VIII

The Scientific Program

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The yearly ASTS scientific meetings have been the important unifying focus for our members and therefore our organization. Beginning with the inaugural meeting in 1975, the program has provided a stimulating forum for presenting new data at the leading edge of transplantation science. Always strong in immunobiology, this event has been characterized by appropriate balance to include important, timely, and relevant contributions in areas of clinical transplantation science. The lively and often critical discussion periods after manuscript presentations have been a hallmark of each meeting. This annual event is enthusiastically anticipated by the membership. Attendance has grown annually, and competition for a coveted place on the meeting program has always been keen (Figure 1).

Inaugural Meeting

The first ASTS scientific meeting (May 23, 1975) was truly memorable. The program committee, chaired by Tom Marchioro, selected 24 manuscripts for presentation beginning Friday morning, May 23. The initial session was chaired by our first president, Thomas E. Starzl. The sessions began with three manuscripts from the University of Minnesota. The first paper addressed pioneering work from John Najarian's department on serum creatinine values among renal transplant recipients with diabetes. It was presented by Arthur Matas, then a house officer; coauthors included Richard L. Simmons, Frederick C. Goetz, David E. R. Sutherland, and John S. Najarian. As E.W. Lampe was called to the podium to present the third manuscript, "Autotransplantion of Porcine Islets of Langerhans," President Starzl quipped, as the institutional affiliation was to be announced, " . . . from the University of Transplantation!" The morning session included 14 papers on various topics spanning relevant areas of clinical and experimental transplantation. Presentations focused on experimental islet transplantation, allograft rejection monitoring, technical considerations in renal transplantation, immunologic considerations in clinical renal transplantation, and adverse consequences of immunosuppressive therapy. The final manuscript of the session was from the University of Wisconsin group discussing

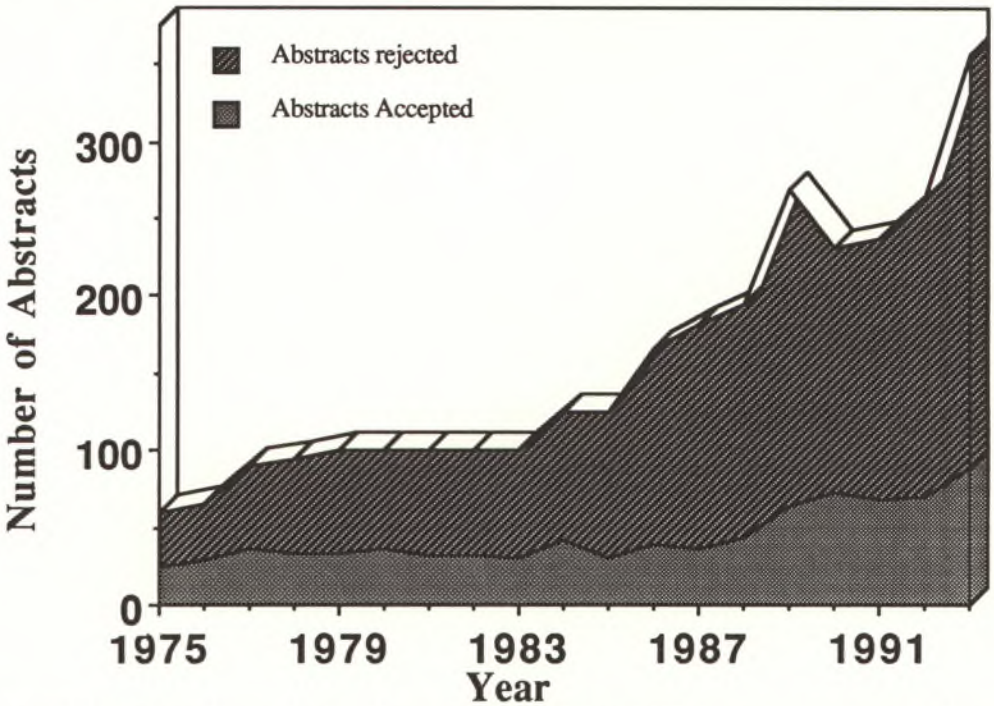


Figure 1. Yearly growth, annual scientific program of ASTS, 1975–1993. Acceptance rates ranging from 40% in the early years to more recent rates approximating 25% reflect keen competition for a place on the annual program.

an observation that remains unresolved today: some stable renal transplant recipients can discontinue immunosuppression without sustaining allograft rejection.

The afternoon began with Starzl's presidential address, "Preface to a Society." Scientific papers addressed such topics as organ preservation, transplantation immunobiology, and immunologic monitoring after renal transplantation. The results of initial clinical application from experimental work on active enhancement using ALS and donor bone marrow were also presented. The immunologically successful application of this technique in a sensitized recipient demonstrated the feasibility of donor marrow administration without graft-versus-host disease (GVHD) or overt rejection. The first scientific meeting concluded with a memorable evening at Fred Merkel's lakefront home on the north shore of Lake Michigan.

1976–1980

The success of the initial meeting both solidified the need for our new society and set an exciting tone for its annual scientific forum. During the next five years, Tony Monaco chaired the Program and Publications Committee. Under Tony's leadership, the committee set a pattern of demanding high-quality scientific work, based solidly in transplantation biology. The program balance emphasized experimental transplantation, with ample inclusion of relevant studies in clinical transplantation. It was a

stimulating framework, a catalyst for growth in the field. Yearly, the transplantation community provided a stimulating environment for presentation and discussion of new work. The excitement surrounding each annual scientific meeting attracted increasing numbers of eager surgical trainees into the fertile area of experimental and clinical transplantation. Appropriately, the annual scientific program reflected and often challenged the dogma surrounding experimental transplantation. Reports addressed the still elusive goal of harnessing the negative regulatory arm of the cellular immune response. Strategies, presented from many laboratories, included surface modulation of donor cells, attempts to identify and expand the "suppressor" cell population, active immunologic enhancement, and the beneficial effects of blood transfusion on allograft survival. Other notable reports addressed problems underlying mechanisms of allograft rejection, cell trafficking during the allograft response, and various aspects of immunologic monitoring.

Importantly, experimental reports included areas of transplantation for organ failure beyond kidney disease. Liver transplantation work was principally reported from Starzl's group at Colorado, while experimental and clinical studies in cardiac transplantation came from Shumway's group at Stanford. The potential for pancreas transplantation as possible therapy for diabetes was investigated at Minnesota, and work on islet transplantation was reported from the groups at both Minnesota and Columbia. Other reports in cellular transplantation included studies in parathyroid grafting and cultured hepatocytes.

Growth of the clinical organ transplant experience continued. The important adverse consequences of immunosuppression under azathioprine, corticosteroids, and antilymphocyte antibody preparations became increasingly evident. Regularly emphasized were problems associated with anti-HLA antibody sensitization and aggressive (or too aggressive) treatment of allograft rejection, including development and consequences of opportunistic infections and malignancy. Those years were also characterized by reports on refinements in protocols for azathioprine and prednisone dosing, rejection therapy using corticosteroids and antilymphocyte antibody preparations, and the search for relevant strategies to improve posttransplant monitoring. Each annual meeting was an exhilarating experience: animated discussions highlighted controversial thought and generated new hypotheses for further study.

The 1980 meeting was a harbinger of events that would unfold during the next several years. During the president's Special Session on New Modalities of Immunosuppression, Sam Strober discussed encouraging results using total lymphoid irradiation, Starzl discussed experience with thoracic duct drainage, and, importantly, Sir Roy Y. Calne discussed the frustrating preliminary clinical results with a new fungal endecapeptide called cyclosporin A.

1981–1985

The now well-established annual ASTS meeting continued to gain in stature with progressive growth in attendance and in the number of submitted manuscripts. By 1981, several U.S. transplant centers had begun trials with lower cyclosporin A doses than

used in the initial Cambridge trial, combined with low-dose prednisone. The results were encouraging, but the important toxicities associated with cyclosporin A became increasingly apparent. The 1981 program included a report of early results from a randomized renal transplantation trial comparing cyclosporin A with conventional azathioprine-based immunosuppression; a report of cyclosporine hepatotoxicity among renal allograft recipients; and reports of encouraging results with experimental lung transplantation using cyclosporin A. Among other interesting presentations, the use of monoclonal antibodies recognizing T lymphocyte subsets as a renal allograft monitoring strategy was reported from the Massachusetts General Hospital group.

As clinical trials using cyclosporin A progressed, the promise of a major advance in clinical transplantation results became increasingly apparent. Enthusiasm surrounding clinical and experimental aspects of the growing cyclosporin A experience seemed to overshadow other important work during the 1982 and 1983 meetings. The 1983 meeting also included presentation of dramatically improved results after clinical heart, lung, and liver transplantation.

The 1984 and 1985 scientific programs continued to emphasize the growing cyclosporin A experience. More than 25% of the presentation addressed some aspect of cyclosporine. However, the emphasis also moved away from the traditional focus on renal transplantation: nearly 60% of the presentations reflected work in other transplant areas. Highlights of the 1984 meeting included experimental work suggesting potential feasibility of small intestinal transplantation using cyclosporine; a bold move into the area of living related donor pancreas transplantation at Minnesota; and the increasingly favorable experience with liver transplantation under cyclosporine. The 1985 meeting again emphasized cyclosporine immunosuppression and the dramatic growth in liver, pancreas, and cardiac transplantation. It also inaugurated the annual ASTS/Upjohn Award for the outstanding manuscript submitted by a resident or fellow (Table 1).

The widespread clinical success, resulting principally from the introduction of cyclosporine, brought other important changes to our field. The potential to "cure" irreversible liver and heart failure, illnesses for which there were no therapies except transplantation, suddenly focused public attention on the shortage of donor organs. Our promising, albeit previously quiet, academic field was suddenly receiving tremendous attention in the mass media. Heartfelt appeals from desperate family members for needed organs became common during the evening television news.

Additionally, cyclosporine, as a prototypic immunosuppressive drug, generated hope for application not only in transplantation, but also in autoimmune diseases. This suggested an economic potential that brought immunosuppressant development strategies into the boardrooms of major pharmaceutical companies. At nearly the same time, a host of new molecular techniques were developed that would rapidly accelerate understanding of the immune system in general and the transplantation response in specific. Many of these technologies also shared a newfound economic potential. Transplantation seemed a fertile area for biotechnology applications.

Table 1.
ASTS/Upjohn Annual Award for the Outstanding Manuscript Presented by a Resident or Fellow

Year	Awardee	Title	Mentor
1985	J.P. Waymack	Immunomodulation of Donor-Specific Transfusions	J. W. Alexander
1986	S.J. Knechtle	Liver Transplantation into Sensitized Recipients: Demonstration of Hyperacute Rejection	R.R. Bollinger
1987	D. Shaffer	Studies in Small Bowel Transplantation Prevention of Graft-versus-Host Disease with Preservation of Allograft Function by Donor Pretreatment with ALS	A.P. Monaco
1988	Y. Yamaguchi	The Role of Class I MHC Antigens in Prolonging the Survival of Hepatic Allografts in the Rat	R.R. Bollinger
1989	M.D. Stegall	Interstitial Dendritic Cell Depletion by Donor Pretreatment with Gamma Irradiation: Evidence for Differential Immunogenicity between Vascularized Cardiac Allografts and Islets	M.A. Hardy
1990	T. Kamei	Delivery of Prostaglandin E2 Induces Donor-Specific Tolerance in Rat Cardiac Allograft Recipients	M. W. Flye
1991	A.D. Kirk	Renal Allograft Infiltrating Lymphocytes: A Prospective Analysis of In Vitro Growth Characteristics and Clinical Relevance	R. R. Bollinger
1992	M. Ferraresso	Mechanism of Rapamycin and Rapamycin/ Cyclosporine Induced Unresponsiveness in Rats	B.D. Kahan
1993	Y.L. Colson	A Nonlethal Approach to Achieve Stable Mixed Allogeneic Chimerism and Donor-Specific Transplantation Tolerance	S. T. Ildstad

Together, these forces catalyzed an explosion of interest in the annual ASTS scientific meetings.

Beyond the scientific program, the ASTS meetings between 1983 and 1985 reflected the public enthusiasm and interest in our growing field. A press room was provided at the annual meeting, and our members were regularly interviewed. Similarly, the meeting program began to reflect this new public dimension in the field. Albert Gore, Jr., of Tennessee, principal author of the 1984 National Organ Transplant Act, delivered a recorded address at the 1984 meeting. Dr. Henry Desmaris, then director of the Bureau of Eligibility, Reimbursement, and Coverage at HCFA, delivered an invited lecture entitled "DRG and Transplantation Reimbursement" in 1985. Importantly, our leadership recognized the potential danger to the fabric of our society as they persevered to reaffirm our central scientific mission. Regardless, we formally entered a more public and political era during those eventful years. Our leadership recognized the need for ASTS to provide a strong and responsible voice, representing clinical and experimental transplantation, on behalf of all patients who would benefit from this remarkable therapy.

1986–1990

Annual meetings during the second half of the 1980s reflected the rapid and widespread acceptance of organ replacement as optimal therapy for many forms of organ system failure. Past controversies surrounding renal transplantation gave way to its nearly universal acceptance as the therapy of choice for end-stage renal disease. Similarly, cardiac and hepatic transplantation blossomed, while pancreas transplantation as appropriate therapy for complicated cases of diabetes mellitus moved cautiously from the experimental to the therapeutic arena. Additionally, the dramatic success with clinical lung transplantation resulted in its nearly overnight acceptance for end-stage pulmonary diseases. Beyond the clinical successes, the sobering reality that the "cyclosporine era" would not end the myriad of problems associated with clinical immunosuppression became increasingly evident. Many presentations reflected the challenges to patient care resulting from applying cyclosporine to an increasingly broad patient population. Additionally, the accelerated growth in understanding molecular aspects of immune responses was regularly reflected in many exciting scientific presentations during those years. Hope for the future of our rapidly growing field was high. Each annual meeting was exciting, with animated dialogue and ever-apparent general enthusiasm.

The meetings between 1986 and 1988 emphasized the accelerating clinical transplant experience. Refinements in immunosuppression resulting from critical analyses of results with cyclosporine were reported. Joint symposia with the American Society of Transplant Physicians examined transplantation and AIDS, cytokines and transplant rejection, controversies in organ sharing, and the evolving thought regarding renal transplantation among sensitized patients. Highlights of the scientific sessions included reports of continuing controversies surrounding HLA matching in renal transplantation, the reduced clinical importance of pretransplant blood transfusions after renal transplantation under cyclosporine, documentation of the efficacy of OKT3 as the first monoclonal antibody widely applied to combat rejection, further refinements of cyclosporine-based regimens, and analyses of posttransplant complications and side effects among cyclosporine recipients. Experimental strategies designed to induce immunologic unresponsiveness received continued attention. An initial clinical experience with renal transplantation after infusion of donor bone marrow and ALG was reported from the University of Alabama at Birmingham. Additionally, the growing experience with liver, heart, and pancreas transplantation was increasingly prominent. Particularly important were presentations on identifying objective risk factors to predict cardiac and liver transplant outcome and on improvements in pancreas allograft monitoring with such strategies as biopsy and urinary amylase determinations. Other presentations endeavored to expand the organ donor pool through use of donor organs previously considered suboptimal, debated the appropriateness and feasibility of reduced-size liver transplantation, and began to outline objective beneficial effects of pancreas transplantation on some of the secondary complications of diabetes.

