompatibility antigens, pp56<sup>lck</sup> at the inner surface of the plasma membrane is dephosphorylated by the cytoplasmic tail of the CD45 (T200) membrane-bound phosphatase. Then pp56<sup>lck</sup> is autophosphorylated at a different position to generate the active enzyme that phosphorylates the CD3  $\zeta$  chain, thereby triggering a poorly understood cytoplasmic pathway that is independent of  $\text{PIP}_2$ , DAG, and PKC.

TcR-CD3 complex activation is generally accompanied by, but not exclusively dependent upon, increased intracellular  $\text{Ca}^{2+}$ , which is triggered, for example, by Interleukin-1 and/or Interleukin-6. The calcium signal, which by itself is tolerogenic, stimulates DAG and PKC species distinct from the  $\eta\zeta$  pathway, as well as  $\text{Ca}^{2+}$ , calmodulin-, or cyclic nucleotide-dependent, protein kinases and phospholipase C activities. Treatment with a combination of calcium ionophore plus PKC activator/tumor promoter mimics the alloantigen signal. Additional surface markers



are crosslinked during TcR-CD3 complex activation in mature lymphocytes—namely, the CD45 phosphatase, and a nonpolymorphic 50 kDa CD2 protein. TcR/CD3 membrane triggered calcium-dependent activation events are also linked to rotarase enzymes that alter protein conformation from extended to globular structures, including cis-trans peptidyl-prolyl isomerases.

Nuclear activation after TcR/CD3 stimulation depends upon the appearance of inducible enhancer binding proteins, resultant from enzymatic generation, conformational changes, or protein synthesis. These regulatory proteins cooperatively bind enhancer sites on DNA, thereby attracting RNA polymerase II activity, which is necessary for de novo transcription of over 70 gene products associated with the T cell response. The majority of these genes are cycloheximide resistant—namely, their transcription does not depend upon preliminary protein synthesis; in contradistinction, the lesser group of cyclohexamide-sensitive, protein synthesis-dependent genes act at the later stages immediately prior to or following the initiation of cell division. The earliest antigen-induced (cyclosporine-resistant) genes during the  $G_0$ - $G_1$  transition of T cell activation are *c-fos*, which encodes a 55 kDa nuclear DNA-binding phosphoprotein Fos, and *c-myc*, which produces a nuclear protein involved in DNA synthesis and critical for entry into S phase. The *c-jun* protooncogene is up-regulated upon IL-1 stimulation to express a 39 kDa regulator, activation protein -1 (AP-1), which binds Fos to form one of a system of four transcriptional regulators of IL-2 synthesis. These enhancers, which lie 5' to the IL-2 gene, probably represent paradigms of regulatory motifs controlling other critical growth events. One CsA-sensitive regulatory protein, nuclear factor of activated T cells (NFAT-1), is generated after TcR-CD3 (but not PKC/phorbol ester) triggering and requires protein and RNA synthesis. The other two enhancer sites include the ubiquitous octamer binding protein, Oct-1 and NF- $\kappa$ B (see below).

Alternate activation pathways mediated by cytokine receptors or CD28 surface markers provide signals qualitatively different from TcR-CD3 stimulation. The CD28 pathway is an alternative to CD2-linkage that uniquely activates a GMP-dependent, CsA-resistant, protein kinase enhancing lymphokine mRNA transcription. Among the cytokine pathways, the best understood involves IL-2/IL-2R. Individual activation stimuli, including PKC, calcium ionophores, antigen-MHC, anti-TcR-CD3 antibodies, or IL-2/IL-2R $\beta$  (p75) chain binding induce IL-2R $\alpha$  (p55) chain transcription to assemble highly avid  $\alpha/\beta$  chain IL-2R complexes. A major regulatory protein of this pathway is nuclear factor- $\kappa$ B (NF- $\kappa$ B), which is similar to the enhancer controlling constitutive expression of Ig  $\kappa$  light chain genes in B cells. After phosphorylation of its inhibitory protein by PKC, NF- $\kappa$ B is activated, dimerized, and translocated to the nucleus to bind homologous DNA sequence elements. IL-2R $\alpha$  chain expression is also controlled by multiple enhancers. IL-2R-mediated protein events, which occur during the  $G_1$  phase and are CsA-resistant, include IL-2 internalization and binding to the nucleus, protein kinase activation, and up-regulated lipoxygenase activity. IL-2R triggering leads to transcription of *c-myc*, and uniquely of *c-myb*, but not of *c-fos*, protooncogenes. Another cytokine IL-6 acts synergistically with phytohemagglutinin lectin



stimulation and independent of IL-2 and PKC to activate lymphocytes. Inhibition of the IL-2 and IL-6 pathways represents a unique mode of action of rapamycin.

Both TcR-CD3 and cytokine stimulation pathways increase ornithine decarboxylase transcription during  $G_1$ . This activity represents the rate limiting factor for the synthesis of the polyamines putrescine, spermidine, and spermine-organic cations required for many growth-related functions of nucleic acid and protein synthesis. Improved understanding of histocompatibility antigen surface recognition systems and intermediate intracellular signal transduction pathways inducing gene expression should open new horizons to sabotage allorejection.

### **Immunosuppression Timeline**

The four stages of the immunosuppression timeline parallel developments in immunology. The first stage, which spanned seven decades, harnessed radiation or chemical agents to nonselectively destroy all rapidly dividing cells. In 1908, Benjamin and Sluka documented that total-body irradiation impairs the capacity of rabbits to produce precipitating antibodies toward bovine serum. In 1914, Murphy showed irradiation mitigated the development of immunity toward tumor allografts. In 1915, Hektoen concluded that lymphocytes produce antibodies, since irradiation both depleted lymphoid structures and impaired humoral immune responses. The unique radiosensitivity of lymphocytes was confirmed by the Taliaferros in 1951. Total-body irradiation prolonged canine renal allograft survival in the work of Mannick et al. as well as of Rapaport et al., and yielded 9/25 patients with successful human kidney transplants beyond two years in Hamburger's series. Although the total-lymphoid irradiation method of Kaplan as applied in renal transplantation by Strober and colleagues and the wide field method of Myburgh have refined the technique, most transplant practitioners think that this modality displays a particularly "slippery slope" of immunosuppression—namely, a propensity toward not-infrequent, slowly reversible, and rarely predictable toxic side effects accompanied by a high mortality from infection.

The pharmacologic era of immunosuppression began in 1914 when Murphy — and, two years later, Hektoen—documented the effects of the simple organic compounds benzene and toluene. In 1952 Baker prolonged allograft survival by administration of nitrogen mustards. In 1959 Schwartz and Dameshek initiated the modern era of pharmacologic immunosuppression by documenting that the antiproliferative drug 6-mercaptopurine (6-MP), which was developed by Hitchings and Elion as a competitive inhibitor of purine salvage pathways, dampened antibody production and prolonged rabbit skin allograft survival. In order to avert the susceptibility of the unshielded mercapto-group to gut hydrolysis, an imidazole derivative of 6-MP was demonstrated by Calne under Joe Murray's direction, to prolong the survival of canine renal transplants from 7.5 to 23.7 days. How well I recall the thunderous applause when Calne ended his presentation at the 1962 New York Academy of Sciences meeting by showing the azathioprine-treated dog exercising the prerogative conferred by his successful transplant!



Our members Zukoski and Lee in conjunction with Hume not only confirmed the activity of azathioprine, but also documented the benefit of antiinflammatory corticosteroid therapy—first in the canine model and then in humans—thereby extending Krohn's observations on rabbit skin allografts. For the dozen years 1966 to 1978, "conventional" therapy was the double-drug azathioprine-prednisone combination. Its "slippery slope," although not as steep as radiation, not infrequently caused despair over bone marrow aplasia, gastrointestinal visceral perforations, and/or overwhelming fungal infections. Is it any wonder that members of this society who were initiated into clinical transplantation using double-drug therapy now have great ambivalence in prescribing these toxic drugs that created the "slippery slope" that frequently defied our technical successes?

Two attempts to improve the immunosuppressive efficacy of azathioprine-prednisone were unsuccessful: Godfrey and Salaman documented that local graft irradiation introduced by Wolf et al. actually reduced renal allograft survival. Thoracic duct drainage, originally constructed in rats by Woodruff and Anderson, based upon Gowans' description of the critical role of this avenue in lymphocyte recirculation, was applied to man by Franksson and Bloomstrand in Scandinavia, as well as by many of our members: Newton, Richie and colleagues, Tilney et al., Fish, Fitts et al., and Starzl et al. However, thoracic duct drainage showed an absolute requirement for pre-transplant initiation, was frequently difficult to establish and maintain, and had only transient effects.

The second stage in the immunosuppression timeline focused the attack upon T cells. Antilymphocyte sera produced in 1899 by Metchnikoff were reapplied 70 years later in rodent models by Russell and Monaco and by Levey and Medawar. Rapid translation to the clinical arena by Starzl and Marchioro, with subsequent refinements by Najarian and Simmons, led to powerful polyclonal reagents of high immunosuppressive activity. Although the broad degree of T cell inactivation improved the clinical efficacy, the wide spectrum of susceptible, nonspecific host-resistance elements not infrequently exacerbated the dangerous incline of the double-drug slope, although clinical acumen in its application increased the overall graft success rate.