The 1989 and 1990 meetings seemed to reflect maturation of the "cyclosporine

era." Investigators began to refocus their priorities on future transplantation strategies. Our annual forum for scientific exchange enjoyed unprecedented popularity: a record 269 abstracts were received for consideration by the Program and Publications Committee. This necessitated the move to parallel scientific sessions as a supplement to our traditional plenary meeting format (Figure 1). Provoking presentations explored barriers to xenotransplantation, the beneficial effects of ultraviolet irradiation, and the effectiveness of monoclonal antibodies to the L3T4 protein and TNF. Potential new pharmacologic strategies highlighted several new agents including FK506, 15-deoxyspergualin, rapamycin, and RS-61443. Pancreas transplantation for diabetes moved more solidly into the therapeutic arena. Refinements in cardiac and pulmonary transplantation technique, monitoring, and immunosuppression were emphasized. Similarly, reports on liver transplantation focused on strategies to reduce morbidity and mortality. Long a highlight of the annual meeting, the president's invited lecture was named as a memorial to David M. Hume (Table 2).

1991–Present

The 1990s began with a memorable 1991 annual meeting honoring Nobel laureate Joseph E. Murray for his pioneering work in transplantation. The meeting was attended by many of Murray's former trainees from this country and around the world, each of whom have become renowned in their own right. Murray delivered a moving address highlighting his personal recollections of early experiences with experimental and clinical renal transplantation. Additionally, Fritz Bach, the David M. Hume Lecturer, delivered an inspiring discourse on the future of xenotransplantation entitled "Transplantation: Moving into the 21st Century." The scientific program reflected tremendous enthusiasm for the future, with notable presentations on clinical use of the new agents FK506 and RS-61443. Experimental presentations focused on a growing list of other new agents, including rapamycin, brequinar, and 15-deoxyspergualin. Additional highlights involved heart-lung, pancreas, liver, experimental small intestinal, and cross-species transplantation.

Similarly, the immunobiology sessions were exciting, with several reports of ongoing work applying modern molecular technologies to transplantation. Also discussed were the effects of "humanizing" OKT3 gene sequences, efforts to demonstrate peripheral chimerism after transplants preceded by donor-specific bone marrow transfusion, and documentation of stable chimerism with UV-B and bone marrow in a rat islet and cardiac allograft model. Stimulating discussions followed presentations demonstrating successful induction of long-term specific tolerance in the allogeneic miniature swine model, work documenting CD8 T cell subset recognition in the mixed lymphocyte hepatocyte culture, and experimental evidence supporting the importance of soluble HLA molecules in allo-recognition. Undoubtedly, this memorable meeting invigorated those in attendance as they returned to their respective institutions determined to participate in the exciting forward movement of our field.

The most recent two years maintained the high-quality program so characteristic of the ASTS scientific meetings over the years. Competition for a place on the annual

Table 2.
ASTS Annual Scientific Program, Invited President's Lecture*

Year	ASTS President	Invited Lecturer	Title
1975	Thomas E. Starzl		
1976	Folkert O. Belzer	Francis A. Moore	Lessons We have Learned from the Transplant Experience
1977	Thomas L. Marchioro		
1978	John S. Najarian	Sir Peter Medawar	The Wider Implications of Transplant Surgery
1979	Frederick K. Merkel	Robert Good	Hematopoietic Transplantation in Clinic and Laboratory—A Vital Approach to Organ Transplantation
1980	Jeremiah G. Turcotte	Thomas E. Starzl Samuel Strober Sir Roy Y. Calne	New Immunosuppression Modalities
1981	James E. Cerilli	Hon. Phillip Crane (Illinois)	Legislative Initiatives in Transplantation
1982	Richard L. Simmons		Workshop—Problems in Clinical Transplantation
1983	G. Melville Williams		
1984	Oscar Salvatierra, Jr.	Hon. Albert Gore (Tennessee)	The 1984 National Organ Transplant Act
1985	H.M. Lee	Henry Desmaris	DRG and Transplantation Reimbursement
1986	Anthony Monaco	M. Garavoy L. Lachman G. Sonnenfeld R. Soberman	ASTS/ASTP Panel—Cytokines and Rejection
1987	Robert J. Corry	Prof. Walter Land, J. Southard	ASTS/ASTP Panel—Pancreas Transplant in Europe and Organ Preservation
1988	John C. McDonald	Bruce Rosner	Induction of Tolerance by Liver Transplantation
1989	J. W. Alexander	Herman Waldman	Monoclonal Antibodies for Immunosuppression and Tolerance
1990	Barry D. Kahan	John W. Kappler	T Cell Repertoire
1991	David E. R. Sutherland	Joseph Murray, Nobel Laureate	Experiences with Clinical and Experimental Transplantation
		Fritz Bach	Transplantation: Moving into the 21st Century
1992	Arnold G. Diethelm	M. D. Cooper	Evolution of the Immune System
1993	Clyde F. Barker	Jonathan Sprent	The Thymus in Self and Non-Self Discrimination

** In 1990, the annual lecture was renamed the David M. Hume Lecture in memory of Hume's pioneering work in our field.*

Figure 2. ASTS president Dr. David Sutherland; Nobel laureate Dr. Joseph Murray; and ASTS Program and Publications Committee chairman Dr. Marc Lorber during the 1991 Annual Scientific Meeting. The statue of the chimera in the foreground (pictured also in photo below) was presented to Dr. Murray, commemorating the pioneering work for which he was also awarded the 1990 Nobel Prize in Medicine and Physiology.

program has been increasingly keen, while innovative clinical and experimental transplantation science has generated enthusiastic discussion and debate. Developing technologies have provided important new insights into mechanisms underlying immune responses, and our membership has provided impetus for application to the transplant problem. The alphabet soup of new pharmacologic agents undergoing experimental and clinical study provide near-term hope for improvement. Islet, small intestinal, and cross-species transplants shine brightly on the horizon. At the same time, we struggle with critical practical issues, including the continued desire for improved organ preservation, more effective immunologic monitoring, and better use of the potential pool of organ donors.

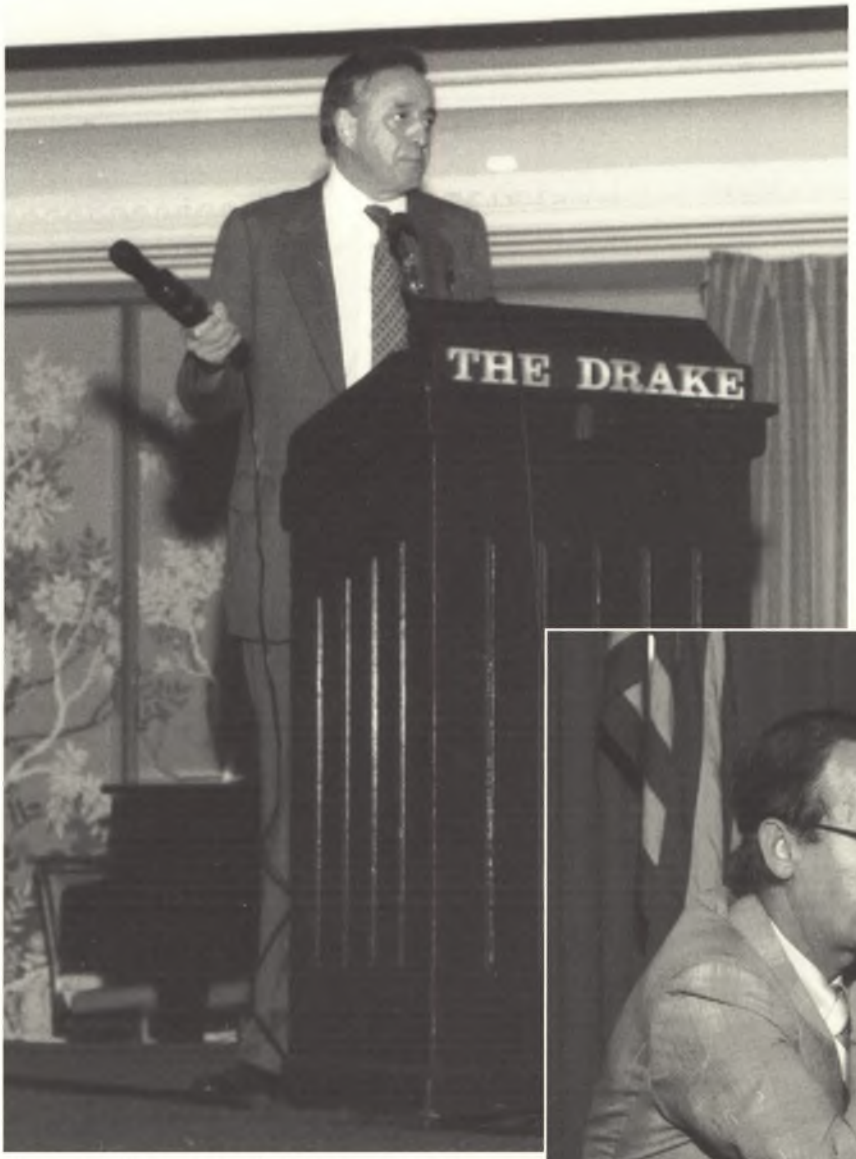
Perspective

Reviewing ASTS scientific programs of the past 20 years provides a remarkable catalogue of the rapid growth in our field. The yearly meeting has become an enthusiastically anticipated annual event. It brings the best in our field together for discussion and debate over burning scientific, and at times societal, issues. Beginning with the early meetings of the 1970s, the scientific sessions have provided critical impetus for progress as new data have been presented and established dogma has been challenged. The 1980s were characterized by rapid growth in clinical renal transplantation; the potential demonstrated by the pioneering early work became therapeutic reality as cyclosporine-based regimens were refined. The decade was also characterized by an explosion in clinical transplantation of other organs including pancreas, heart, lung, and liver. The rich character of our society was also enhanced by such events as the 1985 introduction of the annual ASTS/Upjohn Award, the 1990 dedication of the president's lecture to the memory of David Hume, the opportunity to honor Joseph Murray's Nobel Prize, and now the upcoming celebration of our 20th anniversary. Throughout this period, the ASTS membership has jealously guarded the high-quality scientific focus of the annual meetings. The continued dedication to principles of open and critical scientific dialogue set forth by our founding members should serve us well as we anticipate another 20 years of exciting progress.

FAMILIAR FACES

1979 Annual Scientific and Business Meeting

PHOTOGRAPHS COURTESY OF FRED MERKEL



Honorary Member Dr. Robert Good delivering the 1979 invited lecture at the Drake Hotel

Fred Belzer moderating the scientific session

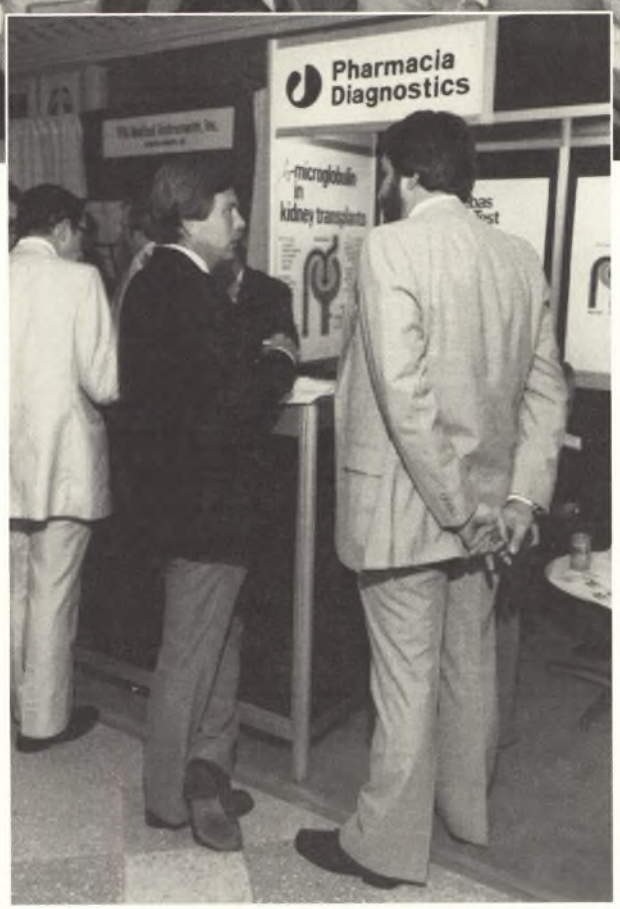
Marty Moses and Richard Dickerman participating in discussion following a scientific presentation

Chuck Shields making his scientific presentation

Olga Jonasson, first woman transplant surgeon, and Luis Toledo-Pereyra participating in discussion of paper

Ben Cosimi and Tony Monaco offering comments

Lunch at the Drake



Scientific and commercial exhibits, an important component of each annual meeting

Nicholas Feduska, Ron Filo, Duane Freier, Carl Groth, and Richard Simmons

Sol Penn taking notes on a patient for the transplant tumor registry

Frank and Judy Thomas

Sang Cho, Gerry Mendez-Picon, and Ted Mackett listening intently to a presentation

ASTS members enjoying The Chicago Brass Quintet at the Chicago Art Institute

Fred Merkel hosting annual banquet

Annual Banquet 1979

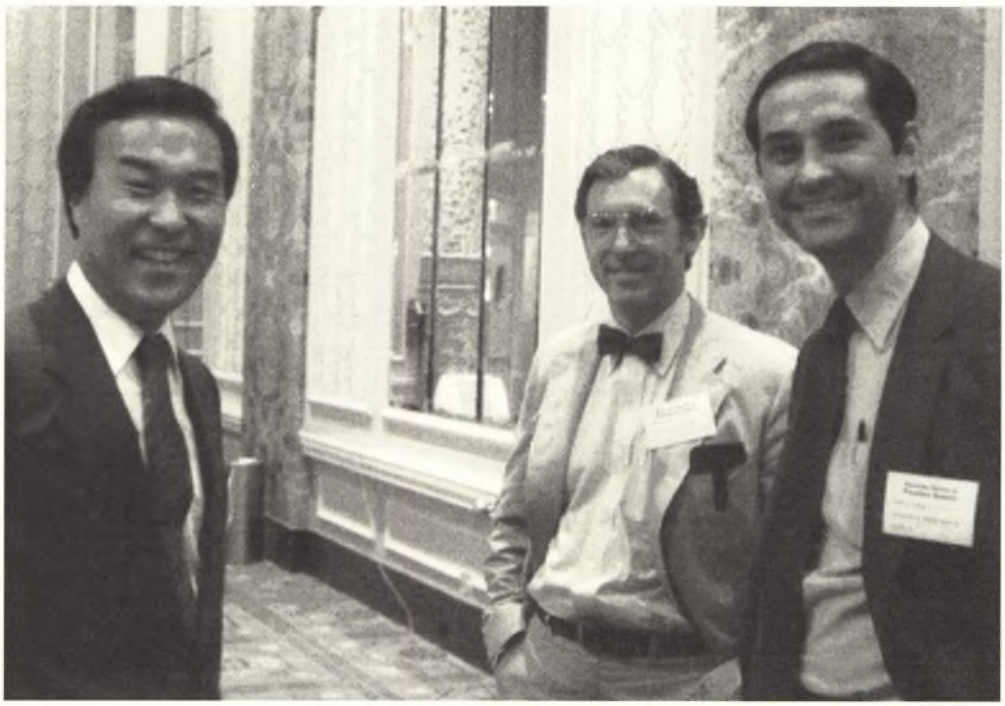
Annual Banquet 1979

Annual Banquet 1979

MORE FAMILIAR FACES

1985 ASTS Annual Scientific and Business Meeting

PHOTOGRAPHS COURTESY OF H.M. LEE



Fritz Bach, Hume Lecturer; Joseph Murray, Nobel Laureate; David Sutherland, ASTS President

IX

Scientific Progress: Immunobiology, Organs and Cells

Immunobiology

ANTHONY P. MONACO

The evolution of the immunobiology of organ transplantation can be traced clearly through the proceedings of ASTS. Over the past 20 years our members have been in the forefront in the discovery of new principles of immunobiology and in the application of immunobiologic methods to clinical transplantation studies. Important immunobiologic papers that have not been reviewed elsewhere in this monograph will be discussed in this chapter, with full titles and authors listed at the end.

The 1975 proceedings saw the first expression of what would be a long-term interest in suppressor cells and in the monitoring of immune activation and responsiveness, in association with rejection. It had been previously shown that rodent spleens harbor a population of T lymphocytes that can suppress immune responses and graft-versus-host disease (GVHD). Using a mixed lymphocyte culture (MLC) technique, Sampson's group (1) was one of the first to identify that such cells existed in humans. Spleen cell suppressor activity in MLC was nonspecific and could be abrogated by various immunosuppressive drugs.

Kerman et al. (2) correlated acute rejection in renal transplant patients with the percentage of active T cells (as defined by rosette formation) relative to total T cell counts. Active T cells fell with rejection and returned to normal levels with reversal of rejection or transplant nephrectomy. They concluded that active cells exited the blood to accumulate in and attack the target end organ, an immunobiologic principle proved years later with graft cell infiltration studies and sophisticated cellular markers.

Thomas et al. (3) made the first report of immunologic monitoring relative to immunosuppressive drug effectiveness. They correlated T and B lymphocyte levels and PHA and Con A reactivity with renal allograft rejection. If T cell levels and immune responsiveness were kept below 20% of normal with antilymphocyte globulin (ATG), they demonstrated that rejection reactions did not occur. In 1976, this focus on immunologic monitoring continued in further attempts to evaluate the immunologic capability or reactivity of transplant recipients pre- and posttransplant.

These monitoring studies focused on use of a battery of in vitro and in vivo assays, which were unfortunately limited by their nonspecific nature. Nevertheless, Thomas et al.(4,5) and Kerman and Geis (6) identified patients with a reduced tendency to reject allografts (so-called "low" or "non-responders") vs. others with a strong tendency to reject their grafts (so-called "high responders"). In the same area, the paradoxical situation of aggressive rejection by well-matched patients was investigated by Cerilli and Holliday (7). They made their first pioneering report on the identification of a recipient antiendothelial antibody in rapidly rejecting renal transplant recipients, an antibody directed to a vascular endothelial antigen not related to the major histocompatibility complex (MHC).

At the next two meetings the emphasis shifted from immunologic monitoring to in vivo and in vitro dissection of the types of immune mechanisms present during rejection and long-term survival. In 1977, Wood et al. clearly showed that long-term survival of enhanced cardiac allografts was reversible by a number of biologic methods (8). Stuart and Garrick (9) used the rat renal allograft model to stress the importance of fixed (as opposed to mobile) passenger leukocytes in allograft sensitization. Weber et al. (10) showed a salutary protective effect of islet transplantation on renal function and morphology in short- and long-term diabetic rats—an important observation to justify the expanding emphasis on islet transplant research to cure diabetes. At the 1978 meeting, Weiss, Stuart, and Fitch (11) studied the immunologic basis for long-term acceptance of LBN renal allografts by Lewis rats treated with donor spleen cells and antiserum against donor alloantigen. Using the in vivo graft-versus-host popliteal node assay, they showed that enhanced recipients can recognize and respond to donor alloantigens. However, there was an absence of immunologic memory in enhanced renal allograft recipients, as evidenced by failure to generate secondary cytolytic T lymphocyte (CTL) reactions.

Ascher, Rio, and Simmons (12) used the sponge allograft model to dissect the various cells involved in acute allograft rejection. They found that immune cells infiltrating a graft represent an enriched population of end-stage differentiated killer cells without helper and memory characteristics, while the spleens of recipient mice contained memory, helper, and a small number of killer cells. A most important finding was that specific cytotoxic cells appeared in both syngeneic and allogeneic sponge grafts of the same immune recipient, implying that the migration of the killer cells is only partially dependent on the chemoattractant capacities of specific alloantigens, i.e., nonspecific inflammatory factors may also be important in killer cell migration.

Two groups analyzed the potential role of suppressor cells in ameliorating human allograft rejection. Salvatierra et al. (13) showed that, when responder cells from 6-day-old bulk MLR cultures were added to new MLR, cultures containing responder cells autologous to the added bulk MLR cells, there was significantly less response to the allogeneic stimulator cells—consistent with the concept of proliferation of suppressor T cells in the initial bulk MLR. Suppressor activity was specific over a narrow range of MLR combinations. Similarly, Miller and associates (14) postulated that generation of specific suppressor cell activity was a mechanism of prolonged graft acceptance and might be a means to induce long-term graft tolerance clinically.

In the 1979 proceedings, Ascher, Hoffman, and Simmons extended their studies of cellular mechanisms of rejection. Using their sponge allograft model, they provided strong evidence that local alloantigen is not necessary for in vivo migration of specifically sensitized lymphocytes and that the local inflammatory reaction of healing may be a nonspecific chemoattractant. Also, the presence of certain chemoattractant factors at the sites of rejecting allografts precedes the influx of sensitized cytotoxic lymphocytes (SSCL). Such SSCL are activated and show both enhanced random and directed migration, compared with lymph node lymphocytes—a fact that could account for their previous observation (see above) of specific SSCL in syngeneic grafts. Thus, these studies first demonstrated that allograft sensitized SSCL have enhanced mobility and that chemotactic factors within a rejecting allograft probably affect lymphocyte migration.

The same model was used by Ferguson, Condie, and Simmons (16) to study the effect of ATG treatment on cells infiltrating an allograft sponge graft. ATG did not inhibit sensitization and development of specific cytotoxic cells after a sponge allograft; it only slightly delayed appearance of CTL in the sponge allograft, but dramatically decreased the number of specifically cytotoxic cells infiltrating the graft. However, this decrease in infiltrating cells was not due to peripheral depletion, since adequate alloreactive cells were found in the periphery. The authors hypothesized that ATG may also act in an unexplained way by interfering with active SSCL migration to the graft.

Hopt and Sullivan (17) from Minnesota later showed that specifically sensitized lymphocytes are able to initiate an increased recruitment of other unsensitized lymphocytes to the rejecting graft. Only small numbers of such SSL were required to initiate the increased recruitment, which was dependent on the continuous interaction between alloantigen and SSL and which continued during the rejection period. This phenomenon was postulated as a possible important amplifying mechanism in graft rejection. It is of interest that upregulation of MHC antigens on rejecting grafts was not known at the time, but could have easily explained this observation.

The immunobiologic focus of the 1981 and 1982 proceedings shifted again to the role of suppressor cells and suppressor factors. Thomas et al. (18) previously showed that prolonged allograft survival in rhesus monkeys could be achieved by a short course of ATG therapy and that persistent graft survival continued after T cell recovery. With coculture experiments, they showed that suppressor cells developed in ATG recipients and persisted for several weeks after cessation of ATG. At the same time, Maki, Simpson, and Monaco (21), using coculture MLR studies, showed in mice that nonspecific suppressor cells develop after ALS treatment. They further showed that the additional antigeneic stimulation by skin allografting shifts the antigen specificity of suppressor cells from nonspecific to specific for donor antigens. In mice, these suppressor cells were Lyt 1- 2+ T cells. Clearly, these two studies provided the strongest evidence that generation of suppressor cells accounted for a significant portion of the immunosuppressive effect of polyclonal ALG.

Furthermore, Maki, Okasaki, Wood, and Monaco (19) used standard lymphocyte transfer suppressor assays and MLR coculture techniques to show that suppressor

cells play an important role in the induction and/or maintenance of unresponsiveness to skin allografts in ALS-treated, blood-transfused mice. This finding was strongly reinforced by Agostino, Kahan, and Kerman (22), who used a suppressor cell assay involving a one-way MLC to show that clinical recipients of more than 5 blood transfusions had enhanced (nonspecific) suppressor cell function. They suggested that enhanced survival after transfusion could be due to suppressor cells; measuring suppressor cell function preoperatively might discriminate potentially less responsive allograft recipients. At the same time, the extraordinary role of antibody in inducing prolonged survival of at least experimental allografts was dramatically illustrated by Stuart, Fitch, and McKearn (23), who showed for the first time in the LB NF_1 to L rat renal allograft model that organ allograft survival can be enhanced by passive immunization with antiidiotype antibody against an anti-class I monoclonal antibody. The antiidiotypic antibody was also strikingly effective in suppressing a primary anti-BN antibody response to BN lymphoid cells.

An additional important 1981 report was by Cerilli and Brasile (20), who dramatically showed that poor graft survival, regardless of HLA match grade on negative T or B cell crossmatches, frequently occurred when a positive monocyte crossmatch was detected pretransplant. They had previously shown that sera containing antibody to a monocyte also reacted to vascular endothelial cell (VEC) antigen from the specific donor. This strongly suggested that the VEC is the clinically important antigen of the antimonocyte antibody. They suggested that a pretransplant positive antimonocyte crossmatch might be a contraindication to transplantation. A year later at the 1983 meeting, this same group (Cerilli, Brasile, Clarke, Galouzis) reported on the vascular endothelial cell specific antigen system (28). They showed that antibody to VEC correlated with aggressive rejection in the absence of positive crossmatches to T and B lymphocytes.

A dominant theme in transplantation immunobiology was not evident in the 1983 and 1984 meetings. Maki and Monaco (24) used a somatic cell hybridization technique to obtain hybridoma cell lines of antigen-specific and nonspecific suppressor T cells derived from mice rendered unresponsive to skin allografts with ALS and blood transfusions. Antigen-specific and nonspecific suppressor molecules were produced by these T suppressor cell hybridomas, which were capable of suppressing various MLR in vitro. Cyclosporine A induces reversible inhibition of T helper cells, a circumstance known to induce donor-specific suppressor cells. Yasumura and Kahan (25) produced prolonged survival of rat renal allografts using a combined protocol of cyclosporine and solubilized donor-specific antigen. They demonstrated that the prolonged survival induced by this protocol was also mediated by suppressor cells. There was renewed interest in experimental small bowel transplantation. Raju, Cayirli, and Didlake (26) showed very significant prolonged survival of both heterotopic and orthotopic small bowel allografts in dogs, using cyclosporine and prednisone. Xylose absorption was found not to be a useful marker of rejection. Pomposelli, Maki, et al. (27) detailed the clinical syndrome of graft-versus-host disease (GVHD) after small bowel transplantation in rats, using a one-way GVHD model. They demonstrated for

the first time that clinical GVHD correlates well with nonimmunologic and immunologic assays of GVHD such as splenomegaly and in vivo popliteal lymph node assays.

In 1985, Oluwole, Lau, Reemtsma, and Hardy reported that pretreatment of AC1 rats with W irradiated donor-specific Lewis blood prolonged survival of Lewis cardiac allografts in this weak responder combination. In the AC 1 to Lewis (strong responder) combination UVB transfusions are ineffective. However, with addition of a modest course of peritransplant cyclosporine, UVB irradiated blood transfusions were markedly effective even in the strong combination (29). A very important paper by Pierce and Watts showed that, in a model of tolerance produced by donor bone marrow infusion with fractionated sublethal recipient irradiation, the tolerance was transferred (and most likely maintained) by persistent donor lymphoid cells (30). They postulated a T cell mediated donor antihost receptor response or a veto cell type mechanism. Interestingly, in the bone marrow and polyclonal antilymphocyte serum tolerance model, a "veto" cell mechanism has clearly been identified (see below).

Also in 1985, van Buren et al. provided some of the first evidence that nutrition was important in immune function (31). They showed that dietary nucleotides were a requirement for helper-inducer T lymphocyte function. Nucleotide-deprived mice failed to exhibit normal levels of Thy 1.2 and Lyt 1 + lymphocytes after immune stimulation. The phenotypic shift was associated with depressed IL-2 production and with increased susceptibility to opportunistic infection. Yoshimura and Kahan presented evidence that specific T suppressor cells, isolated from rats with prolonged grafts secondary to cyclosporine and donor-specific antigen treatment, could be expanded with increased suppressor cell effect by in vitro cultivation with specific soluble transplantation antigen (32). Brasile et al. (33) reported on the identification of antibody to VEC in cardiac transplant recipients who had aggressive rejection in the absence of cytotoxic antibodies to lymphocytes (i.e., a negative lymphocyte crossmatch). This study showed that anti-VEC antibody may explain hyperacute rejection in cardiac allograft recipients as it has for certain renal allograft recipients.