Monoclonal antibody technology offers the possibility of selective reagents not only to dissect, but also to neutralize, cells bearing specific surface markers. Fortunately, recent work portends advances from the relatively nonspecific bludgeon OKT3, an IgG<sub>2a</sub> monoclonal antibody pioneered by our member Cosimi et al. Although useful, it has been associated with frequent, occasionally serious, and even lethal adverse reactions due to cytokine release and to a remarkable propensity for lymphoma development when administered in conjunction with prophylactic equine antilymphocyte globulin, azathioprine, cyclosporine, and prednisone. Indeed, one must question whether there is any real indication for OKT3 use, since it certainly has not shown superior results to the previous polyclonal reagents and since there is not infrequent production of antimouse antibody that will prevent patients from receiving second-generation murine monoclonal antibodies. Four new selective reagents include the IgG<sub>2b</sub> anti-T-cell receptor reagent, produced by Kurrle and used in Europe by Land and colleagues and by Wonigkeit and Pichlmayer and in the U.S. by our



Houston group. Because it may react with a common epitope on the TcR, this monoclonal antibody may interfere with T cell triggering, thereby deviating the antidonator response toward an ineffective, anergic pathway. Anti-CD4 antibodies that have been used in animal models, singly and in combinations, are being prepared for clinical trials. Anti-IL-2 receptor reagents that may selectively destroy activated cells have been administered per se by Cantarovich et al. and by Soulillou et al. in France, and in the U.S. by our member Kirkman, as well as in immunoconjugated form. Chimeric human Fc-mouse F(ab2)' monoclonal antibodies with anti-CD 7 specificity have recently begun clinical trials. Although elimination of the murine Fc piece reduces, it does not abrogate the possibility of patient antibody production toward variable-region determinants, an antiidiotypic response that vitiates the possibility of repeat treatment. In addition, the high incidence of vascular complications (3 of 15 patients) producing graft loss suggests a greater propensity of Fc-receptor bearing elements to mediate reactions toward the human Fc pieces on the chimeric human/mouse anti-CD7 antibody.

The third stage of immunosuppressive therapy utilizes agents that inhibit cells regulating the maturation of alloreactive immune elements. The prototype cyclosporine was isolated in 1969 from *Tolypocladium inflatum Gams*, a member of the *Fungi imperfecti*, contained in soil samples derived from Hardanger Vidda, a high treeless plain in southern Norway. Although it had little promise as an antibiotic, Jean-Francois Borel resurrected cyclosporine as a potent immunosuppressive agent in transplantation and autoimmune disease models. David White et al. documented that short-term administration markedly prolonged allograft survival in animals. On the one hand, cyclosporine inhibits lymphokine synthesis and cytotoxic T cell generation; on the other hand, it spares suppressor T cell maturation. Although cyclosporine displays an amazingly low immunosuppressive hazard and a secure path on the "slippery slope" of therapy, its array of pleiotropic nonimmunologic nephrotoxic side effects prevents administration of sufficient doses to fully exploit its potential in transplantation. However, cyclosporine has provided the major, much-needed impetus for the transplant enterprise. It has kindled the development of new immunosuppressive agents: pharmacologics such as deoxyspergualin, mycophenolic acid analogs, and the lipophilic carboxy-cyclic actinomycete macrolides FK506 rapamycin, and molecular mimics such as cytokine receptor analogs.

Future rational use of immunosuppressive agents will depend upon elucidating their individual molecular targets and pharmacologic interactions. At the level of the surface membrane, the molecular targets are presumed from the putative specificity of each monoclonal antibody. However, their individual mechanism of action may be more complex than simple receptor "blindfolding," endocytosis, or shedding. At the level of membrane transduction to nuclear activation, corticosteroids inhibit m-RNA transcription (such as IL-1 $\beta$ ) via specific DNA steroid response elements. Cyclosporine and FK506 probably inhibit related regulatory DNA-binding proteins, which are necessary for enhanced transcription of T cell activation genes. While peptidyl prolyl cis-trans isomerases bind cyclosporine, FK506, and/or rapamycin, increasing data suggest they are not the exclusive target of drug action. Finally, aza-



thioprine and mycophenolic acids prevent DNA synthesis by inhibiting enzymes of the purine salvage pathways. It is not unreasonable to expect that by the end of this decade, synergistic immunosuppressive drug combinations will produce negative regulation of T cells with minimal toxic side effects, akin to the principles widely applied in cancer chemotherapy. However, this impenetrable shield over the specific immune system almost inevitably engenders risks of neoplastic and infectious diseases.

### Tolerance Timeline

The ultimate immunosuppressive therapy selectively depresses host reactivity toward foreign donor antigens by inducing immunologic tolerance: specific donor, but not third-party, grafts survive without the need for chronic immunosuppression. The tolerance concept originated with the observation that fetal hosts exposed to foreign cells lost their immune responses to donor antigens. In 1914 John Murphy reported the outgrowth of Rous chicken sarcoma cells upon the chorioallantoic membranes of duck or pigeon egg embryos, but not upon implantation into adults. The unresponsive state of the embryo was reversed by inoculation of adult chicken lymphoid cells, particularly small lymphocytes. Demonstrating that the synchorial placenta of freemartin, nonidentical calf twins described by Lillie permitted blood exchange, Ray Owen proposed that mutual tolerance was acquired by fetal exposure to “nonself” constituents. Billingham et al. extended Murphy’s observations in inbred mice, Hasek verified the concept with membrane bridges between chicken egg embryos, and Woodruff confirmed the state in newborn rats.

Burnet then replaced his earlier “self-marker” theory, which suggested that host cells bore a marker that identified them as “self” and thereby protected them against attack by lymphocytes, with a clonal selection theory: The immune system is purged of “self” (auto-) reactive lymphoid clones during ontogeny. The “central” thymic purging process includes two steps: positive selection of T cells recognizing antigen in a context of “self”-MHC products, and negative selection (deletion) of T cells reactive with body constituents. Similarly, autoreactive immature B cells are inactivated in the bone marrow by deletion. Kappler et al. showed that transgenic mice, the bone marrow-derived cells of which synthesize the I-E antigen, which was not normally expressed in those hosts, only displayed specific amino acid sequences in the variable portion of the  $\beta$  chain ( $V\beta$ ) of the TcR on lymphocytes in the thymus—and not on peripheral T cells. This observation elegantly supports the concept of clonal deletion in the thymus. A therapeutic extension of this hypothesis achieved remission of experimental allergic encephalomyelitis by depleting cells bearing TcR with specific  $V\beta$  sequences. Thus, a “natural” mechanism of self-tolerance is inactivation of immature elements upon contact with antigen in a central lymphoid organ. These observations suggest that the continuous presence of donor “non-self” antigen in the central immune compartments of the recipient maintains a balanced state of host-versus-graft and graft-versus-host tolerance.

Chimerism is not a feasible clinical strategy. It demands “debulking” the immune system to provide “space” for the second population, deplete peripheral lymphoid



cells, and recreate the "pristine" fetal state. In animal models, chimerism has been established after total-body or total-lymphoid irradiation (TLI), particularly in combination with donor or Fl bone marrow cells. However, adult allogeneic T cells in the bone marrow pose the hazard of graft-versus-host disease unless "purged" from the donor inoculum with anti-theta 1.2 antisera or by use of nu/nu (T cell-deficient) donors. Hematopoietic chimerism seeds donor-type dendritic cells into the thymus, thereby negatively selecting (removing) donor reactive T cells. Thus, hosts displaying the "chimeric" type of tolerance show either an absence or a changed repertoire of donor-reactive cells, in some instances associated with increased numbers of  $\gamma\delta$  TcR+ elements.

Can tolerance be produced without the bludgeon of "debulking" and/or the reversion to the pristine fetal state? The "horror autotoxicus" concept of Ehrlich postulated tolerance to be a natural process within the immune repertoire, suggesting that lymphocytes could be rendered tolerant even after they had left the thymus. In the 1920s Felton showed that administration of high doses of slowly metabolized, pneumococcal polysaccharide induced unresponsiveness, rather than immunity, upon rechallenge with antigen. A decade later Sulzburger as well as Landsteiner and Chase found per os administration, rather than percutaneous application, of antigen evoked unresponsiveness rather than delayed-type hypersensitivity. Martinez and colleagues tolerized murine hosts toward allogeneic skin grafts with multiple intravenous injections of F<sub>1</sub> cells. This "peripheral" form of tolerance occurs in spite of the presence of T cells that have the potential to recognize alloantigen. Transgenic models elegantly document the phenomenon: fertilized mouse eggs microinjected with constructed restriction enzyme fragments encoding foreign alloantigens are transferred into pseudopregnant Swiss mice to mature into native-type animals bearing unique markers. In spite of foreign I-E class II molecules restricted in expression to the acinar pancreas and kidney, or to pancreatic islet beta cells, these tissues do not elicit rejection responses. T-helper cells react *in vitro* to the alloantigen, but are presumably inactive *in vivo* due to a reduced affinity or altered activation capacity for the foreign antigen. Adoptive transfer of T cells from normal virgin hosts kills the transgenic cells bearing foreign alloantigen.

Three mechanisms may explain post-thymic "peripheral" unresponsiveness: "veto" cell generation, T cell anergy and/or suppressor cell action. "Veto" elements possibly bearing a special form of donor antigen inactivate precursor, but not mature effector, alloreactive cytotoxic T cells, in a fashion resistant to exogenous costimulatory factors. While "veto" activity was not documented in a minor histocompatibility system, Thomas et al. reported that this mechanism mediates allograft survival in hosts conditioned with antilymphocyte serum and donor bone marrow inocula, and Martin and Miller as well as Van Twuyver et al. implicate it in the generation of unresponsiveness after pretransplant allogeneic lymphocyte transfusions.

Anergy represents an unresponsive state of antigen-reactive lymphocytes. Bretscher and Cohen proposed that this unresponsiveness is due to a failure of helper-inducer T cells to produce the appropriate second humoral activation signal. T-helper cells recognize alloantigen, but neither proliferate nor secrete IL-2, addition of which



reverses the anergy. On the one hand, anergy may result from ineffective stimulation, for example following treatment with immunogens modified by crosslinking fixation or by planar membrane array. On the other hand, it can be produced by direct contact of antigen with immature T or B cells without suitable presentation. The critical role of the helper cell second signal to B elements was documented by the failure of B cells expressing the transgene-encoded, membrane immunoglobulin to secrete antibody upon confrontation with the homologous chicken lysozyme epitope. This hyporesponsive state was associated with decreased surface membrane IgM (but continued membrane IgD) expression—a not uncommon phenotype among normal spleen cells, possibly representing anergic B elements.

Some rodent and/or canine tolerance models abrogate helper-inducer function by nonspecific bludgeons: massive doses of single or multiple monoclonal antibodies in combination with cyclosporine, or, alternatively, large cyclosporine doses alone. However, the staggering morbidity of strategies based solely upon nonselective attack upon T-helper elements is unacceptable: such intense immunosuppression clearly provides a setting for infection.

Gershon and Konda documented a third “infectious” tolerance mechanism based upon the capacity of lymphoid “suppressor” cells to adoptively transfer unresponsiveness. One theory proposes that suppression is mediated by a distinct cell lineage—namely, one CD4<sup>+</sup> inducer and two MHC-restricted CD8<sup>+</sup> effectors—as proposed initially by Dorf and Benacerraf and translated to rat alloimmune reactions by Hutchinson et al. Utilizing *in vitro* allostimulation of human lymphocytes, Engelman and colleagues described populations of distinct phenotypes: an “inducer” CD4 Leu 8 population that activates effector CD8 Leu 9.3 suppressor cells—possibly similar to those found in TLI-conditioned, donor-unresponsive, long-term renal allograft recipients. An alternate theory suggests that suppressor activity does not reflect a distinct lineage, but rather a response within the differentiation repertoire of all cells.

Suppressor activity has been implicated in seven tolerance models: animals rendered neonatally tolerant to class II MHC antigens show a higher frequency of tolerogen-reactive lymphocytes than normal mice, yet their cells transfer an unresponsive state to naive mice but mediate neither cytotoxicity nor delayed-type hypersensitivity. TLI treatment induces both donor-specific and nonspecific suppressor components. “Debulking” strategies of tolerance induction using cyclophosphamide to produce clone stripping show initial deletion evolve to suppressor mechanisms. Suppressor cells effect the unresponsiveness produced by ALS combined with bone marrow, as well as by high-dose cyclosporine treatment, particularly in combination with extracted antigen. Finally, suppressor T cells—possibly of the CD4<sup>+</sup> phenotype—mediate classic humoral unresponsiveness associated with “enhancing” antibody.

Suppressor cells may act via unique “processed” donor antigen, production of humoral inhibitors, or antiidiotypic mechanisms eliminating cells bearing donor-specific TcR. Antiidiotypic,  $\alpha/\beta$  TcR<sup>+</sup> CD3<sup>+</sup> CD8<sup>+</sup> cells specifically proliferate upon confrontation with allo- or antigen-specific TcR. Batchelor et al. demonstrated that CD8<sup>+</sup> spleen cells in rats bearing long-term allografts adoptively transferred *in vivo* suppres-



sion, and proliferated in vitro upon confrontation with syngeneic lymphocytes bearing the anti-donor TcR idiotypic.

In vitro assays may differentiate deletion or veto from anergy or suppressor mechanisms in unresponsive individuals. The latter but not the former two phenomena are vanquished by in vitro mitogen activation of, or exogenous cytokine addition to, cytotoxic lymphocyte precursor frequency assays (f[CTLp]). For example, the low anti-donor f(CTLp) in one long-term allograft recipient was reconstituted to a fully expressed  $\alpha/\beta$  and  $\gamma/\delta$  TcR repertoire upon in vitro activation. Also, f(CTLp) assays suggest a contribution of suppressor cells if there are biphasic profiles showing paradoxically reduced cytotoxic responses at high cell numbers. Although the f(CTLp) assay proffers a ready tool to predict and monitor alloreactivity, there are two areas of concern: First, the genetic and environmental variation in the frequency and specificity of reactivity among healthy volunteers and between mouse strains is both considerable and unexplained. Second, two congenic rat strains have been shown to display identical f(CTLp) values, in spite of widely disparate donor allograft survivals in vivo.

The mixed lymphocyte reaction, an in vitro model of allojection, may show proliferation of cells from hosts displaying the anergic form of tolerance—namely neonatally class II-tolerant animals as well as successful renal and bone marrow allograft recipients. Suppressor mechanisms may be documented in vitro using post-transplant recipient cells to dampen in vitro antidonor MLR and/or CML responses by the patient's own pretransplant lymphocytes (the "three cell assay"). Because in vitro activities correlate poorly with in vivo events, systemic transfer experiments remain the gold standard of "suppressor" activity. Thus, the past three decades have witnessed the progression of tolerance investigations from intact hosts to in vivo transgenic and in vitro cellular models. Future dissection of tolerance mechanisms will undoubtedly rely upon incisive molecular technologies.

*Extracted antigens as tolerogens.* One approach to induce tolerance disrupts allorecognition of foreign tissue at the antigen level. Reduction of surface antigen content by somatic point mutation, inhibition of a regulatory protein, or insertion of a repressor homeobox gene sequence protects targets of alloimmune reactions, but has only remote clinical application. Contrariwise, manipulation of the foreign antigenic stimulus to deliver a signal that induces lymphocyte unresponsiveness rather than activation has great clinical potential. This timeline begins with Medawar's observation that pretreatment with semisoluble, crude antigenic extracts modestly prolonged the survival of donor-type murine skin grafts. He suggested that truly soluble extracts might induce tolerance, since they proffer an "unnatural" form of foreign epitope that may "deviate" the host to an ineffective immune response. Dresser had previously shown that administration of soluble monomeric, but not sedimented aggregated, gamma globulin induces antigen-specific suppression of the immune response. Weigle and colleagues found that the rapid and durable development of peripheral T cell tolerance to monomer was due in part to anergy from defective triggering of IL-1 production. Some investigators suspect, but others doubt, the participation of suppressor cells in the phenomenon.

On the one hand, administration of bone marrow or other intact cells, platelets,



subcellular membranes, or transfected cells bearing foreign class II MHC alloantigen induces unresponsiveness. On the other hand, extracted antigens have numerous potential advantages for this purpose, since they are less likely to carry unacceptable, unpredictable risks of sensitization; unable to replicate, therefore posing no risk of graft-versus-host disease; molecularly well-defined, with only a limited array of epitopes; likely to display altered pharmacokinetic or immunologic metabolism possibly bypassing tissue or nodal structures; and susceptible to chemical modification to cover immunogenic and/or reveal cryptic suppressogenic epitopes.

Medawar's prophecy has not been entirely fulfilled: pretreatment with putatively soluble materials prepared by low intensity sonication, by salt extraction, by detergent dispersion, or by papain hydrolysis produced only modest prolongation of allograft survival. Large amounts of detergent-stabilized, class I protein micelles only prolonged rat allograft survival when administered one week before, but not at the time of, transplantation. An unequivocally soluble, cytosolic form of class I antigen extracted from rat, but also present in human liver cells, which lacks the hydrophobic transmembrane domain because of alternative mRNA splicing of exon 5, induced only modest prolongation of survival in some, and had no effect in other trials. Indeed, a 200 ng/ml serum concentration of foreign, soluble, truncated class I antigen endowed by transgenic methods did not by itself achieve allotolerance. These extracted materials bear immunogenic activity: they induce accelerated rejection of donor allografts *in vivo*, and both detergent-dispersed and genetically engineered antigens activate T cells *in vitro*, displaying a high affinity for their TcR ( $kD = 0.1 \text{ mM}$ , 385). Thus in spite of extraction, these materials *per se* preferentially trigger T cell activation.

In order to mitigate the activation pathways, donor extract treatment has been combined with adjunctive immunosuppressive agents: namely, hydrocortisone, polyclonal antilymphocyte sera, cyclophosphamide, cyclosporine, and TLI. One injection of 3M KCl extracted antigen the day prior to transplantation combined with three cycles of three *per os* doses of cyclosporine (10 mg/kg) produced permanent survival of 40% of rat renal (but not cardiac) allografts. Repeat-donor, but not third-party, skin grafts were accepted by these unresponsive hosts. The phenomenon appeared to be mediated by antigen-specific suppressor cells documented by both systemic adoptive transfer assays and *in vitro* tests. At ten days after transplantation, host splenic suppressor elements dampened MLR and CML performances, in spite of a normal *f*(CTLp) upon limiting dilution analysis in the presence of exogenous IL-2. Because this assay did not show a biphasic pattern, there appeared to be an additional component of anergy. Multiple intravenous antigen injections combined with cyclosporine prolonged survival of cardiac allografts. TLI (1600 rads) provided more potent immunosuppression in combination with one injection of 3M KCl extract the day before transplantation. There was uniform, indefinite, donor-specific, cardiac allograft survival. The unresponsive hosts contained donor-specific, suppressor spleen cells that adoptively transferred a state of total and permanent unresponsiveness to syngeneic virgin hosts and produced biphasic *f*(CTLp) patterns.