In 1986, Shelby et al. provided evidence that inhibition of prostaglandin synthesis by prostaglandin inhibitors at the time of blood transfusions had a detrimental effect on induction of transfusion-induced immune suppression—a finding consistent with elevated prostaglandin levels in patients receiving multiple blood transfusions (34). Further examination of the transfusion effect was presented by Terasaki et al. They showed that blood transfusion with peritransplant immunosuppression prolonged graft survival—a result consistent with a clonal deletion hypothesis (i.e., that transfusions pretransplant immunize the host and then supplemental immunosuppression kills the responding clones of activated cells) (35). In clinical studies, Billingham et al. showed that in patients given DST and azathioprine pretransplant, specific T cell priming occurred—a finding consistent with the conclusions of Terasaki et al. (36). Along these lines, Jordan et al. (37) presented evidence that the reported inhibition of functional responses of bulk lymphocyte populations by prostaglandin E2 was subset specific. Using a variety of in vitro assays, they showed that allosensitized helper cells—but not effector T cells—are functionally inhibited by PGE2 in a subset-specif-

ic fashion. In addition, these observations provided additional evidence of distinction between these two classes of T cells.

In 1987, less emphasis was on immunologic mechanisms. Rather, the focus was on efforts to modify defined immunologic reactions in experimental systems. Shaffer and the Harvard-Deaconess group presented studies for the Upjohn Award. For the first time, they showed that GVHD in the rat after small intestinal transplantation could be prevented by pretreating the donor with polyclonal antilymphocyte serum. Obviously, this new concept of donor pretreatment before organ procurement was ideally suited for potential clinical application (38). Van Buren et al. showed that a nucleotide-free diet was synergistic with cyclosporine in prolonging rat cardiac allograft survival, again emphasizing that such a diet might be clinically useful as adjunctive immunosuppressive therapy (39). Grant et al. from London, Ontario, gave a landmark paper showing that cyclosporine reliably prevented rejection after small bowel transplantation in pigs and allowed not only long-term survival, but also excellent nutrition and normal growth. These were the first large animal studies to emphasize and demonstrate the potential of small intestine transplantation for clinical short gut syndromes (40).

In 1988, two important biologic presentations were given for the Upjohn Award. First, Yamaguchi et al. from Bollinger's group (41) provided strong evidence that Class I MHC antigens prolonged survival of rat hepatic allografts—a concept now strongly supported by certain clinical observations and other experimental studies. Second, Barber (42) presented the first of his pathfinding clinical reports on the salutary effect of cryopreserved donor-specific bone marrow infusion on cadaver renal allograft survival.

Chester and Sachs (43) further defined the mixed chimerism protocol as a preparative tolerogenic regimen, showing that reconstitution with various mixtures of donor-recipient bone marrow ratios led to tolerance in multiple allogeneic donors. Sollinger et al. (44) provided evidence that enhanced thyroid allograft survival after organ culture was due to loss of antigen presentation, although Class I targets were preserved. Quigley et al. (45) described interesting experiments showing that induction of immunologic unresponsiveness by antigen pretreatment was mediated by CD4+ T cells, which appeared transiently in the splenic compartment and later in the thoracic duct lymph (45). Diflo et al. (46) demonstrated the existence of subclinical GVHD in the fully allogeneic rat small intestine transplant, with prolonged survival due to cyclosporine. These studies emphasized the potential need to institute other measures (such as donor pretreatment) to prevent GVHD, even with effective immunosuppression.

In 1989, Kahan et al. (47) analyzed the mechanism of tolerance induced in rat cardiac allografts by total body irradiation and solubilized donor-specific antigen. They showed that tolerant animals had not only activated suppressor elements but also reduced cytotoxic precursor cells. These studies were among the first of many on tolerance induction in adult animals, emphasizing that multiple immune mechanisms (here suppressor cells and clonal deletion or reduction) are involved in tolerance induction or maintenance. In an Upjohn Award presentation, Hardy and the Colum-

bia group (48) described the effect of interstitial Class II positive cell depletion by donor pretreatment with gamma irradiation in a rat allograft model. They presented evidence of differential immunogenicity between vascularized cardiac allografts and islet allografts. The apparent greater immunogenicity of cardiac allografts, compared with islets, may be due to either (1) a quantitative difference in the number of residual Class II-positive cells in hearts over islets or a greater non-MHC antigeneic load in hearts due to their larger size or (2) a qualitative difference between hearts and islets secondary to the presence of vascular endothelium in the immediately vascularized heart that can present alloantigen and provide a greater immunostimulation for rejection.

Also in 1989, Thomas et al. (49) studied the immunosuppressive effect of FK506 by in vitro induction of allogeneic unresponsiveness in human CTL precursors. They analyzed the immunosuppressive mechanism of action of FK506 on human allogeneic MLR-induced CTL activation, showing that FK506 induced suppression of cell-mediated lymphokines by peripheral blood mononuclear cells in vitro.

In addition to suppressing the response of alloreactive CTL precursors, FK506 reduced the ability of irradiated allogeneic PBML to induce CTL generation, thus emphasizing the multiplicity of effects of this and presumably other immunosuppressive drugs. In additional tolerance studies, Guzzella et al. from Sachs' group showed nicely that kidney allograft tolerance could be induced across MHC barriers using bone marrow transplantation in miniature swine (50). Expanding on the use of bone marrow as a tolerogen in large animal models, Hartner et al. (51) from Harvard-Northeastern showed that tolerance induced in renal allografts in dogs with ALS and donor bone marrow could be augmented with cyclosporine—an important point relative to clinical application. Expanding on their previous studies with anti-CD4 mAB, Madsen et al. (52) showed that tolerance could be induced with anti-L3T4 antibody and donor MHC antigen in mouse cardiac allografts. Synergism in tolerance induction was also demonstrated by Florence et al. from Kahan's group (53), who also showed a synergistic effect of extracted donor antigen with total lymphoid irradiation (TLI) to induce alloantigen-specific unresponsiveness.

In a 1990 Ortho Award presentation, Shaffer et al. (54) from Harvard-Deaconess showed that certain antilymphocyte monoclonal antibodies given as donor pretreatment before small intestine procurement effectively prevented GVHD in the recipient posttransplant. Pan-T mAB were more effective than specific subset mAB but none was as effective as polyclonal antilymphocyte antibodies. These studies also emphasized that, to prevent GVHD in the recipient, an effective antibody must be given to the donor—with appropriate doses and timing—to deplete the mature T cells in the mesenteric lymph nodes of the donor small bowel graft. In a similar mode, Dunn et al. (55) from Minnesota showed that pretreatment of Fl hybrid recipients with a short segment of parental small intestine, followed by transplantation of the entire parental intestine, protected them from lethal GVHD. Several mechanisms for this protective effect were proposed: generation of recipient cytotoxic lymphocytes directed at donor MHC receptors, recipient antibodies directed at donor MHC, or production of specific suppressor elements.

A number of 1990 papers analyzed the activity of specific subsets of lymphoid cells in alloimmunity and tolerance. Thomas et al. (56) presented elegant renal allograft studies showing that immunologic tolerance induced in primates with polyclonal antilymphocyte serum and donor-specific bone marrow was mediated by a veto cell mechanism. They used MLR-induced CTL assays to show that bone marrow cells (BMC) specifically suppressed CTL activity to peripheral blood lymphocytes (PBL) from the bone marrow donor. The suppression was mediated by a small population of BMC that expressed a CD2+, CD8+, CD16+, DR-, CD3-, CD38- phenotype. In vitro studies strikingly correlated with in vivo studies. ALG-treated primates given DR-BMC or DR CD3- DBMC infusions had significantly prolonged graft survival. But in recipients given CD2-DBMC or DR-CD16-DBMC infusions, the tolerance-inducing effect of BMC was absent. They concluded that a veto mechanism may control the induction phase of allograft tolerance in this model. Such a mechanism might provide a critical period of CTL suppression to allow development of host immunoregulatory mechanisms necessary for maintaining graft tolerance.

Additional evidence that a veto mechanism could be operative in the ALS-bone marrow tolerance model was provided by Takahashi and Maki of Harvard-Deaconess (57). They showed that IL-3 dependent suppressor cell clones could be developed from normal mouse C3H/He bone marrow; these clones were capable of suppressing specific anti-C3H/He (self) responses. They also showed that cloned cells of this type induced specific prolonged survival of C3H/He allografts in ALS-treated recipient mice. Sablinski et al. of Tilney's group (58) provided interesting evidence for a differential role of CD4+ cells in the sensitization and effector phases of accelerated graft rejection. In their model of accelerated cardiac allograft rejection induced in rats with prior skin grafting, a CD4 mAB given in the sensitization (between the skin and heart transplant) but not in the effector phase (after the heart transplant) phase abrogated the fulminant (<36 hour) rejection and prolonged cardiac graft survival to up to 11 days. This important first report of the successful use of CD4 mAB in sensitized recipients of vascularized organ transplants stressed, very appropriately, the role of CD4+ cells as potential targets for immunosuppression therapy in the sensitization phase of accelerated transplant injury. The salutary effect was probably due to both depletion and functional inhibition of CD4+ T cells and, surprisingly, was achieved with minimal doses of anti-CD4+ mAB.

In 1991, the immunobiologic focus continued to be on tolerance. Ming-Sing et al. (59) showed that UV-B modulation of donor bone marrow cells facilitated the induction of lymphohematopoietic chimerism and transplantation tolerance in rat islet and heart allografts. This constituted another unique application of W-B to facilitate nonresponsiveness. Smith et al. of Sachs' group (60) identified another tolerogenic effect of donor bone marrow. They studied miniature swine that initially had induction of tolerance to kidney donor Class II antigens by bone marrow transplantation, in association with x-ray and cyclophosphamide treatment. A short course of cyclosporine allowed the induction of specific tolerance in fully allogeneic renal allografts. A major observation was reported by Barber et al. (61), who identified peripheral blood chimerism by polymerase chain reaction in renal allograft recipients transfused with

donor bone marrow. Importantly, this showed that chimerism was closely associated with an absence of rejection reactions and that chimerism waxed and waned over the posttransplant course. Of special note was the small percentage of control patients who became donor chimeras even though they did *not* receive donor bone marrow infusions. The low level of chimerism in control patients was due, in all probability, to migration of cells from the graft. The potential significance of this concept was later brilliantly expanded by Starzl.

In 1992, emphasis shifted in part to tolerance induction by intrathymic alloantigen injection. Markmann et al. (62) provided evidence for at least short-term and partial clonal deletion in adult mice after intrathymic inoculation with lymphoid cells. Nakafusa et al. (63) also showed that intrathymic injection of splenocyte alloantigen induced specific tolerance in cardiac, but not in skin or renal, allografts. The variability of this model by species and protocol was emphasized by Ohzato and Monaco (64), who showed that induction of specific tolerance in skin allografts could be produced in ALS-treated mice with intrathymic splenocyte injection. The degree and duration of tolerance induced was a function of the dose and timing of intrathymic splenocyte alloantigen, as with other types of adult tolerance models. Additional evidence for the veto concept as a mechanism of tolerance associated with hematopoietic cell infusion protocols was provided by Pierce and Watts (65). They showed that Thy 1 + donor cells functioned as veto cells in the induction and maintenance of tolerance across an MHC disparity in mixed lymphoid radiation chimeras. Auchincloss et al. (66) reported initial studies in skin graft rejection in Class II deficient mice. Although rejection was modified in association with Class II deficiency, it was not prevented.

In 1993, the immunobiologic studies continued to focus on tolerance, but also considered other important areas. Verbanac et al. (67) provided provocative studies suggesting that transforming growth factor-Beta (TGF) may play a part in the veto mechanism that functions in transplant tolerance induced by polyclonal antilymphocyte serum and donor bone marrow. Smith et al. (68) also presented an elegant and sophisticated study, using transgenic mice to assess the donor bone marrow cell-derived chimerism in tolerance induced with ALS and bone marrow. They also showed that chimerism varied in different tissues at various times posttransplant and correlated moderately well with absence of rejection. Wren et al. (69) extended the mixed chimera tolerance model to show that both rat and mouse T lymphocytes from xenogeneic chimeras (rat- and mouse-to-mouse) are positively selected to be restricted to mouse, and not rat, thymic stromal MHC for antigen presentation. In the intrathymic tolerance model, Ohzato et al. from Harvard-Deaconess (70) used limiting dilution analysis and mAB to specific T cell receptors. They showed that intrathymic tolerance was associated with clonal reduction, but not complete clonal deletion, in long-term specifically tolerant animals. Additionally, Rosengard et al. from Sachs' group (71) extended their tolerance model in miniature swine (cited above) to show that renal allograft tolerance persists after retransplantation. In extraordinarily comprehensive and technically demanding studies, Dahmen et al. (72) from Pittsburgh showed that partial or "split" tolerance could be identified in the

mouse after orthotopic liver transplantation. Auchincloss et al. (73) extended these studies in Class II deficient mice: Class I and Class 11 deficient mice were crossed to produce MHC "knockout" mice, whose allografts were rejected. These interesting studies among other things attested to the redundancy present in the alloimmune rejection reaction.

In summary, I have discussed only a portion of the significant ASTS presentations over the years. These presentations have exemplified the fundamental principle that makes ASTS unique: Transplant surgeons are equally capable and conversant with the clinical as well as the immunobiologic aspects of transplantation. Not only have ASTS transplant surgeons been able to understand and apply new basic immunologic principles and methods to their clinical transplant efforts, but also they have been in the forefront of creating and defining this new knowledge. Indeed, a conversation I had with a visiting basic immunobiologist who attended one of our early meetings was telling. After listening to a superb immunobiologic paper delivered by one of our senior members introduced as the chief transplant surgeon at a certain institution, the basic immunobiologist—who had long admired this member's previously published immunologic papers—leaned over and said to me, "Gee, I never realized he was a surgeon!"

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Kidney

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The first ASTS scientific meeting was held on May 23, 1975, at the Drake Hotel in Chicago, Illinois. The meeting consisted of a single day during which 24 scientific papers were presented—most on the topic of kidney transplantation. Certainly, one of the highlights of this meeting was the Presidential Address by the first president, Thomas Starzl. All transplant surgeons, especially the younger generation, should read this excellent paper, published in 1976 in *Surgery.* Starzl clearly outlined the goals and possible pitfalls of a young society. The society can be proud to look back 20 years and realize that most of the goals as outlined by Starzl were actually met.