A second approach to mitigate T cell activation seeks to present extracted antigen



under conditions suboptimal for T cell receptor stimulation or for binding by accessory coreceptors LFA-1 or CD4/CD8. Monovalent peptide fragments rather than multivalent transplantation antigens may cause occupancy, yet produce functional inactivation of T cell receptors. HLA peptides of  $\alpha$ -helical structure, particularly with a central tryptophan, bind T cells. Schneck et al. found that both  $10^{-7}$  M intact soluble class I molecules and  $10^{-4}$  M amino acid 163-174 peptides inhibited a weakly crossreactive H-2 response. Residues 61-69 of a synthetic H-2K<sup>b</sup> peptide arrayed on Ia-bearing antigen-presenting cells selectively activated helper elements. Further,  $10^{-4}$  M of a synthetic peptide mimicking amino acid residues 98113 of the HLA-A2  $\alpha_2$  domain specifically inhibited target cell recognition by CTL, in the fashion of a free hapten. In vitro CTL reactions discriminated among mutant H-2 or HLA peptides differing by only three (152, 155, and 156) amino acid residues in the  $\alpha_1$  or a similar restricted length in the  $\alpha_2$  domain. Furthermore, a naturally processed 10-15 amino acid, H-2 peptide complex extracted from the cytoplasm of antigen-presenting cells bound to T lymphocytes. These experiments suggest that peptides occupying (without crosslinking) T cell receptors potentially produce T cell inactivation. In addition to the possibility of presenting native peptides, host CTL might be subverted by introducing related, but immunologically noncrossreactive, peptides that either deviate the reactivity of existent cells bearing clonotypic receptors or lead to the assembly of competing peptide-histocompatibility antigen complexes.

A third tolerance strategy seeks to enhance suppressogenic or mask immunogenic domains of the major histocompatibility antigens. Antigenic determinants are classified as either linear (continuous) epitopes composed of 2 to 8 (average, 6) residues in the primary amino acid sequence, or discontinuous epitopes conformationally stipulated by molecular folding and side chain association. Although analyses using synthetic peptides bearing individual amino acid substitutions combined with specific monoclonal antibodies suggest the entire protein surface is potentially antigenic, T cell responses toward model antigens, including hen egg lysozyme, sperm whale myoglobin, cytochrome C, and staphylococcal nuclease are in fact directed toward only a restricted number of immunodominant epitopes. The immunodominant epitopes are readily exposed during antigen processing; crossreactive with epitopes seen during previous bacterial infections; amphipathic, firmly anchored structures, and/or avidly bound by MHC molecules in the fashion of "superantigen" complexes. Peptide analysis, as well as work using domain-shuffled molecules, suggests that allorecognition is effected by nonlinear epitopes created by conformational interactions.

Similarly, there is evidence of specialized suppressogenic molecular regions. Sercarz et al. found that amputation of the N-terminal peptide on hen egg lysozyme that by itself induced tolerance via multiple mechanisms, including suppressor cell generation and clonal inactivation, converted "nonresponder" H-2<sup>b</sup> mice to "responder" hosts toward the immunogenic, amino acid 46-61 domain. Suppressogenic epitopes separated by isoelectric focusing from immunogenic determinants within crude 3 M KCL extracts of tumor cells enhance neoplastic outgrowth. Furthermore, insertion of trinitrophenyl epitopes onto the surface of intact rodent cells modestly prolonged subsequent donor graft survival. Zhang et al. reported that peptide fragments of



bovine serum albumin bind murine antigen-specific suppressor, but not helper, T lymphocytes. Presumably molecular probes could target subtle differences in the epitope or conformational specificity of  $\alpha/\beta$  TcR formats on CD4 or CD8 suppressor versus helper/cytotoxic elements. A combination of tools, including chemical dissection overlapping synthetic peptides, x-ray crystallography, and genetic analyses by exon shuffling, may be applied to design strategies to modify the chemistry, size, and polarity of extracted transplantation antigens or their peptides.

A more incisive approach utilizes site-directed mutagenesis to prepare hybrid antigens bearing point amino acid substitutions, as probes of molecular fine structure for testing in transplant models, either via transgenic animals or as extracts of production vectors. These mutations may alter binding of agretopic residues to MHC molecules on the antigen-presenting cell, or epitopic residues to the TcR. Successful combinations of molecular modeling with site-directed mutagenesis by Roberts et al. enhanced antibody affinity, and by Good et al. produced more immunogenic *Plasmodium falciparum* circumsporozoite proteins. In fact, site-directed mutagenesis of a fragment of genomic HLA-B27 DNA at position 67 has already been shown to produce side chain size distortion in the  $\alpha_1$  domain helix, thereby reducing antibody binding. Systematic application of site-directed mutagenesis to uncover suppressogenic versus immunogenic epitopes may elucidate the microstructure of transplantation antigens and afford insights into rapid, direct, chemical methods to treat fresh cadaver donor subcellular extracts in order to obtain tolerogenic materials.

### Prospects for the Coming Decade

Just as the aforementioned confirms the scientific progress toward understanding and manipulating the biochemical basis of individuality, so will rigor in clinical investigations promote our goals: science demands it, our patients deserve it. "Clinical investigation by testimonial" in the present limelight only sabotages the transplant enterprise, at a time when our society is facing unprecedented challenges. My presidential year began in June 1989, addressing a (thankfully) unsuccessful, New York State legislative proposal that raised the specter of an additional level of governmental regulation. In fall 1989, our society commenced an initiative to rectify the inequitable financial compensation for renal transplantation. Not only has this problem existed for almost two decades, but also federal physician payment reform legislation threatens to exacerbate it. Through a consensus-building process on visit patterns, by direct administrative contact, and via written testimony, ASTS delineated many unique aspects of transplant practice. The Physicians Payment Reform Commission and the Health Care Financing Administration have now both recognized the need to develop a specific relative value scale for our procedures in relation to other surgical operations. During the present Congressional session, ASTS endorsed, but made suggestions for amendment of, the 1990 reauthorization bill for the National Transplant Act of 1984. We recommended discrete funding for demonstration projects to test new approaches to organ donation and continuation of the Organ Procurement and Transplant Network (OPTN), as well as extension of Medicare coverage of immuno-



suppressive drugs from one to three years, thereby co-terminating with federal disability benefits. In May 1990, a position paper was developed by a panel of our members in response to the proposed "Medicare Regulations for Liver Transplantation." Although we concur with the procedures and criteria for center selection, we objected to the excessively truncated proposed list of "indications" for liver transplantation. Later this week, we address the educational challenge with the first Postgraduate Course, which will instruct members and their fellows in the Excalibur of our Society—immunosuppressive therapy. It is our skill to wield this sword that distinguishes us from "uninitiated" surgeons. Through this eventful journey our new vehicle *The Chimera* has updated the membership.

These challenges wane compared with the major obstacle to our enterprise—the reduced number of organ donors. The problem is multifaceted: first, circumstances unrelated to transplantation have decreased the number of potential donors—namely, seat belt laws, reduced speed limits, cycle helmet regulations, improved trauma care, nursing shortages, handgun rules, and rigorous efforts against drunken driving. A second problem directly arises from recent events: the medical community's fear of latent AIDS infections in donors displaying "high-risk" profiles, and formal opposition to organ retrieval by members of the "pro-life" movement. Third, anecdotal information suggests increased public discomposure about the procurement system, including the ground rules for retrieval, distribution equity, and ownership of organs. Efforts to promote public attention to improve clinical successes have not been complemented by sufficient attention to reasoned public, executive, and legislative discussion of the policy implications of this technology transfer. A fourth problem has been engendered by at least two unanticipated, negative effects of the National Transplant Act. "Required request" legislation—namely the law designed to ensure that a request be tendered to every potential donor's family—has erroneously invested untrained, ambivalent paraprofessionals with the mantra of our enterprise. Has this ineptitude caused the eroding public enthusiasm evidenced by the finding that the major difference between 1989 and 1986 was an increased number of family refusals to organ donation requests? Indeed, the social forces that resist the legislative "fix" of "required request" will most certainly backlash toward "presumed consent." Another unexpected adverse aspect of the legislation has resulted from the creation of monopolistic organ procurement organizations (OPO), particularly in privatized so-called "non-profit" entities, which have distanced the transplant team from a process long recognized to depend upon interprofessional communication and trust. The unfortunate decline in organ donations during the past five years reinforces the wisdom of our intuitive, previous approach which was based upon the American tradition of independence from, rather than dependence upon, legislation. It is hoped that the rapidly deteriorating organ retrieval situation can be reversed by a systematic, rational public health approach to organ donation, based upon the knowledge and expertise of our society's members, rather than ill-founded speculations of neophyte OPO dilettantes.

Although these mechanistic issues have recently intensified the shortages, the continuing problem is that the American public (and their professional representative, the neurologic surgeon) are only "inclined," but not "committed," to organ dona-



tion. Whereas belief comes relatively easy, and true acceptance a bit harder, commitment is much rarer; and the decision to act is the most difficult of all. On the one hand, the unique social circumstances of donor death, wherein 78% of candidates are less than 45 years of age and almost all have been ill for less than 72 hours, emphasize the fragility of life and capriciousness of disease to a society that stigmatizes the ill and disadvantaged. On the other hand, both the public and health care professionals are ambivalent about the brain-death concept. Part of the problem may be semantic. Gaylin's term "neomort" conveys the sense of neonate (newly born) and mort (dead). Confusion is evident when recipients are told that organs are being kept "alive" in a donor who is "dead." The power of language is underscored by public repugnance toward an albeit fictional "bioemporium," the "Jefferson Institute" of *Coma*, a holding ward of neomorts to serve training, experimentation, and transplant needs. Transplantation may thus erroneously evoke the technologic arrogance of Dr. Frankenstein.