Kjellstrand from Minnesota presented a series of 94 patients with insulin-dependent diabetes mellitus who underwent 99 renal transplants between June 1969 and January 1975. The cumulative 5-year patient survival was 62% for living related and 42% for cadaver transplants. One of the important observations in this series was that visual acuity, which had rapidly deteriorated in uremic diabetics, remained stable posttransplant. Another important communication was the paper presented by Salvatierra from the University of California, San Francisco, showing that a policy of low immunosuppression did not jeopardize graft survival and that patient survival was significantly improved. Salvatierra compared two groups of patients, one transplanted between 1968 and 1972 and the second between 1972 and 1975. In the earlier group with high immunosuppression, 1-year patient survival with cadaver donors was 79%; graft survival, 49%. In the second group with low immunosuppression, 1-year patient survival with cadaver donors was 91%; graft survival, 55%. Toledo-Pereyra from Minnesota compared cold-stored kidneys with pulsatile-perfused kidneys and showed a 20% better overall 3-year functional survival of the perfused kidneys. This paper contradicted the findings presented by Terasaki from a cooperative group, which suggested that pulsatile perfusion was associated with a high rate of transplant failure. This debate continued for several more years. Monaco from Boston presented a most interesting clinical case in which a cadaver kidney recipient was treated with antilymphocyte globulin (ALG) and, on the 25th postoperative day, received bone marrow cells from the original donor. Previous studies in mice by this

group had suggested that this protocol produced increased graft survival, compared with antilymphocyte serum (ALS) alone; they suggested that this resulted from a type of active enhancement. More than a decade later, the Birmingham group reestablished this protocol in patients receiving cadaver kidneys.

The second scientific meeting, 1 1/2 days long, was held on May 21-22, 1976, in Chicago. This was the first meeting in which the ASTS president was given the privilege to invite a guest lecturer. We were fortunate to have as our first guest lecturer one of the pioneers in organ transplantation, Dr. Francis D. Moore from Boston, who spoke about the lessons we had learned. Corollary to his lecture was a paper by Stuart from Chicago on "progress in legal definition of brain death." It is interesting to realize that at that time only 12 states in the U.S. had accepted the concept of brain death. Criteria from the National Institutes of Health (NIH) included (1) unresponsivity, (2) apnea, (3) dilated pupils and absence of cephalic reflexes, (4) electrocerebral silence, and (5) a confirmed test of absence of cerebral blood flow by angiography, isotope bolus curve, retinoscopy, or echoencephalography. Thomas from Richmond presented a most interesting paper on immunologic monitoring of long -surviving renal transplant recipients. His team studied a group of patients, imperfectly matched for HLA antigens, who had received their graft 2 to 12 years before. Of the successful long-term recipients, 73% showed high serum levels of mixed lymphocyte culture (MLC) blocking activity. Successful long-term transplantation was consistently associated with a specific defect in recipient ability to generate cytotoxic cells against donor, seen at 8 to 12 years. Cerilli from Columbus presented a paper entitled "Antivascular endothelium cell antibody: Its role in transplantation." His team tested eight groups of patients for the presence of circulating antibody (IgG) directed against vascular endothelial cell antigens. They suggested that indirect immunofluorescent antibody tests (IFA) consistently detected antibody in serum samples that were negative for lymphocyte toxic activity and that the presence of IFA antibody to vascular endothelial cells had a much better correlation with both clinical course and renal allograft rejection than the lymphocyte toxic panels.

Two papers were presented on the influence of presensitization on the success rate of transplantation: "Host presensitization and renal allograft success at a single institution" by Ferguson et al. from Minnesota, and "The influence of presensitization on graft survival rate" by Salvatierra et al. from San Francisco. It had been suggested at that time that presensitization negatively influenced subsequent graft survival. But both of these papers suggested the opposite: with a sensitive crossmatch, the results for presensitized patients were no different than for nonsensitized patients. Both papers emphasized the need for frequent recipient serum sampling so that transient high levels of cytotoxin would not escape detection. Interestingly, in subsequent years, this concept was challenged—especially by the Canadian group—in that an immediate pretransplant serum sample and sensitive crossmatch were sufficient.

The third ASTS scientific meeting was again 1 1/2 days long and held in Chicago. Three papers were presented on clinical kidney preservation by the San Francisco, Indianapolis, and Alabama groups. The San Francisco and Indianapolis groups used perfusion preservation with either cryoprecipitated plasma or an albumin perfusate,

and the Alabama group used cold storage. All three presented an approximately 24% postoperative dialysis rate. One major difference was that the San Francisco group included a large number of patients who received kidneys from non-heart-beating cadavers. Thomas from Virginia emphasized the importance of the potency of antilymphocyte globulin (ALG) in clinical transplantation. ALG potency was tested by its ability to prolong skin graft survival in primates. In this series, 76 cadaver transplant patients given a high-potency ALG immediately posttransplant showed no graft loss to rejection. Pfaff from the University of Miami studied the effect of rabbit antithymocyte globulin (ATG). No benefit accrued in haploidentical living related recipients. In cadaver kidney recipients, ATG improved graft survival as measured at 3 months, but not at 12 months. Cerilli from Columbus presented an analysis of haploidentical living related transplants for high mixed lymphocyte complex (MLC) stimulation and low MLC stimulation. Donor-recipient combinations with a stimulation index of greater than 5 resulted in a 50% rejection rate; those combinations at low MLC stimulation only had a 5% rejection rate.

At the fourth scientific meeting, Feduska from San Francisco addressed the question of the beneficial effect of blood transfusions in a paper entitled "Do blood transfusions really enhance the possibility of a compatible transplant?" His group's conclusion was that a beneficial effect was achieved with one to five transfusions pretransplant, but that more transfusions resulted only in increased sensitization. This group, of course, later introduced the concept of donor-specific transfusions in living related transplantation. Two papers considered the efficacy of ATG or ALG in the immediate postoperative period for cadaver recipients. Diethelm from Alabama suggested that the adjunctive use of ATG significantly increased the graft survival of these patients, and Bennett et al. from Philadelphia came to the same conclusion using Minnesota ALG. Stuart et al. from Chicago analyzed the role of splenectomy in clinical renal transplantation. In their series, graft survival in the splenectomy group at 1 year was 72%, compared with 30% in the nonsplenectomized group. Today's readers must realize that splenectomy before renal transplantation was widely practiced in the U.S., especially in the Midwest. It also is of interest that splenectomy was subsequently abandoned before the introduction of cyclosporine. Firlit from Chicago was one of the first to use serum B7 microglobulin radioimmunoassay as a reliable indicator for the early recognition of acute rejection in children receiving renal transplants. Serum creatinine can be a poor indicator for rejection in small children who receive adult homografts. Ascher from Minnesota presented her group's paper on "Analysis of 100 second renal allografts: Results from a single transplantation center." They suggested that, because of extremely poor results, retransplants may not be justified for patients who suffered early rejection of their first graft. With the scarcity of donor organs, retransplantation of high-risk patients is still debated today.

At the fifth scientific meeting, several papers focused on the prevalence and morbidity of cytomegalovirus virus (CMV) infection in renal transplant recipients. Whelchel from Alabama showed that symptomatic recurrent CMV infection drastically influenced patients and graft survival, compared with nonsymptomatic infection. Andrus from Rochester, New York, even suggested that all recipients and donors

should be tested for antibodies to CMV and that only positive donors should provide kidneys to CMV positive recipients. Cochrum from San Francisco presented the first report on donor-specific blood transfusions in haploidentical related allografts with high MLC stimulation. That paper, as well as several others from the same group, initiated the great enthusiasm in the use of donor-specific transfusions. Again, many papers were presented regarding the use of ATG or ALG in clinical transplantation, either prophylactically or for reversal of acute rejection. These papers were presented by Shield from Boston, Alexandre from Brussels, Brendel from Germany, and Thomas from Virginia.

At the sixth scientific meeting, rather than an invited guest lecturer, a special session was held on new modalities of immunosuppression. The speakers were Strober from Stanford (total lymphoid irradiation) Starzl from Colorado (thoracic duct drainage), and Calne from Cambridge, England (cyclosporine). The results of cadaver renal transplantation had leveled off at about 40% to 50% long-term graft survival, so all ASTS members were anxious to hear about new horizons in this field. This was one of the first presentations on cyclosporine which, of course, revolutionized organ transplantation in the subsequent decade. Two papers were on the management of renal artery stenosis in transplant recipients. Mendez-Picon from Virginia advocated an aggressive surgical approach, while Sniderman from New York presented one of the first papers on percutaneous transluminal dilatation as an alternative treatment (balloon dilatation had emerged as an alternative treatment in peripheral vascular surgery). The role of blood transfusions, again, was addressed by several presentations. VanderWerf from Phoenix studied donor-specific transfusions in a small number of haploidentical high-MLC living related combinations and suggested studying this approach in a multicenter randomized trial. Corry from Iowa suggested that blood transfusions given on the day of transplant had a beneficial effect, without the detrimental effect of possibly sensitizing the recipient against the potential donor. Spees presented data from the Southeastern Organ Procurement Foundation (SEOPF) data base, concluding that a major benefit was associated with blood transfusions given more than 10 days pretransplant in primary cadaver renal allograft recipients. Kerman from Houston presented "Improved allograft survival of strong responder high-risk cadaver recipients with adjuvant immunosuppressive therapy," suggesting that low responders could be treated with Imuran and prednisone only, but that high responders should be treated with prophylactic ATG.

At the seventh scientific meeting, papers began to appear for the first time on cyclosporine. Kerman from Texas reported on 6 cadaver allograft recipients treated with cyclosporine, and concluded it was a potent immunosuppressive agent capable of improving allograft survival, even in strong responder high-risk recipients. Rynasiewiciz from Minnesota studied 12 patients treated with cyclosporine and compared them to 12 patients in the azathioprine-ALG group. Although there was no patient or graft loss in either group, more patients in the conventionally treated groups required treatment for rejection. These authors noted that serum creatinine was higher in the cyclosporine group, although it was not statistically significant. Klintmalm, then from Denver, reported on 66 cadaver kidney recipients treated with

cyclosporine and prednisone. The initial dose of cyclosporine in this series was 17.5 mg/kg; 14 of these patients developed hepatotoxicity. Reducing the cyclosporine dose normalized the serum bilirubin. Lum from Minnesota described 89 primary kidney transplants recipients under 10 years of age. Most grafts were from parents, although 21 were from cadavers. Patient survival at 5 years was 86%; graft survival, 57%. Her group concluded that transplants maximized growth and development, and thus should be performed at the earliest age possible .

Cerilli from Iowa State presented more of his work regarding the concept of an antigen system distinct from the HLA antigens, present on vascular endothelial cells. In a paper entitled "A preliminary study of the significance of monocyte cross-matching in renal transplantation," his group suggested that sera containing antibodies to a monocyte also reacted to the vascular endothelial cell antigen from the same donor. They suggested that recipients with a positive monocyte crossmatch to the donor should not be transplanted, regardless of the tissue match for the crossmatch result with PMV lymphocyte. Mendez from Los Angeles presented 20 haploidentical high stimulating MLC living related donor recipient pairs who underwent donor-specific transfusions (DST). Of these patients, 85% had successful results; Mendez's group concluded that DST appeared to be a highly successful technique for primary living related donor transplantation. Spees from Baltimore presented findings that preoperative, but not perioperative, blood transfusions improved primary cadaver and living related transplant graft survival; this contradicted an earlier study by the Iowa group, suggesting that they had equal beneficial effects. The many papers over the previous 7 years on the influence of blood transfusions reflected the great interest of the transplant community in this particular subject. Hammer from Germany introduced the topic of fine-needle aspiration cytology in the care of transplant recipients, suggesting it was safe and could distinguish acute rejection from acute tubular necrosis (ATN). In 12 patients, fine-needle biopsies were done at l- to 2-day intervals without apparent detrimental effect. Schweitzer from Hartford Hospital reported on a method of rapid in situ cooling, which was used in 150 human cadaver kidneys. Femoral catheters were inserted in the donors, either after cardiac arrest or immediately before impending cardiac arrest. The results, with tubular necrosis, were better than or equivalent to immediately excised kidneys with sustained circulation. With the present renewed interest in the use of non-heart-beating cadaver donors, these excellent results speak for themselves.

One of the highlights of the eighth scientific meeting in 1982 was the delightfully humorous Presidential Address by Dick Simmons. Kidney transplantation topics still dominated. Fish from Texas presented evidence that thoracic duct drainage does not prevent hyperacute rejection, as had been suggested by other authors. Mozes from Chicago presented a paper entitled "Splenectomy or partial splenic embolization and ALG: Evidence for an additive effect on cadaver renal allogram survival." One of the problems of this study was not that the splenectomized group did so well, but that the control group did extremely poorly—32% 1-year graft survival. Novick from Cleveland did one of the first controlled prospective randomized double-blind studies of ALG as an immunosuppressive adjunct in cadaver renal transplantation.

Although the number of patients in this study was small (only 67), the 1-year graft survival was 68% in the ALG group, 47% in the control group. Both Light from the Walter Reed Army Medical Center and Whelchel from Birmingham suggested that stored blood for DST was as effective as fresh blood and decreased the rate of sensitization. Schulak from Iowa presented "The effect of DR matching on rejection in first cadaver kidney transplantation," showing that better matched patients for DR had fewer rejections and better long-term graft survival. It is interesting that the effect of DR matching on primary and retransplanted recipients was much debated during this time. Even with today's improved immunosuppression the DR effect still seems quite important. Two papers addressed the significance of a positive B cell crossmatch in cadaver renal transplantation. Morrow from Minnesota suggested that patients with a positive B cell crossmatch to the donor had worse graft survival than those with a negative B cell crossmatch; Equenazi from Miami showed no difference. Kirkman from Boston presented a paper on "Late mortality and morbidity in recipients of long-term renal allografts," reporting on 235 patients who had functioning kidneys between 5 and 20 years posttransplant. In that series, the most common cause of death was chronic liver failure. The most common cause of graft loss was chronic rejection, as expected.

At the ninth scientific meeting, papers covered a variety of subjects. Sheil from Australia reported on a prospectively randomized trial of cyclosporine versus Imuran and prednisone in cadaver renal transplantation. The conclusions were that cyclosporine was a powerful immunosuppressant, but that it delayed achievement of best function and reduced best function in many cadaver donor grafts. Alexandre from Brussels presented a most interesting paper on "ABO incompatible living donor kidney allografts." His group has continued to champion this approach in living related transplant recipients conditioned by splenectomy and preoperative plasmapheresis. Three papers discussed DR matching. Adams from Milwaukee suggested that DR matching was of no importance, while Sutherland from Minnesota urged the use of living related donors with no DR mismatches. Two papers reported on highly sensitized patients. Delmonico from Boston suggested that positive historical crossmatches for both T and B should not be an impediment to transplantation. Bollinger, speaking for SEOPF, suggested that a concerted regional effort using shared peak sera from highly sensitized patients could significantly increase the rate of transplantation of patients with acceptable patient and graft survival.

Belzer from Wisconsin suggested that adenosine and phosphate in perfusion preservation had a beneficial effect. Rosenthal from Pittsburgh showed no difference in the acute tubular necrosis rate between machine-perfused kidneys and cold-stored kidneys. An important paper was presented by Vincenti from California entitled "The function of the solitary kidney of donors remains normal after a follow-up of 13.0 to 18.5 years." That group showed that renal function was not adversely affected by many years of compensatory hypertrophy, suggesting that the hyperfiltration injury had not played a role. Weiland from Minnesota presented results on 628 living related kidney donors at a single institution with 1- to l9-year follow-up in 472 cases. They showed

zero mortality with low morbidity, suggesting that living related donation was safe and desirable.