Although families rationalize refusal of organ donation requests based upon religious precepts, superstitions, and perceived racial or economic exploitation, I submit that fundamental cultural taboos are more likely sources of resistance to our enterprise—namely, fears about premature termination of life; subliminal coercion; infliction of additional suffering; violation of the sanctity of the body by assault, disrespect, or diabolical pollution; negation of the possibility of resurrection at the Second Coming of Jesus Christ; destruction of the soul/mind/body composite; and the corpse *per se* (and particularly its return). Our culture's traditions demand that due respect be paid to the corpse by the living, in order to ensure the speedy release and future well-being of the departed spirit, particularly during the fraught period after death and before burial.

Can payment for organs in the fashion that commercialization of blood, sperm, and even the rental ("womb space") of body parts—do anything but increase public resistance? While commercialization of organs of living unrelated persons, as practiced in several Asian countries, is generally accepted to be reprehensible, several Mephistophelian alternatives of "rewarded giving" have been recommended for cadaver donor families: direct remuneration, defraying burial expenses, providing insurance, or forgiving legacy duty. The sordid saga of anatomic donation provides a lesson. A perceived scarcity of supply, due to dissection being recognized as a punishment worse than death, was addressed by legions of body snatchers (or "resurrectionists" as they became euphemistically known), including executioners, undertakers, grave-diggers, aspiring surgical students, and eventually murderers ("burkers"), who bartered corpses for any of the aforementioned motives. The public's brittle tolerance of dissection, due to the very traditions regarding the dead and fears of their mutilation cited above, was unfortunately ridiculed by members of the medical profession as "vulgar prejudice," rather than addressed as a legitimate public ambivalence. In the same way, negative aspects muddle the positive "giving" side of organ donation, as emphasized by Youngner.

O'Flaherty distinguishes two pancultural motifs: the hunter, a person who has to experience everything physically, and the sage, one who uses mental powers to learn about other people's lives. The distinction is reminiscent of my father's adage: "He



who learns from his own experience is a wise man; he who learns from others' experiences is even wiser." The sages whisper that entrepreneurial medicine that regards organs as a commodity has no role in our enterprise. Commercialization or "rewarding" demeans the spiritual value of the act. Indeed, it creates exactly the undesired impression that the body is a token of exchange subject to commercial dealing, rather than an object worthy of respect.

The sage might reason that the failure to declare a positive act of commitment results from the vacuum in the ethical and moral fabric of what Joseph Campbell calls the demythologized American society. Myths no longer shape our lives with meaning and concern; rather, outer appearances may go so far as to overwhelm inner spiritual values. Is the lack of a shared, meaningful American mythology or imagery for the sense of "community" (as opposed to "individual") an inherent societal barrier to organ donation? Is donorship not personally meaningful to families because populist thought views death from the perspective of an individual rather than of a humanity which is joined in nature as well as in culture? Altruistic donorship ratifies the bond between the individual and the human race; it confirms that one has been initiated into the purpose and meaning of life. It recognizes adverse events as being in accord with nature, as representing a challenge to unleash one's spiritual potential. The donation act in the setting of death affirms a life lived within the harmony of society; it recognizes donation as a procedure in accord with the way of nature and not impulsive. In our society, donorship should symbolize the timeless, pancultural theme of rebirth, which was identified by Mircea Eliade as the salve that soothes the spirit to confront, bear, and interpret grief. Donation is a heroic act. It is beyond a human act. It is the extraordinary, albeit final, act of which an ordinary person is capable. The donor (and the family) give life to something bigger than themselves.

Since our culture has denigrated books to a degree only exceeded in Bradbury's *Fahrenheit*, oral tradition must be established via the visual media. The effort is not merely a device to satisfy a medical exigency or to proselytize a political agenda (as some of our legislators have demeaned the problem), but rather an enterprise to weave a new skein in our cultured fabric. The organ donation skein recognizes adaptation to death, a common and inevitable event, as a rite of passage through life. It provides a trusted anchor to face this dark encounter and understand this universal reality. It offers a road map to deal with the mythic situation of brain death by doing something in the best interests not only of the afflicted but also of humanity. It offers a basis for commitment.

Mythologic terms immediately capture the positive value in what appear to be negative events, providing meaning to what would otherwise be a senseless tragedy. The classical heroic myth that from a "given" life comes new life cannot be more literally interpreted than by transplantation. The ritual of organ retrieval is a mythic act, reminiscent of the legendary phoenix that, at the end of its lifetime, is consumed by flames on its newly constructed pyre, only to emerge as a seed, then finally the fully developed bird of the sun. The transplantation enterprise that begins with mythical stories of Ganesha, Pien Ch'iao, Ezekiel, and Cosmas and Damian will thus achieve its



goals through public recognition of the symbolic heroism of the organ donor, whose altruistic act is the ultimate expression of the donor's humanity.

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# Allo- and Xenotransplantation without Immunosuppression: Lessons from Horticulture in Comparative Biology

DAVID E. R. SUTHERLAND, 1990-91

I chose the topic of transplantation in the Vegetable Kingdom for three reasons: 1) It successfully preceded transplantation in the Animal Kingdom by several centuries; 2) One of my childhood heroes was Luther Burbank, who became a household name as a plant transplant surgeon at the turn of the century; and 3) I thought it would be fun. I did not know much about plant grafting, but I always had a green thumb. Therefore, I took a course in the College of Agriculture at the University of Minnesota (Horticulture 101: Plant Propagation) to prepare for my address. One of my medical student advisees, Clayton Chau, helped me with the laboratory exercises and the homework, and Professor Peter Ascher (my instructor for the course) was most generous, engaging in discussion comparing transplants in his world (vegetable) and mine (animal).

I also had extensive discussions on comparative biology with my colleague Jeffrey Platt, whose main interest is xenotransplantation. He accompanied me on a trip to the University of Minnesota landscape arboretum, where I photographed several examples of tree grafts for my talk. Some were xenografts (even highly discordant ones can sometimes succeed in the plant world).

I spent several hours in the arboretum library, not only browsing but also running with my findings to horticulture professor and curator Michael Zins for more discussion on comparative transplant biology. Numerous horticulture publications on plant grafting have appeared since the invention of the printing press, and I used examples from many in my lecture (Figure 1). The members of the ASTS should also be grateful to the science of plant propagation, since without it we would not be able to enjoy the French wines we do today. *Phylloxera vastatrix* (a root louse) destroyed most of the

A Booke of the Arte and maner,  
howe to plant and graffe all sortes of  
trees, howe to set stones, and sove Pe-  
pines to make wylde trees to graffe on, as al-  
so remedies and medicines. VVith diuers o-  
ther newe practise, by one of the Abbey of  
Saint Vincent in Fraunce. practised with his  
owne handes, divided into seauen  
Chapters, as hereafter more  
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With an addition  
in the ende  
of this booke, of certayne Dutch practises,  
set forth and Englished, by Leo-  
nard Malcall.



In laudem incisionis distichon,  
Hesperidum Campi quicquid Romanaque tellus,  
Fructificat nobis, incisione datur.

Imprinted at London by Henrie  
Denham, for Iohn Wight.

Figure 1. Suggested Reading

French vineyards in the 19th century. The vineyards were rescued by grafting French vines onto California grape roots that were resistant to this louse.

In my address I went into the science of plant propagation, with emphasis on inter- and intraspecies grafting. Without the techniques developed several centuries ago, we would not have a uniform supply of apples, oranges, plums, and other fruits



we so much enjoy. Most seedlings give scrub fruit. Useful varieties must be propagated by grafting. The science of plant propagation is as useful—if not as complex as—the science of immunology, but it is too much to reiterate here.

Grafting is used for plant propagation to perpetuate a true variety whenever this cannot be accomplished by seed propagation or rootings of cuttings. A variety of surgical techniques are available. Today, propagation can be accomplished by cellular engineering as well. Although all grafted plants are chimeric in the Greek mythology sense, in horticulture the term is usually reserved for plants whose tissue consists of intermingled cells of more than one genotype.

Much of the terminology in plant propagation is similar to that in transplant immunology. For example, there are clones, and a clone can evolve within a variety that has been cultivated vegetatively for a long time. Members of a vegetative clone have the same genotype until spontaneous mutations occur, as is the case in the animal world. Selection is the most effective process by which plant breeders (propagators, grafters) alter the traits of cultivated (cloned) plants, in conformity with human desires.

Clonal selection is based on the recognition and the isolation and evaluation of biotypes of a polyclonal variety. The methods are similar to those we use, with *in vitro* experiments leading to *in vivo* application.

The terms encountered in textbooks of plant propagation are familiar. Compatibility and incompatibility are well described. Are graft compatibilities and incompatibilities exhibited in the vegetable world (allo- and xeno-) relevant to those in the animal world? Intraspecies grafts take easier than interspecies grafts, but there are examples of the latter in which a take is a regular occurrence. Tendency toward this occurrence is termed affinity (the behavior of the scion toward the root stalk in the grafted stage). Some grafts will survive for years, and then wither. Is delayed incompatibility of plant grafts akin to chronic rejection of animal grafts?

Plant grafts are free grafts, but become neovascularized (yes, plants do have vascular systems). Do plants have an immune system? Yes, at least a primitive one. There is a cellular response to injury with proliferation, walling off, and healing.