The tenth scientific meeting began with greater emphasis on immunobiology. Sanfilippo reviewed the SEOPF experience and showed that delayed graft function after cadaver renal transplantation resulted in a significant risk for eventual graft and even patient survival. The importance of delayed graft function had been controversial for many years. Sutherland from Minnesota presented an important paper on the long-term effect of splenectomy versus no splenectomy in renal transplant patients (a reanalysis of a randomized prospective study). This reanalysis showed no long-term benefit of splenectomy on graft or patient survival. In the ensuing years, splenectomy has been abandoned by most transplant centers. Thistlethwaite from Boston presented an important paper on "Evolving use of OKT3 monoclonal antibody for treatment of renal allograft rejection." This was the first ASTS paper on this new antirejection agent. The authors treated 14 patients with acute rejection and were able to reverse it in 13 of them. Anderson from St. Louis presented "Pre-treatment of renal allograft recipients with immunosuppression and donor-specific blood." In their series, with a DST protocol concomitant with Imuran, only 3 of 58 patients became sensitized. Whelchel from Alabama gave a follow-up on the effect of pretransplant stored donor-specific blood transfusions, showing that the beneficial effect on graft survival with 1-haplotype-matched living related donors remained significant at 24 months post-transplant. Sollinger from the Wisconsin group, in "Donor-specific transfusions in unrelated and related HLA mismatched donor-recipient combinations," showed that the beneficial effect of DST was not restrictive to 1-haplotype-matched living related donors. Feduska from San Francisco presented "Donor-specific transfusions dramatically improve the success rate for renal transplants in diabetic recipients." Taylor from Pittsburgh presented "The influence of DR matching in cadaver renal transplantations performed with cyclosporine A," showing no impact of DR matching on either patient or graft survival in an 18-month follow-up. Finally, Sampson from San Francisco and Palo Alto presented "Clinical observations on the use of total lymphoid irradiation in human cadaver renal transplantation." In a group of 8 patients treated with total lymphoid irradiation (TLI) in combination with ATG and 10 mg of prednisone, all patients did well, without any rejection with a follow-up to 16 months.

At the eleventh scientific meeting, Salvatierra presented the largest group of DST patients in "Seven-year experience with donor-specific blood transfusions." His group reported an 88% 5-year graft survival in DST patients, compared to 82% in HLA-identical patients. Fryd from Minnesota presented "Improved results of transplantation with cyclosporine in patients over 50 years of age," concluding that cyclosporine helped reduce the risk of transplantation in older patients. Terasaki from Los Angeles presented "Impact of cyclosporine" and showed, in addition to other findings, that the transfusion effect was still strong. This concept, however, has been challenged in more recent years; most transplant centers at present do not transfuse patients electively. The question of monotherapy versus quadruple therapy was addressed by Melzer from San Francisco in "Use of cyclosporine and ATGAM in the early postoperative treatment of cadaver transplant recipients," concluding that the combination of

drugs produced excellent patient graft survival and did not lead to either morbidity or mortality. Alijani from Washington, DC, presented "Single donor cold storage versus machine perfusion in cadaver kidney preservation," noting an ATN rate of 63% in cold-stored kidneys versus 17% in perfused kidneys. Graft survival after 1 year was not altered by the preservation method. Bennett from Loyola, California, and Koyama from Baltimore addressed the role of oxygen free radicals in kidney preservation. Both of these studies in experimental animals suggested that free radical scavengers, such as superoxide dismutase (SOD) and allopurinol, could improve the immediate function of hyperthermically preserved kidneys. Subsequent clinical trials, unfortunately, showed no dramatic effect of these free radical scavengers.

The twelfth scientific meeting was again held at the Drake Hotel in Chicago. The first paper, presented by the Minnesota transplant group, was "Can renal transplantation be safely done without prior chronic dialysis therapy?" Adult diabetic recipients of primary cadaver renal transplants were compared in two groups: dialyzed vs. not dialyzed pretransplant. Two-year patient and graft survival was 72% and 82%, respectively, in both groups. Although the title of this talk is surprising from today's viewpoint, this was one of the first papers supporting transplantation before dialysis.

The discussion of local use of cadaver kidneys vs. sharing and of the impact of HLA matching was evaluated for the SEOPF group by Alexander from Cincinnati. In this large series, it was apparent that cyclosporine had overcome the marginal benefit of better HLA matching obtained by sharing. However, the best results (79.5% 1-year graft survival) were obtained in locally used, well-matched kidneys. In contrast, Terasaki of Los Angeles presented data on the long-term (5-year) effects of HLA matching in the cyclosporine era. Terasaki concluded that even after 5 years, HLA-A, B, and DR mismatching can influence graft survival by 15% to 20%.

The beneficial effect of ALG induction, with later addition of cyclosporine, was presented by Sommer from Ohio State. This was one of the first papers advocating the benefits of quadruple immunosuppression including a 14-day course of ALG, azathioprine, a tapering prednisone course, and cyclosporine started after the creatinine fell to less than 2.5. Two-year graft survival of 86% was achieved for primary cadaver recipients. This immunosuppressive protocol, with minor modifications, has continued to be used by a large number of transplant centers.

This 1986 ASTS meeting was the first to not devote most of the program to renal transplantation. It included many papers on liver, pancreas, and heart transplantation. This content reflected the successful and broadening clinical application of extrarenal transplants.

The thirteenth scientific meeting, in 1987, was again held at the Drake Hotel in Chicago. Of the 37 papers presented, 21 pertained to renal transplantation. Several papers addressed the impact of cyclosporine on previously sensitized patients, patients with poor HLA matching, and patients with and without preoperative blood transfusions. In general, the impact of each of these three factors decreased with cyclosporine. For instance, Ferguson's group from Ohio State presented data showing no difference between HLA-mismatched living related transplants treated with DST vs. cyclosporine. Results from his group and from Minnesota confirmed that

cyclosporine tended to override the benefit of DST or HLA matching on 1- and 2-year graft survival.

Stratta from Wisconsin described a protocol of steroid withdrawal in haploidentical or HLA-identical living related donor kidney recipients. Of 40 patients, 34 were successfully weaned from steroids with no graft or patient loss. This study offered one successful approach toward selective use of steroids in well-matched kidney recipients. Another ground-breaking paper, from the University of Chicago, was on re-exposure to OKT3 in renal allograft recipients. They reported that 9 patients whose acute rejection episodes were resistant to steroids responded to retreatment with OKT3, with no recurrence of rejection. This was one of the first demonstrations that the presence of antiidiotypic antibodies after initial exposure to OKT3 would not preclude the use of a second course to treat steroid-resistant rejection.

Of note at this conference was that ASTS had outgrown the capacity of the traditional Drake Hotel; this was the last scientific meeting held there.

The fourteenth scientific meeting was 3 days long and convened at the Fairmont Hotel in Chicago. In the first session, Barber, the Sandoz fellowship recipient, presented an interesting paper on the use of cryopreserved donor bone marrow in cadaver kidney allograft recipients. His early results demonstrated that donor bone marrow infusion was safe and could potentially be used in a protocol to induce donor-specific tolerance. This paper marked the beginning of the clinical study at Alabama on the use of donor bone marrow to induce tolerance.

Najarian presented the Minnesota experience in renal transplantation for type I diabetes mellitus. He concluded that these patients could be successfully transplanted, with stabilization of eyesight in 60% of them.

Belzer's group from Wisconsin gave two papers on improved methods of perfusion preservation of the kidney. The first, presented by Hoffmann, described a new perfusate containing hydroxyethyl starch as the colloid for oncotic support; 85 consecutive cadaver kidneys were preserved and transplanted with the new solution and compared with 189 preserved and transplanted with an albumin-based perfusate. The new solution resulted in a more rapid decrease in postoperative creatinine values, with no primary nonfunction. These data supported the continued use of perfusion preservation as an alternative to cold storage.

The Alabama group presented a series of 190 transplants from 95 donors in which one kidney from each pair was transplanted into a primary and the other into a retransplant recipient. Retransplant recipients had lower graft survival and were at increased risk of ATN, early rejection, and nonfunction. This paper underscored the importance of sensitization by a previous transplant and its impact on renal retransplantation.

The fifteenth scientific meeting was again held at the Fairmont Hotel in Chicago. The opening paper was presented by Southard from Wisconsin, who explained the important components in the UW solution and outlined its biochemical basis.

Two papers on experimental renal transplantation proved interesting. Hartner from Northeastern University and New England Deaconess Hospital in Boston presented a study of canine renal transplantation using antilymphocyte serum (ALS),

donor bone marrow treatment, and cyclosporine. ALS plus bone marrow alone had some efficacy. But maximal renal allograft survival was achieved with 20 mg/kg/day of cyclosporine for 60 days after ALS plus bone marrow treatment. Although this study demonstrated the efficacy and safety of donor bone marrow infusion, it is interesting that the addition of relatively high-dose cyclosporine was necessary to achieve long-term survival in most recipients. The utility of bone marrow transfusions to prolong renal allograft survival in miniature swine was reported by Guzzetta of Sachs' group at the NIH. Kidney transplants 6 to 12 months after bone marrow transfusions, matched at MHC class I and II with the donor bone marrow, resulted in long-term graft survival in most recipients without additional immunosuppression.

In a randomized prospective comparison of OKT3 and ALG in cadaver renal transplantation, Hanto from Washington University in St. Louis showed similar patient and graft survival rates in each group. OKT3 was associated with a higher incidence of rejection, but these episodes were more frequently steroid-responsive.

The long-term results of HLA-identical living related transplants were reported by the Minnesota group using prednisone and azathioprine. For nondiabetics, 10-, 15-, and 20-year actuarial patient survival was 85%, 75%, and 71%, respectively. For diabetics, 10- and 15-year survival was 65% and 36%. This paper emphasized that three-quarters of graft loss was secondary to patient death. Morbidity remained a problem: half of nondiabetics and almost all diabetics had at least one complication posttransplant.

Dafoe from the University of Pennsylvania presented a series of renal transplants performed in the setting of weakly positive crossmatch using OKT3 induction. Excellent 1-year graft survival was achieved in the OKT3 group, suggesting a role for OKT3 induction in sensitized patients.

Only 20 of the 64 papers presented at the 1989 meeting dealt directly with renal transplantation, reflecting the rising importance and success of extrarenal transplants.

The sixteenth scientific meeting in, 1990, was again held at the Fairmont Hotel in Chicago. The first plenary session opened with "Long-term results of the controlled prospective study with transfusion of donor-specific bone marrow in 50 cadaver renal allograft recipients." Barber et al. from Alabama demonstrated that using cryopreserved donor-specific bone marrow was associated with improved allograft survival. However, they believed a more effective induction protocol was needed to reduce the overall number of rejection episodes. Platz and Sollinger from Wisconsin presented their initial results using RS-61443 in canine renal allografts. The combination of RS-61443, cyclosporine, and prednisone significantly prolonged canine allograft survival. Likewise, Thomas and her group from the East Carolina School of Medicine presented work using donor bone marrow cells to induce long-term renal allograft survival in rhesus monkeys. They speculated that this long-term survival was due to a veto mechanism mediated by donor bone marrow cells of the NK or LAK lineage.

The session on kidney transplantation, moderated by McDonald and Cosimi, opened with a paper entitled "Doctor: what are my chances?" by Fischel et al. from Minnesota. Their study of 1,850 primary renal transplant recipients showed that

long-term allograft survival has improved with the introduction of cyclosporine, but may be attributed to better first-year graft survival and a reduction in deaths with a functioning graft. Using an analysis for immunologic graft loss that excluded deaths with a functioning graft, they found that the long-term outlook for 1-year graft survival was excellent. Dunn et al. from Minnesota and Jordan et al. from Pittsburgh demonstrated that ganciclovir was an effective treatment of invasive CMV in renal transplant recipients.

Kirkman and the Brigham and Women's Hospital group presented "A randomized prospective trial of anti-Tac monoclonal antibody in human renal transplantation." Their study demonstrated that the prophylactic use of anti-Tac significantly reduced early rejection episodes. This reduction, however, did not affect patient or graft survival. The final paper of the kidney session was "Factors affecting 10-year outcome of human renal allografts," by Ranjan from the University of Miami. In 631 renal allograft recipients, factors that adversely affected long-term graft outcome were being black, having type I diabetes, and failing to comply with long-term protocols. HLA matching did not appear to influence cadaver graft survival. Ranjan's group also indicated that immunologic monitoring played a major role in maintaining optimal immunosuppression, which helped minimize opportunistic infections and graft loss due to rejection.

In the plenary session entitled "Ways to increase the donor pool," Alexander from Cincinnati opened with "Use of marginal donors for organ transplantation: The older donor." His group found no difference in graft survival with donors age 55 to 65 or with donors over age 65.

The seventeenth scientific meeting, again at the Fairmont Hotel in Chicago, opened with an honorary address by Nobel laureate Dr. Joseph Murray, who related his experiences with experimental and clinical renal transplantation. The first plenary session began with a paper by Sollinger from Wisconsin and Deierhoi from Alabama, in which they presented their results in a phase I clinical trial and pilot rescue therapy using RS-61443. They concluded that RS-61443 was safe and well tolerated without evidence of nephrotoxicity, hepatotoxicity, or bone marrow suppression. Likewise, a lower incidence of rejection episodes was observed with increasing doses of the drug. In the session on immunosuppression, chaired by Thistlethwaite and Kahan, Alexander et al. from Cincinnati presented "Immunologic hyporesponsiveness is induced by donor-specific transfusions (DST) and cyclosporine (CSA) in human cadaver transplants." Recipients receiving DST and cyclosporine 24 hours pretransplant had less severe rejection episodes; posttransplant MLC responses against preserved donor lymphocytes were hyporesponsive in DST patients but stimulatory in controlled patients.

In the immunobiology plenary session chaired by Diethelm and Lorber, Barber et al. from Alabama presented "Peripheral blood chimerism demonstrated by polymerase chain reaction in renal allograft recipients transfused with donor bone marrow." By using PCR to identify donor type DNA in recipient lymphoid cells, 4 of 7 patients who received donor bone marrow were chimeric 1 year or more posttrans-

plant. The ability to detect chimerism may be an indication of allograft tolerance and may allow marked reduction in immunosuppression.

In the kidney transplantation session chaired by Alexander and Thomas, the first paper was "Renal transplant function after 10 years of cyclosporine (CSA)." Almond et al. from Minnesota presented 504 cyclosporine recipients, 351 of whom had function for more than 55 months. They found, in long-term renal transplant recipients, no evidence of progressive deterioration in renal function resulting from cyclosporine nephrotoxicity. Pfaff et al. from Gainesville presented "The relationship of cyclosporine blood concentration to early rejection and graft survival of cadaver renal transplants." The rejection incidence was 2 to 3 times higher in patients whose cyclosporine blood concentrations were less than 400 ng/ml in the early postoperative period. Maintaining higher concentrations of cyclosporine levels improved graft survival and lessened costly rejection episodes, without mortality or neoplasia. The final paper of the kidney session was by Lazda from the Regional Organ Bank of Illinois, entitled "The impact of HLA frequency differences in races on access to optimally HLA-matched cadaver renal transplants." This analysis of 448 consecutive renal transplants showed that a better donor-recipient HLA match was achieved when both donors and recipients were of the same race. Thus, a larger number of black donors are needed to improve the quality of HLA matching for potential black kidney transplant recipients. In the plenary session on "Organ procurement: Increasing the donor pool" chaired by Bollinger and Rohr, the first paper was by Ploeg from the University of Leiden, entitled "Efficacy of UW solution in kidney transplantation: Results of a clinical comparison with Eurocollins (EC) solution." This multicenter trial examined 695 patients who received cadaver kidney transplants. UW solution decreased the incidence of delayed graft function, reduced primary nonfunction rates, improved renal function, and increased graft survival, compared to the Eurocollins solution.

At the eighteenth scientific meeting, held at the Chicago Hilton and Towers, the plenary session on transplantation science opened with a paper by Nakafusa from St. Louis, entitled "Intrathymic injection of splenocyte alloantigen induces specific tolerance to cardiac but not skin or renal allografts." His group concluded that exposure of maturing T lymphocytes to MHC mismatched donor alloantigen in the thymic microenvironment produced donor-specific tolerance to cardiac, but not to renal or skin, allografts. They speculated that this was a result of tissue-specific antigens not expressed on splenocytes given intrathymically. In the same session, Tilney from Boston presented a paper on the role of cytokines and adhesion molecules in the pathogenesis of chronic rejection of rat renal allografts. This study concluded that the activities of cytokines and adhesion molecules are particularly important in the etiology of chronic rejection and that antibody-mediated host responses may be less influential than previously supposed.

In the session on immunosuppression, Knight et al. from Houston presented "Low dose rapamycin potentiates the effects of subtherapeutic doses of cyclosporine to prolong renal allograft survival in the mongrel canine model." This study showed only mild toxicity.

The plenary session on clinical transplantation began with a paper by Ferguson et

al. from Ohio State, entitled "Acute rejection episodes—Best predictor of long-term primary cadaver renal transplant survival." They concluded that the predominant factor dictating long-term cadaver kidney graft survival was the presence or absence of one or more rejection episodes in the early posttransplant period. Their data suggested that chronic rejection occurred almost exclusively in patients treated successfully for acute rejection.

In the renal session chaired by Campbell and Bollinger, Tesi from Ohio State presented a prospective study of the use of low-risk hepatitis C virus (HCV) positive donors. Of the 25 recipients with HCV positive donors, none developed hepatitis. They concluded that exclusion of all HCV positive donors was probably not justified. Almond from Minnesota presented "Risk factors for chronic renal transplant rejection (CR)." With all the risk factors analyzed, only acute rejection was identified as a major risk factor for the development of chronic rejection. Clearly, prevention of acute rejection is the most important factor in preventing chronic rejection. Nicol from Halifax demonstrated that combined CMV hyperimmune globulin and acyclovir was better than either agent alone in preventing CMV disease in negative recipients of positive donors, and that CMV hyperimmune globulin combined with acyclovir allowed safe transplantation of CMV negative recipients with CMV positive kidneys. In a related paper, So from the Washington University suggested that children— for undefined, but perhaps immunologic, reasons—appear less susceptible to symptomatic CMV disease; routine use of prophylactic CMV hyperimmune globulin or high-dose acyclovir in donor-positive/recipient-negative pediatric renal transplants is not cost-effective. The final two papers of the renal session dealt with the use of cyclosporine G in cadaver renal transplantation. The first paper, by Henry from Ohio State, concluded that the efficacy of cyclosporine G was similar to that of cyclosporine A; however, patients tended to have better renal function and improved blood pressure control, with fewer antihypertensives required. Lindholm from Houston concluded that cyclosporine G was significantly more hepatotoxic than cyclosporine A and not convincingly less nephrotoxic. This trial was terminated at the end of the open-label study because cyclosporine G did not present significant advantages over cyclosporine A. In the plenary session on "Preservation/donor access" chaired by Miller and Ferguson, Schilling from Wisconsin presented "Five- to seven-day kidney preservation with aspirin and furegrelate." Aspirin (an inhibitor of cyclooxygenase) and furegrelate (an inhibitor of thromboxane synthetase) improved canine kidney preservation. These studies suggested that the suppression of thromboxane production prevents reperfusion injury caused by vasoconstriction, platelet aggregation, and reduced renal blood flow.

The nineteenth scientific meeting was held for the first time in a city other than Chicago—Houston, Texas. In the first plenary session, chaired by Barker and Sollinger, the University of Miami group presented "Quantitation of hepatitis C (HCV) RNA using competitive substrate PCR: Application to kidney preservation and transplantation." This study examined the effects of variations of standard kidney preservation procedures on a number of HCV viral copies in organs from HCV positive donors with an HCV-RNA quantitative RT-PCR method. They concluded that

the use of renal pulsatile perfusion coupled with additional viral depletion steps—such as dilution, filtration, or immunoabsorption—may allow the practical elimination of HCV transmission risk.

In the immunosuppression session, chaired by Kahan and Makowka, McChesney of the Rush-Presbyterian-St. Luke's Medical Center presented "Evaluation of leflunomide in the canine renal transplantation model." This group demonstrated that leflunomide blocks IL-2 signal transduction when combined with cyclosporine, providing a five-fold increase in canine renal allograft survival. In the session on preservation chaired by Hanto and Belzer, Kinzler presented a paper from Loyola University and the University of Chicago entitled "Retrieval of kidneys from non-heart-beating human cadavers using in situ perfusion and iced saline peritoneal lavage." Twenty kidneys were harvested from 10 deceased non-heart-beating donors after infusing UW solution via a balloon catheter and using iced saline peritoneal lavage. These kidneys were placed on perfusion; histologic samples demonstrated normal histology in one pair, mild ATN in five pairs, and moderate to severe ATN in four pairs. They concluded that retrieval of kidneys from non-heart-beating donors resulted in acceptable kidney perfusion pressures, perfusion flow rates, and histology. In the final paper of the session, Belzer from Wisconsin presented "The role of tissue typing in cadaver renal transplantation in the 90s." This study of 542 cadaver and 264 living related renal transplants demonstrated that 4-year survival of cadaver kidneys with at least one DR match was equivalent to 4-year survival of haploidentical living related transplants. This group recommended that, until more effective immunosuppression is available, optimal graft survival could be obtained with at least one DR match.

In the kidney transplantation session chaired by Matas and Barber, McDaniel from Alabama presented "Peripheral blood chimerism in renal allograft recipients transfused with donor bone marrow." Of 30 bone marrow transfused recipients, 23 (77%) demonstrated the presence of chimerism at some point during the 12 months after marrow transfusion, compared with 7 of 23 (24%) untransfused recipients. Likewise, a correlation between the presence of chimerism and rejection was seen, with fewer rejection episodes in the chimeric patients who received transfusions as well as in chimeric patients who did not receive transfusions. In "A preliminary report of cyclosporine-sparing with diltiazem (DILT) and ketoconazole (KETO) and their effect on transplant outcome," Patton from Gainesville suggested that the cyclosporine dose could be reduced by inhibiting the P450 system with ketoconazole or diltiazem; this had no adverse effect on graft survival. In the final paper of the renal session, Najarian from Minnesota presented "The importance of the quality of initial graft function in cadaver kidney transplantation." Najarian concluded that the quality of initial function was an important predictor of 1- and 2-year graft survival. The data suggested that efforts should be increased to improve immediate posttransplant function and not the antigen match.

Liver and Intestine

THOMAS E. STARZL

The special branches of liver and intestinal transplantation developed outside of ASTS, and became well represented at our meetings only after their maturation was far along. Most of the key advances first appeared in conventional clinical journals, including those devoted to surgery. The evolution of the major steps can be most easily traced in the issues of *Transplantation Proceedings* that contain biennial reports from the Transplantation Society meetings and off-year conferences endorsed by the parent organization. These developments will be used as background (but not annotated) in the following account, on which ASTS program presentations will be superimposed and systematically cited. For each, notations are included about ASTS manuscripts, including those not published in the official journal of the society — *Surgery* in 1975 and 1976, *Transplantation* thereafter.

Successful clinical transplantation of any whole organ rests on 5 specific laboratory-based struts: surgical technique, preservation technology, tissue matching, immunosuppression, and (least appreciated) incidental induction of variable degrees of donor-specific nonreactivity, without which none of our patients could be rehabilitated for long. Liver and intestinal transplantation contributed to all 5 categories, but only the first 2 have been prominent themes in the published ASTS proceedings. However, because of their generic importance to all of transplantation, the last 3 topics (tissue matching, immunosuppression, and tolerance) will be discussed separately, as influenced by the liver and intestine, in the third section entitled *Transplantation Immunology.*

Liver

Liver replacement was fully developed experimentally by 1958 at Harvard Medical College and independently at Northwestern University, Chicago. The liver was the first nonrenal vital organ to be transplanted clinically (1963) in attempts that were crowned with long survival in 1967. Those involved were largely from the ranks of the kidney transplant surgeons who either belonged to ASTS or were well-known to its

membership. Yet only 4 experimental (1-4) and 6 clinical papers (4-10) covered liver transplantation during the period of its most explosive development (1975-1984). Abstracts about the liver either were not being submitted or were not being selected, or perhaps both factors contributed to the paucity. All the while, a pool of chronically surviving recipients was enlarging. By 1989, when Scantlebury (Colorado-Pittsburgh) reported the successful pregnancy of 17 women (16 of whom were 2 to 18 years post-transplant), the oldest child was already 13 years old (11).

Of those 4 early experimental studies, 3 were of hepatic (or hepatocyte) transplantation to ectopic sites. In 1977, Hong, working with the late Samuel Kountz (Brooklyn), reported a new technique for auxiliary liver transplantation in dogs (1). After Kountz's death, Moritz and Jarrell (12) from Philadelphia (Jefferson, 1989) described the successful treatment of fulminant hepatic failure with an allograft placed in the right paravertebral gutter; the auxiliary liver was allowed to reject and involute after the native liver had recovered. Hepatocyte transplantation intrasplenically and intraperitoneally, respectively, were introduced to ASTS in 1979 by Mito (Asahikawa, Japan) (3) and Makowka (Toronto, 1980) (4), using rat models that have subsequently been widely used for a variety of experimental purposes. Makowka showed that the mortality of experimentally induced fulminant failure could be reduced equally with allogeneic or xenogeneic (rabbit and pig) hepatocytes.

Virtually all other presentations have involved liver replacement (orthotopic transplantation), with a heavy clinical emphasis on technical problems. The first of these (5) described the incidence, etiology, and prevention (or secondary correction) of biliary tract complications (Colorado, 1976). Since then, biliary reconstruction, once the Achilles heel of liver transplantation, has been revisited at ASTS 4 times: by Lerut (Pittsburgh, 1986) (13), Sanchez-Urdazpal (Mayo Clinic, 1991) (14), Hefron in connection with reduced-size livers (University of Chicago, 1991) (15), and Sankary (16), who described a modified biliary reconstructive technique (Rush-Presbyterian, Chicago, 1993).

The Achilles heel designation passed in 1985 to allograft revascularization. Andreas Tzakis (Pittsburgh) documented the frequency of hepatic artery thrombosis, which had a predilection for infants and small children (17). He also accurately delineated the syndromes that could result from dearterialization, including silent occlusion in about a third of cases. Langnas (Nebraska) reported emergency revascularization of the occluded artery in 1990 (18). Stevens (University of Chicago, 1991) noted no greater incidence in reduced-size pediatric livers than in whole ones (19). Portal vein complications, which occur much less frequently, were described by Reed (Wisconsin, 1991) (20).

Until the end of 1982, only 2 or 3 liver transplant teams were able at a technical level to obtain results resembling today's. Training the next generation was facilitated in 1983 by the introduction in Pittsburgh of a veno-venous bypass technique. It allowed decompression of the obstructed portal and vena caval beds while the diseased liver was removed and the new one sutured in place. Although liver replacement could be performed by skillful surgeons without a veno-venous bypass, as emphasized by Wall (London, Ontario, 1986) (21), most new teams adopted the bypass technique

for their first cases after Shaw's report at the American Surgical Association in 1984. Convinced of its value, they have used it in the succeeding years, either routinely or as indicated by test occlusion of great veins.

Bleeding caused by fibrinolysis can occur with or without venous bypass. Pohorecki (Nebraska, 1993) reported that such bleeding could be ameliorated by epsilon amino caproic acid (EACA) (22), a drug that had been used for the same purpose in the early 1960s but abandoned because of clotting complications. A discriminating revisit to the past also was reported by McAlister (London, Ontario, 1992), who described right diaphragmatic paralysis in several pediatric liver recipients (23). This previously had been attributed to crushing of the right phrenic nerve with the suprahepatic venal caval clamp at the diaphragm, a conclusion validated by McAlister with meticulous scientific rigor.

Cataloguing quality of life issues and nontechnical complications after liver transplantation largely recapitulated an analogous literature 2 decades earlier in renal transplantation. An exception, because it concerned a new disease, was a report by Tzakis (Pittsburgh, 1989) on the postoperative course of 25 patients (15 liver recipients) with HIV (24). By systematically screening stored and current blood samples, it was shown that 11 of these recipients had the disease pretransplant; the other 14 were infected by blood products or allografts in the course of perioperative treatment before the availability of detection methods. Other viral infection studies (25-28) have been of cytomegalovirus and its prophylaxis (Stratta, Nebraska; Freise, San Francisco, 1990); Epstein Barr (Langnas, 1992); and hepatitis C (Mateo, Pittsburgh, 1993). Bacterial infections in OKT3-treated liver recipients were reported by Wall (London, Ontario, 1990) (29). Koep (Colorado, 1978) noted a high incidence of lethal sepsis from colon perforation (7).