Just as in our world of transplantation, horticulture is filled with personalities and characters. Luther Burbank is only one example. He was born in 1849 and died in 1926. He exhibited several traits in common with our members: passion and ego. He once said, "See, I am about the same height as Napoleon and my hat is about the same size as his, although my head is growing and increasing in size all the time." Burbank was the epitome of a scientist who followed Pasteur's dictum: Chance favors the prepared mind.

Burbank immigrated from Massachusetts to Santa Rosa in Sonoma County, California, in 1875 to become nurseryman extraordinaire. (I am indebted to John Rabkin for making a trip to Santa Rosa to collect memorabilia for my talk.) Before leaving Massachusetts, he had developed the Burbank potato by sheer luck from a rare seed ball, whose descendants included both the Idaho and the Main. In 1881, Burbank produced 20,000 prune trees for setting out in one season by grafting onto growing Almond stock. His first commercial success gave him capital for continuous experi-

mentation. He tried and succeeded with extremely discordant grafts that others had assumed would not work. He dismissed critics with words such as, "Orthodoxy is ankylosis, no one at home; ring up the undertaker for further information."

The Idaho potato has been with us now for more than a century. Even older chance occurrences are easily identified. We all love the Bizzaria orange, half-orange, and half-citron. This originated from an adventitious bud from the callus of a sour orange graft on a citron in Florence, Italy, in 1644, and has been perpetuated vegetatively to the present. We owe it to an observant Medici.

Well, what about the science? What determines plant grafts' compatibility and incompatibility? When opposing cells touch, their walls dissolve and holes appear. The plasmalemma contact each other and release protein molecules that form catalytic complexes. These complexes determine graft compatibility. An example of an incompatible situation is between the pear and the quince.  $\beta$ -glycosidases from pear hydrosylases liberate cyanide from quince prunasin, causing developmental abnormalities at the graft interface and inhibiting union. I would rather deal with T cells than cyanide. Symbiotic relationships between viruses in certain plants can also lead to incompatibilities. Some viruses have a symbiotic relationship in the root stock, but when transferred to a scion have a pathological effect on the graft.

Nonimmune incompatibilities predominate in the world of vegetable grafts. Analogies to animal grafts can be made (nutritional, enzymatic, physical). In the Vegetable Kingdom, a fundamental biological incompatibility that would not support xenotransplantation, even when the immunological problems are solved.

On the other hand, graft-host affinities are common in the vegetable world. The probability of affinity is higher between closely related species (concordant). In what would otherwise be predicted to be discordant combinations, useful exceptions occur.

Is there a lesson in the extremely discordant successful grafts? The most extreme, of course, would be grafting from a vegetable to an animal or an animal to a vegetable. Could a tree stump survive by nutrient diffusion and continuously grow to replace the end chafed by a Captain Ahab stomping on the deck of his ship? Well, I will leave that puzzle to the ASTS members now leading us into the brave new world of xenotransplantation.





## Organ Shortage: A Major Obstacle for Transplantation

ARNOLD G. DIETHELM, 1991–92

I am very appreciative of the privilege to have served as your president during the past year and accept this recognition on behalf of my colleagues at the University of Alabama and the Department of Surgery. I am very grateful to Dave Sutherland for his advice and assistance and to the members of the Council. I would particularly like to thank Mark Hardy, Marc Lorber, and Hans Sollinger. All transplant programs, to be successful, require a strong support base of support by surgeons, nephrologists, tissue typers, research technicians, and others. Our program is no exception, and I would like to particularly thank Drs. John Curtis, Bruce Julian, and Robert Gaston in Nephrology and Drs. Henry Barber, Mark Deierhoi, David Laskow, Steven Poplawski, and Dinesh Ranjan in Surgery. I would especially like to remember Dr. Bruce Barger, director of the Histocompatibility Laboratory, who died of cancer a few months ago. Bruce, a member of the Department of Surgery, built a superb laboratory with outstanding people. He will be greatly missed.

I would like to discuss with you today a subject that appears to me to be an obstacle of major proportions to clinical transplantation and especially to the transplant surgeon. The obstacle, directly in the path of clinical transplantation, is the major limitation to providing appropriate care to patients with end-stage organ failure. Unfortunately, the problem is not as exciting and scientifically challenging as the subject of tolerance, the mechanisms of allograft rejection involving cytokines, adhesion molecules, antigen presenting cells, and the like. In spite of what might appear to be a mundane subject, it is so critical to patient care that I find it reasonable to at least raise that subject with you and hope that the following brief review may provide a platform for further discussion. The comments will only reflect my thoughts about the matter, and if in conflict with others, I would be pleased to review the controversy with each of you.

Clinical transplantation, as we all know, is dependent upon immunosuppression, histocompatibility testing, organ preservation, and procurement. Fortunately, the

spectacular development of new immunosuppressive agents has increased living related donor transplantation at one year to more than 90% with the one haplo-matched recipient, 97% with the two haplomatched recipient, and from 78% to 85% with the cadaver recipient. These results are of course transplant center dependent. The role of organ preservation with University of Wisconsin (UW) solution has had a major impact upon the quality of organ function and greatly simplified the logistics involved in the operative procedures.

The experience in renal transplantation at our transplant center exemplifies that which has occurred in all other centers. As the number of transplant operations increase, the mortality and morbidity of the operation and postoperative care decreases. This quite properly increases the optimism about the possibilities of transplantation and in turn expands the spectrum of recipient patients suitable for organ replacement. All of this increases the number of patients awaiting transplantation and leads me to the subject of today—"Organ Shortage: A Major Obstacle for Transplantation." This problem to a large degree is the result of the scientific accomplishments of transplantation, both clinical and research.

Much has been said about the shortage of organs in the last few years, and I fully recognize that a solution will not be forthcoming today. We—the transplant surgeons—are by nature optimistic individuals and look to the future with enthusiasm. Although our scientific efforts are in general based upon a growing foundation of sound immunologic data, the same is not true with the organ shortage. In this area we must contend with social issues, ethical concerns, moral and religious views—none of which are really based upon the type of scientific data we are accustomed to analyzing. It is difficult to create a P value or develop a Kaplan-Meier curve upon all of this, although we have tried to do so at one time or another. It is even more difficult to ask, or worse yet assign, a young energetic surgeon to spend 10%, 20%, or 30% of his time to increasing organ donation. First, few deans of a medical school or members of a faculty promotion committee would look favorably upon this as "scientific accomplishment." Second, a steady diet of this sort of effort soon becomes tedious.

The potential role of xenotransplantation with or without transgenic animals is exciting to say the least. However, clinical application of xenotransplantation is in the future, and we as surgeons must deal with patient care problems as they exist currently. We can anticipate the future, but must live in the scientific world of today. In the next 15 minutes I will review some aspects of the organ shortage and offer a few suggestions.

### *Required Request*

As a result of the nature of the problem, we transplant surgeons, as a group, have been much in favor of the "quick fix" solution. A reasonable attempt in this regard was the Required Request Law, part of the National Transplantation Act of 1984, which stated that all people entering a hospital were required to provide a statement—yes or no—as to whether or not they wished to become a donor if things didn't work out well. Furthermore, if the patient died, the physician in charge was required to ask the fami-



ly if they wished to donate the organs and tissue of the deceased patient. The concept is simple but has had little, if any, impact upon increasing organ donation. The reasons for the failure of Required Request are quite straightforward.

First, the public as a whole was not adequately educated on the subject of organ donation and had some concerns about the possibility of a premature decision of brain death by the physician. Brain death, a medical concept based upon sound neurological data, is still a bit uncertain to the general population. This level of patient uncertainty could and should be remedied by expanding public understanding of the entire subject, but progress has been slow.

Second, is the matter of consent or who “owns the body.” The next of kin frequently expresses the opinion, in no uncertain terms, that they want the deceased to be “buried whole.” In case any of you are not certain as to the meaning or intent of this statement, you need to see the facial expression of the next of kin who provides this information to you when you ask for organ donation. There is very little room for further discussion.

The third reason contributing to the lack of organ donation is based upon physician apathy in asking the next of kin for organ donation. The attending physician is often uncomfortable about the subject, may know little about it, may be discouraged about the death of the patient, and therefore avoids asking the question. Unless the next of kin thinks of organ donation, the patient will be pronounced dead without any request for organ donation and will be “buried whole.”

### *Presumed Consent*

Unless the patient signs a donor card, has a living will, or has expressed personal feelings about the subject of organ donation to family or friends, he or she will have nothing to say. The subject will be raised when the patient is no longer able to express an opinion. Thus, the real question is “who owns or is responsible for the body?” In some circumstances no one comes forward and the answer should be simple—but legally can be complex. If one wishes to use the “presumed request approach,” this will only raise the ire of the next of kin—the very group who will cause the most trouble if society presumes to tell them what to do with the body of the deceased. The success of “presumed consent” for organ donation that has been noted in European countries may not be forthcoming in the U.S. It should be examined in much detail before being considered. Another approach is to initiate a law that all deceased persons should have their bodies willed to science. My guess is this will never pass muster.

### *Recipient Limitation*

Logic might lead us to conclude that if the organ supply is limited and less than the patient demand, one solution would be to restrict or even reduce the patient demand for the organ. This implies some form of artificial guidelines to be placed upon the selection criteria for the recipient patient. This might include age (e.g., transplant patients only within a certain age range) or certain diseases (e.g., diabetes, lupus, or



focal sclerosis, all of which may recur). Another consideration would be to limit patients to one or perhaps two transplants. This is an artificial notion and one which I believe should be avoided until every other option has been shown to fail. This approach will entangle the transplant surgeon and the patient in a hopeless web of ethical and legal concerns which will not be beneficial to the patient or the field of transplantation.

### *Financial Incentives*

Organ payment to the next of kin has been suggested as a means to increase organ donation and has been used in other countries with varying degrees of success. Fortunately in the U.S. payment for organs is prohibited by law. Another idea—now under study—is a means of compensation in the form of an insurance policy paid to the family for those members who die and donate organs. This at first glance may appear to be of benefit in expanding the donor pool. My guess is it will be another “quick fix” and create some insoluble problems. For example, two teenagers are in a car accident; both eventually become brain-dead, but one does so in 48 hours and the other in 21 days. Both families agree to organ donation. The patient with brain death in the first 48 hours is an excellent donor, while the second has a septic course and is unsuitable as a donor. The first family receives financial compensation while the second family receives none. The discrepancy is obvious. The use of financial incentives is a complex subject with many ramifications touching upon legal and ethical considerations and should be examined thoroughly. This approach may offend those families who believe in the altruistic approach.

Up to this point I have presented to you the problem of organ shortage, its impact upon organ transplantation, and a few proposals to remedy the situation. None of them, individually or collectively, I believe, will be of great help and some could have a negative influence. At the risk of returning to a simplistic concept than is well known to all of you, I would like to suggest another method to improve the situation. It is not a “quick fix.” The idea is not new, not a brain-storm, and requires no new laws. It will require a variety of people to participate with help from the churches, government, the state, private enterprise, and local civic groups. This help is in the form of *education*. This includes education to people of all ages in many places, such as schools from 9th grade to and through college and postgraduate education, places of employment, worship and community groups. The education will include information on the clinical need and benefits of transplantation. It should emphasize that organs cannot be made or purchased—only donated. The public must be made aware of the valuable resource of human organs and tissue, and constantly reminded of the lives that can be saved by the giving of organs. Above all we will need help from private enterprise in terms of ideas and their implementation as well as some financial support. Perhaps a national campaign similar to “buckle up,” improved nutrition with a decrease in cholesterol intake and the antismoking efforts would enhance public awareness. The problem with this approach is that it will take time—at least five or possibly ten or fifteen years from the starting point, and the question is can or will we sustain the effort.



As I mentioned earlier, we as surgeons, especially in the field of transplantation, are impatient and by nature interested in “quick fix” solutions. This proposal is not in that category. Rather it is a long-term investment for a very good cause based upon public education and altruism. It is possible that the government at both the national and state level might be willing to undertake to participate in such an effort, combined with the transplant community and with selected members of the business community. I am quite convinced that we as transplant surgeons have neither the time, expertise nor desire to undertake the task alone. The first step would be to encourage 30 to 45 minutes a year to be devoted to the importance of organ donation in schools including grades 9 through 12. This could be accomplished with the use of video presentations and followed up by the willingness of students to sign donor cards with their families, recognizing it is only an expression of their desire, not a legal document. In four consecutive years all high school students and college students would have the opportunity to express their opinion, and if negative at an early age, perhaps convert their decision to a positive one. Whether or not a donor card is a legal document seems unimportant. What is important is that a conscious decision was made and expressed in writing by the individual. Rarely, in my experience, has a donor card request been disregarded by the family. This simple concept of donor card signature is based upon two features: altruism and education.

#### *Request for Donation*

The most common cause for failure of organ donation is the inability to receive consent from the family. The individual or individuals requesting organ donation are key in obtaining permission from the family, and their approach and sensitivity to the subject is often central to receiving approval. If those asking for permission for organ donation are insecure, uncomfortable, or perhaps even negative, it will be unlikely that a positive response from the next of kin will be forthcoming. Thus, a team including nurses, procurement coordinators, clergy, transplant recipients, and physicians might be especially helpful. This would be called a request team; one or two members would visit the family. Such a team would include representatives of minority groups who would be sensitive to the religious and ethical beliefs of the family. They would have special training in methods of asking for donation and would be available 24 hours a day to assist in the request to the family. The request team therefore would be a combined responsibility of chaplains, physicians, nurses, and other hospital personnel. This request team might increase family consent and avoid the consequences of physician apathy.

As I mentioned at the beginning, organ shortage is not a scientific problem but a public health problem. We surgeons, nephrologists, and physicians will need support from various groups. At least with a broadly based program of education, we are on firm footing and, if carried out in good taste, should not be offensive. At the very least the expanded role of public information should do no harm, avoid new laws and, over a period of time, might be helpful. Altruism remains the cornerstone of organ dona-

tion in this country. A widespread national education program combined with the altruistic attitude of the public will be a sound base for expanding organ donation.

As a final comment, physicians as a group and surgeons particularly are often uncomfortable about the overlap of science and medicine with ethics. In closing, I would like to read a quote of Karl Popper published by Peter Medawar in *The Limits of Science*.

“It is important to realize that science does not make assertions about ultimate questions—about the riddles of existence, or about man’s task in this world. This has often been well understood. But some great scientists, and many lesser ones, have misunderstood the situation. The fact that science cannot make any pronouncement about ethical principles has been misinterpreted as indicating that there are no such principles while in fact the search for truth presupposes ethics.

—Karl Popper, *Dialectica* 32: 342

Thank you again for the opportunity to be your president.





# Rupert Billingham and the Role of Serendipity in the Discovery of Transplant Tolerance

CLYDE F. BARKER , 1992–93

The Presidential Address gave me an opportunity to pay tribute to my teacher, Rupert Billingham, by recounting the early history of transplantation. Informal conversations with Billingham during the six years I spent in his department and during a recent visit to his retirement home on Martha's Vineyard provided me with some little known details of the story. Even ASTS members may not be familiar with all of the contributions that Billingham and others made (many of them largely by chance) to the discovery of tolerance for which Peter Medawar was awarded the 1960 Nobel Prize. Others who could have argued for a share of the prize include John Hunter, Frank Lillie, Ray Owen, Hugh Donald, Emile Holman, J. Barrett Brown, Charles Danforth and Francis Foster, Thomas Gibson, Bill Longmire, and Jack Cannon.

The story begins in the first decade of this century with the realization that even technically successful skin homografts uniformly fail. One of the first good descriptions of rejection is in a paper published in 1922 by Emile Holman, a 32-year-old surgical resident in Halsted's program at Johns Hopkins. He transplanted many small skin allografts to the leg of a 5-year-old boy who had lost most of the skin of his lower extremity in an accident. A month later, Holman performed more pinch grafts to obtain better coverage of the wound. The boy's mother was the donor of both sets of skin grafts. Holman noted that the "second set" of grafts were rejected more rapidly than the earlier ones, thus becoming the first one to describe the so-called second set reaction. Holman, who became chairman of surgery at Stanford, said later that one of the great missed opportunities of his life was a failure to follow up on this observation. Rediscovering the phenomenon, Medawar used it to prove that rejection was an immunological process.

In 1929, two Stanford veterinarians, Charles Danforth and Francis Foster,

observed that skin grafts exchanged between newborn chicks were usually accepted permanently. This suggestion that allograft rejection might be preventable was overlooked until 20 years later when the phenomenon was further explored by two UCLA surgeons, William Longmire and Jack Cannon. They found that skin allografts were rejected by chicks unless they were performed immediately after birth. Recognition that cellular or tissue allografts could survive if transplanted very early in life was crucial to the protocol used later by Medawar and his colleagues to induce tolerance.

Although he was aware of the work of Danforth, Foster, Longmire, and Cannon, it was only by chance that zoologist Peter Medawar became interested in transplantation. During World War II, Medawar was assigned to join plastic surgeon Thomas Gibson at the Royal Infirmary in Glasgow in studying homografts as a possible means of treating burned aviators. They reconfirmed that skin allografts always failed and also rediscovered the second set phenomenon previously described by Emile Holman. Importantly, they recognized that this proved that rejection was an immunological process.

In 1946, Rupert Billingham enters the story. Born in 1921, this grandson of a dairy farmer became Peter Medawar's first graduate student at Oxford. Interestingly, his work is not on the homograft reaction. Instead, he was assigned a project on the esoteric subject of pigment spread. The goal was to explain why the pigmented areas in spotted pigs gradually encroach on the white skin. To observe this phenomenon, Billingham and Medawar transplanted autografts of black skin to white areas on the same guinea pig. Their experiments were the subject of Bill's Ph.D. thesis and first eight publications.

Soon after this, Medawar accepted the chair of zoology at the University of Birmingham. Influenced by the knowledge that Medawar's technician Jean Morpeth had accepted a job at Birmingham, Billingham sought a position in his department where he continued to work on pigment spread.

In 1949, serendipity assumes crucial importance in the story. Medawar had a casual conversation at a cocktail party with a British veterinarian, Hugh Donald, whose research was on the importance of heredity vs. environment on animal behavior. As a model for his studies, he was using twin cattle, but was handicapped since he could not distinguish identical from fraternal twins with certainty. Medawar advised him that this should be no problem. Exchanged skin grafts should be accepted only by identical twins.

When Donald asked him to perform the skin grafting experiments, Medawar was reluctant on two counts: (1) Donald's cows were kept on a farm two hours from Birmingham and (2) Medawar had no experience handling large animals and was uncomfortable with the prospect. Therefore, he enlisted the aid of his junior colleague, Billingham, who was not only expert in skin grafting but as the grandson of a dairy farmer was not afraid of cows. Billingham and Medawar set out on this adventure with little enthusiasm. Although they had minimal scientific interest in the outcome of the skin grafting which they felt was predictable, Billingham, Medawar, and usually Jean Morpeth made many long trips to Cold Norton Farm to perform and examine the skin grafts.



Thrown together as collaborators on this strange project, Billingham and Morpeth were becoming progressively better friends, but the scientific aspects of the project were not going well. After studying 25 twin pairs, they found that 86% of exchanged skin grafts were accepted for greater than 100 days, a surprising result since most cattle twins are fraternal. They discussed this unexpected success of grafts exchanged between fraternal twins with Hugh Donald, who suggested that they read a paper published four years earlier in *Science* by Ray Owen. When they did so, the significance of their results suddenly became clear.

To place the cattle twin chapter of the story of tolerance in proper context, it is necessary to go back in time over 200 years. In 1779, English surgeon John Hunter provided the first anatomical description of the freemartin, a term used for the generally sterile female of a pair of cattle twins of unlike sex. Hunter dissected freemartins, finding that they had masculinized sex organs. That Hunter was unable to explain this curious phenomenon is ironic because he was an expert on the circulation of the placenta.

The next important link in the story was not provided until 1916 when Frank Lillie, an embryologist at the University of Chicago, was sent several specimens of unborn cattle twins. He found that chorions of the twins' placentas were fused, causing a common intrauterine circulation that allowed blood to be exchanged freely between the twins. Like John Hunter, Lillie also found that when cattle twins were of unlike sex, the gonads of the female were usually rudimentary. He reasoned that male hormones circulating through the female embryo inhibited the development of its reproductive organs.

Three decades later, in 1945, Ray Owen, a 39-year-old assistant professor of genetics and zoology at the University of Wisconsin, wrote the next chapter. In studying the red blood cell types of cattle, Owen found that fraternal twins frequently had a mixture of two red blood cell types. Recalling Lillie's finding of placental fusion of bovine twin embryos, Owen concluded that not only hormones but also cellular elements of the blood must be exchanged in utero by twin cattle. He realized that persistence of red blood cell chimerism in adulthood must depend on intrauterine transfer not only of short-lived red blood cell but also of stem cells that would perpetuate them.

Six years after the publication of Owen's paper, Billingham and Medawar read it with fascination and were suddenly able to interpret the outcome of their cattle skin graft experiment. They realized that, like the freemartins studied by Hunter, Lillie, and Owen before them, their twins must have exchanged both cellular and hormonal components of blood in utero. As Owen had shown, their cellular chimerism persisted in adulthood. They reasoned that the stem cells exchanged would be not only those for red blood cells but also for white blood cells, and that since the latter were known to express transplantation antigens, these were probably responsible for skin graft tolerance. They also realized at once with considerable excitement that they could probably reproduce the phenomenon in other species.

In 1951, Billingham and Medawar moved to University College, London, where Medawar became chairman of zoology. It turned out to be a happy move for them both. Billingham and Morpeth were soon married. Medawar said "Thank God we've



left those cows behind.” There, Billingham, Medawar, and graduate student Leslie Brent attempted to induce chimerism and tolerance in mice, a task which proved quite difficult. Initially they used a laparotomy to expose and deliver cellular inocula to fetuses, an operation that caused almost 100% mortality. Not until almost a year later did they hit upon the technique that allowed the first success. After making a skin incision, they could visualize the uterus through the intact but semitransparent layers of abdominal muscle and inoculate the intrauterine fetuses with donor strain cells. In retrospect, they were quite lucky to have achieved any successes. By chance, the inbred mouse strains they chose for the experiments were CBA and A, virtually the only H-2 incompatible strain combination available to them in which neither severe graft-versus-host disease nor incompatibility of skin specific antigens would cause death or rejection of the graft.

In adulthood, survivors of the intrauterine inocula were grafted with skin from the donor strains. Although the results were somewhat inconsistent, prolongation of skin graft survival occurred in 40% to 50% of the recipients. A manuscript was quickly prepared and submitted to *Nature*. But while it was being reviewed, Billingham, Medawar, and Brent were horrified to discover that, due to a mixup in their animal colony, some of their recipients were F<sub>1</sub>'s, which would accept the parental strain allografts on a genetic basis alone. They briefly considered withdrawing the manuscript but fortunately were able to conduct more grafting experiments in time to be reassured that their conclusions were valid.

Their brief paper in 1953 attracted the world's attention. Like the cattle work, it demonstrated that allograft rejection was not inevitable. They had shown that successful transplants could be achieved by a fairly simple protocol. Medawar said that its significance was moral rather than practical.

In 1960, Medawar was awarded the Nobel Prize, largely on the strength of the tolerance experiments. The prize was shared not with Billingham but with McFarlin Burnet, an Australian who had theorized on the mechanism of tolerance. Although Billingham has never acknowledged it, others have frequently asserted that omitting him was unjust. His role was crucial both in the tolerance work in mice and in the earlier cattle work, which was its genesis. To indicate his own recognition of Billingham's contributions, Medawar divided his prize money with Billingham (and Brent). Billingham used his share for a downpayment on a house in suburban Philadelphia.

In 1957, Billingham accepted an offer to head a transplantation research section at the Wistar Institute in Philadelphia. His first recruit, Willys Silvers, shared his interest in pigment spread. They collaborated on experiments on this phenomenon. Somewhat to Billingham's discomfort, they eventually discredited the infectious concept of pigment spread put forth in the early work with Medawar. Instead, they established that pigmented cells actually migrate from black skin grafts into the adjacent white skin of the recipient.

Throughout the remainder of his career, Billingham continued to explore the complex phenomenon of rejection by simple methods such as skin grafting. He said the ingenious experimental designs he used were in the Medawar style. But those of us who worked under him believed the approach to be Billingham's own hallmark.



Despite the many original and important publications generated by this work, neither Billingham nor Medawar was ever again to equal the spectacular success of the tolerance work. But perhaps no other experiment in transplantation has ever approached its impact.

Nevertheless, during his Philadelphia period, Billingham's ideas led to numerous and important findings by his group. Using the classic Billingham model of neonatal tolerance, his graduate student David Steinmuller demonstrated that passenger leukocytes migrating from skin allografts are in themselves sufficient to sensitize their hosts. Along with Wayne Streilein, Billingham pioneered tissue typing with a now-forgotten method called the irradiated hamster test. Through another graduate student, Darcy Wilson, he encouraged seminal work in the mixed lymphocyte culture test. With Will Silvers and with me, he studied privileged sites, such as the hamster's cheek patch. I was lucky enough to collaborate with him in devising an artificial privileged site, which confirmed the crucial importance of the lymphatic circulation in skin allograft rejection. Billingham's 1964 publication in the *New England Journal of Medicine* stimulated interest in immunological aspects of the maternal fetal relationship, a topic largely overlooked until then. Later, the American Society of Reproductive Biology, in electing him to its presidency, referred to him as "the father of reproductive biology." Also during this period, he helped me initiate the human kidney transplant program at the Hospital of the University of Pennsylvania.

In 1971, Billingham accepted an offer to chair the Department of Cell Biology at Southwestern University in Dallas. I feared that his move might end my scientific career, but the background he had provided allowed me to continue the study of privileged sites. The genesis of my group's subsequent work on pancreatic islets was the idea that these cellular grafts might be transplanted to privileged sites. In Dallas, with Alan Beer, Billingham continued his experiments on the maternal fetal relationship. Although they did not fully succeed in explaining the riddle of nature's uniquely successful allograft, their work was highly influential in the development of that entire field.

Ironically, like Peter Medawar's, Billingham's career was eventually cut short by a disabling neurological illness, Parkinson's disease. Nevertheless, his retirement has been gratifying in many respects. Honors have continued to flow his way, such as the honorary DSC from the University of Pennsylvania in 1993.

Medawar said that the impact of the discovery of tolerance was predominantly moral. But time has proven him wrong in believing it would never have practical importance. In fact, tolerance and chimerism seem to be increasingly important, as modern transplant surgeons—following the lead of Billingham, Brent, and Medawar—attempt to mimic nature's experiment, the freemartin. Protocols may eventually allow successful human allografts without immunosuppression. As evidence of the continuing influence of this work, I cite the 12 papers on the 1993 ASTS scientific program dealing with either tolerance or chimerism. Of particular note are the paper by Monaco's group, which for many years has studied the effects of chimerism on tolerance in mice; the attempts by Diethelm and Barber to induce toler-

ance to human kidney allografts with donor bone marrow; and Susan Ildstad's use of mixed donor-recipient lymphoid cell chimerism.

The Philadelphia group's use of the intrathymic tolerance model is a derivative of Billingham's work in two respects. First, intrathymic inoculation of islet cells into the thymus might never have been pursued if the prolonged survival of intrathymic islet allografts had not interested members of my group, brought up on stories of Billingham's fascination with the obscure phenomenon of immunological privileged sites. Second, in rereading the original tolerance papers, we were intrigued by the failure to induce tolerance with nonlymphoid cell inocula, such as kidney or testicle. We reasoned that success of lymphoid cells might depend on their unique capability to home to the thymus, but that kidney or islet cells would be equally effective if they could reach the thymus by purposeful implantation.

Finally, Tom Starzl's recent recognition of the emigration of passenger cells from solid organ transplants and their persistence in successful transplant recipients appears to indicate that these fortunate individuals are often tolerant. That some of them can even discontinue immunosuppressive drugs provides clinical confirmation of the importance of chimerism—a state first recognized in cattle twins and then induced experimentally by Billingham and Brent and Medawar.