Hepatic preservation first appeared on the ASTS program in 1977 with a report by Benichou (Colorado) of successful canine liver storage for up to 18 hours using Collins solution. This technique was repeatedly used for removal of human livers in Los Angeles and their transplantation in Denver (2). These and independent achievements by William Wall and Roy Calne at Cambridge using a plasma-like preservation fluid overthrew the logistic tyranny of donor-recipient proximity, but the "safe" time limit still was only 6 or 8 hours. This was extended 2- or 3-fold with the announcement of the University of Wisconsin (UW) solution by Belzer and his associates at a meeting in Pittsburgh in September 1987. Their claims for UW were promptly confirmed by Todo (Pittsburgh) and then widely by others. This advance was reflected belatedly in ASTS reports in 1989 (Olthoff, UCLA; Stratta, Nebraska) (30, 31).

At the 1989 ASTS meeting, Pienaar (Wisconsin) described 72-hour pump preservation of the ex vivo dog liver using an asanguinous perfusate (32). This was the first new and effective continuous perfusion technique since the experimental and clinical use, by the late Larry Brettschneider (Colorado), of a cumbersome blood-enriched system (which was housed in a hyperbaric oxygen chamber and had permitted 48-hour preservation of canine livers). In 1988 Baumgartner (Johns Hopkins) had described continuous total body perfusion with hypothermic cardiopulmonary bypass during multiple-organ procurement (33), a technique that had been used clin-

ically in Colorado for liver and kidney procurement from non-heart-beating cadavers in the 1960s before the acceptance of brain death. Although a good quality of thoracic and abdominal organs was described, resistance to the complex procedure by personnel at outlying hospitals has limited its subsequent application.

Reduced-size liver transplantation has been a frequent recent clinical topic. This procedure was popularized in the early 1980s by Henri Bismuth of Paris (with Didier Houssin) and the Hannover team of Rudi Pichlymar (including Christoph Broelsch). Between 1987 and 1992, Broelsch's group (then at the University of Chicago) provided 5 ASTS presentations (15, 19, 34-36), 2 of which were delivered by Jean Emond. These described a progression from the use of reduced-size cadaver liver fragments, to the so-called "liver split procedure" in which the allograft was divided and shared by 2 recipients, and finally to the application of the same principles to transplantation of the left lateral segment or left lobe from living donor adults to children. Both Emond (35) and Langnas (Nebraska, 1991) (37) reported disappointing results when 2 recipients were given fragments from a divided liver.

The indications for liver transplantation received little attention at ASTS meetings until the late 1980s. The only exception was a description by Charles Putnam (6) of liver replacement for alpha-l-antitrypsin deficiency (Colorado, 1976) —an early entry, though not the first, on the list of correctable inborn errors that has grown since then to nearly 3 dozen. However, with the shortage of organs that had developed by the late 1980s, candidacy began to be discussed with overtones of organ use restriction. Potential relative or absolute contraindications to liver transplantation formally considered at ASTS (and usually rejected by the speaker) include old age (Stieber, Pittsburgh, 1990) (38), B virus hepatitis (Boston intracity group, presented by Eason, 1993) (39), and hepatic malignancies (Boston group by Haug, 1991) (40).

At about the same time, reports emerged on the management of waiting lists, questions about who should be allowed on them, and the influence of disease severity on outcome (Gordon, Pittsburgh, 1990) (41). Criticisms about the candidacy of alcoholic recipients were largely defused by Turcotte (Michigan, 1993) (42), who confirmed previous observations of a low rate of alcohol recidivism in carefully screened abstaining patients. To meet the growing demand nourished by a shrinking list of contraindications, Wall (London, Ontario, 1989) (43) showed that many older donors could provide satisfactory livers. Rosenlof (University of Virginia) described the use of the monoethylglycinexidide (MEGX) test to distinguish good from bad donors (44).

At first subtly in 1990 and then with unmistakable clarity, the topic shifted to the waste of organs by their "inappropriate" use to treat very ill recipients. However, it has always been evident that what constitutes hopelessness in one center may be entirely routine case material in more experienced or skillful hands. The argument on this uneven playing field has been that high-risk recipients would have predictably poorer posttransplant survival than well ones. Preceding this trend, the first attempt to equate severity of illness (and urgency of need) with outcome was made by Byers Shaw (Pittsburgh, 1985) with a formula (45) that has since been revised and widely used. In an attempt to quantitate the need for an organ and the pace of deterioration

while waiting, Shiffman (Virginia, 1992) proposed sequential pretransplant tests of lidocaine metabolism (MEGX) (46).

Concerns over the complicated interface between urgency of need, the shortage of organs, and their utilitarian use have spilled over to retransplantation. Retransplantation was first mentioned at the 1983 ASTS meeting by Shaw (Pittsburgh) (8) who summarized 21 such attempts in Colorado before 1980, and contrasted the bleak earlier outlook with the better results in Pittsburgh after the advent of cyclosporine. Powelson of the Boston consortium (47) confirmed that many patients whose grafts failed either early or late could be saved, but not with as high a success rate as after primary transplantation (1992). As new teams entered the field, their members were inclined to deplore the inefficient use of organs for retransplantation until confronted with this necessity for their own patients. The propriety of retransplantation, even for patients with B virus hepatitis, was defended from the combined experience of the Baylor (Dallas) and Mt. Sinai (New York) teams (Crippin, 1993) (48), as long as the loss of the primary graft was not from recurrent hepatitis. Otherwise, accelerated hepatitis doomed the subsequent graft, as reported earlier by Todo (Pittsburgh, in *Hepatology,* 1991).

Throughout this recent period, awareness grew that even some of the lowest risk (so-called "boutique") recipients of livers from ideal donors could experience immediate graft failure after an ostensibly perfect operation. The syndrome was called primary nonfunction (PNF). Most centers have reported the need for regrafting in the first month after primary transplantation at a rate of 5% to 10%, including cases with no technical imperfections at the first operation. Excluding this and other identifiable causes, the remaining examples of PNF have been most commonly in patients who had negative lymphocytotoxic crossmatches with their donors.

However, Knectle's important Upjohn Award presentation (Duke) showed in 1986 that PNF caused by a slower liver version of the hyperacute rejection seen with the kidney and heart could be produced experimentally in presensitized rats (49). Gubernatis of Hannover reported similar results in subhuman primates at the Transplantation Society meeting in Helsinki (1986); the same thing was described in sensitized pigs by Merion (Michigan) at the 1989 ASTS meeting (50). Collectively, the animal studies established that a subgroup of candidates at increased risk of PNF should be identifiable with conventional serologic crossmatching.

However, a significant adverse effect of antigraft cytotoxic antibodies on graft or patient life survival could not be found by Gordon (Pittsburgh) as late as 1988 (51), and was not clearly established until a report from the same institution at the Transplantation Society in 1990 and an ASTS presentation by Takaya and Bronsther (52) in 1991. Most human livers were able to survive the insult, but it was clear that the resistance of the liver to antibody rejection, compared with other organs, was only relative. At the succeeding ASTS meetings (1992 and 1993), Takaya and Bronsther (Pittsburgh) reported that perioperative intravenous PGEl—combined with high induction doses of prednisone—practically eliminated PNF, with or without a positive crossmatch (53, 54), and had the additional benefit of reducing FK506 nephrotoxicity. This important finding had considerable practical significance because most liver

transplants are performed before the crossmatch results are known. These 2 reports, along with an earlier one at the American Society of Transplant Physicians by Levy's University of Toronto team, have strongly influenced care of liver recipients. The late sequelae of an aborted antibody reaction have not been well delineated, but Batts (55) has suggested serious intrahepatic bile duct damage (Mayo Clinic, 1987).

In a potentially related experimental study, Murase (Pittsburgh, 1992) confirmed with xenograft hamster-to-rat models that the liver was less vulnerable than the heart to xenospecific antibodies. The damage to both organs could be ameliorated by combining cyclophosphamide, brequinar, RS 61443, methotrexate, and other antimetabolite drugs with FK506 (56). Hyperacute rejection of xenografts, like that of allografts, has eluded full understanding and control since it was described 30 years ago in AB0-mismatched kidney recipients (Denver) and in recipients with positive lymphocytoxic crossmatches (Los Angeles-Denver). Both allografts and xenografts are destroyed by a complement activation syndrome that frequently is triggered by antibodies (classical pathway) but may be antibody-independent (alternative pathway). The prospect of understanding this formidable barrier was enhanced by Valdivia's hamster-to-rat liver xenotransplant experiments (Pittsburgh, 1993), which showed homologous restriction of the predominantly hamster complement found in the long-surviving rat recipients (57). The possibility of MHC restriction of complement within species could help explain why the liver allograft (which like the xenograft transforms the recipient complement environment to its own phenotype) is so relatively resistant to hyperacute rejection.

The often unpredictable early and late course of the human liver recipient, and the morbid or lethal consequences of failing to react in time with therapeutic adjustments to graft dysfunction, have generated numerous attempts to avoid the use of faulty organs and to quickly determine the prognosis when they begin to fail. Prediction of PNF by the presence of fatty infiltration in donor liver biopsies was reported elsewhere in 1989 by Todo (Pittsburgh) and at the ASTS meeting by D'Alessandro (University of Wisconsin) in 1990 (58) . The adverse effect of this and other prognostic factors was studied with multivariate analysis in 1992 by the Wisconsin group (Ploeg, 1992) (59) . The perioperative monitoring of anaerobic metabolic indices pioneered by Aldrete (Colorado) and Kang (Pittsburgh) first appeared on the ASTS program in 1986 (Stock, Minnesota) (60). Asonuma (Pittsburgh and Kyoto, 1990) (61) and Takaya (Pittsburgh, 1993) (54) showed the early diagnosis of this condition by serial measurements of the arterial ketone body ratio.

In vitro monitoring of cellular immunity further along in convalescence was reported by Fung in 1985 (Pittsburgh) (62). The following year, Mohanakumar (Washington) described the postoperative waxing and waning of antidonor HLA antibodies (63). Serial determinations of circulating interleukin II (IL2) or IL2 receptor levels by Perkins (Mayo Clinic, 1988) (64) and Simpson (Harvard-Northeastern, 1990) (65) and of intragraft cytokine gene expression (especially IL5) by Martinez (University of California, San Francisco, 1991) (66) have not been widely used. Foster (67) (Rush-Presbyterian, 1988) reported that eosinophilia postoperatively signaled rejection with a bad prognosis.

As with kidney transplantation, allograft function tests combined with histopathologic studies have provided the most reliable guidelines to monitor liver grafts and evaluate causes of poor performance. This was strongly emphasized by Williams in 1984 of Rush-Presbyterian (Chicago) (10), who obtained biopsies as often as daily through an opening left in the wound. Although this "window" technique has not supplanted the closed needle biopsy, these pioneer studies demonstrated the frequency with which rejection would have been treated with increased immunosuppression without the benefit of biopsy, when in fact the diagnosis was something else. Further experience of the same Chicago group was described by Sankary in 1988 (68). Information of research interest also has emerged from the serial biopsies, exemplified by the studies by So (Minnesota, 1986) of Class I antigen induction of bile duct cells and hepatocytes at the time of rejection (69). Perkins (Mayo Clinic) also described sophisticated immunohistolabeling of the specimens to stratify infiltrating T lymphocyte subsets (70).

Intestine

Only 11 papers on this subject have been on ASTS programs over a 19-year span, none before 1984. The historical roots of bowel transplantation can be traced back to the beginning of the century. But the modern era was signaled by the canine experiments reported by Richard Lillehei of Minnesota at the 1959 American Surgical Association meeting. The following year, at the Surgical Forum of the American College of Surgeons, multivisceral transplantation was described in dogs (Northwestern, Chicago). This was the forerunner of a nearly identical clinical procedure, after which a child survived > 6 months (Pittsburgh, 1987). A variant operation of composite liver-intestinal transplantation permitted genuine rehabilitation of a patient in London, Ontario (Grant, 1988). These 2 cases were the first examples of prolonged human intestinal allograft function and reignited interest in the subject. In 1988, the German Delph (Kiel) reported long-term survival of a recipient of a segmental small bowel graft from a related donor. In 1989, Goulet of Paris transplanted a near-total cadaver small bowel into a child who is still alive nearly 5 years later. Thus, the intestine was no longer a "forbidden organ" by the late 1980s.

The experimental basis in large animals for these trials with cyclosporine-based immunosuppression had been laid during 1981 by canine experiments in Toronto and Pittsburgh, but survival for 1 or 2 years was an unusual accomplishment. Better results in rodents were obtained in several laboratories during the next 3 years. At the 1984 ASTS meeting, Raju, Cavirli. and Didlake (71) reported the greatly increased efficacy of cyclosporine relative to azathioprine in rat Lewis recipients of ACI intestines. In 1987 Grant (London, Ontario) presented a landmark study in pigs at the ASTS meeting (72). In Grant's laboratories, extraordinary efforts were made to provide uninterrupted intravenous cyclosporine, and most animals survived for > 100 days. The irregular and unpredictable absorption of cyclosporine by the intestinal allograft made the intravenous treatment necessary. Two years later, Xia and Kirkman (Harvard-Brigham) reported disquieting news: in rats, intestinal allografts produced

secretory IgA normally, but IgA response to immunization with cholera toxin (73) was deficient or absent.

When FK506 became available, Murase (Pittsburgh) established, by 1989, its superior efficacy relative to cyclosporine in preventing rejection of both isolated intestinal and multivisceral allografts. Absorption of this new oral drug was less influenced by intestinal dysfunction, compared with cyclosporine. The stage was set for clinical trials. At the 1991 ASTS meeting, Todo and Tzakis (Pittsburgh) presented 5 examples of long-surviving human recipients: 4 with liver intestinal grafts, and 1 with an isolated complete small bowel graft (74). Todo and Tzakis returned to the 1993 ASTS meeting with a series of 15 isolated small bowel cases; 12 of the recipients had survived for 1.5 to 19 months (75). However, the emphasis on both occasions was less on the successes than on the difficulty of clinical care and the need for an improved strategy, including better ways of monitoring rejection. A sophisticated means of monitoring was suggested by Morrissey (Yale, 1993), who showed a decline of small bowel fatty acid binding protein with rejection, as well as the potential reversibility of this change (76). However, as with the other whole organs, monitoring at a practical level has been largely dependent so far on serial biopsies.

The next large advance presumably will be therapeutic, with better control of rejection and the induction of a drug-free tolerant state without the penalty of GVHD. As an effort in this direction, 4 rat studies were presented at ASTS meetings over a 6-year period from Monaco's Harvard-Northeastern laboratory. The first, in 1984 by Pomposselli (77), was a detailed study of GVHD (originally described in 1973 by Monchik and Russell) after intestinal transplantation in the parent-to-offspring F_1 hybrid model. In 1987, Shaffer won the Upjohn Award (78) and in 1990, the Ortho Award (79) for demonstrating avoidance of GVHD by lymphoid depletion of the donor pretransplant, or the recipient posttransplant, with polyclonal or monoclonal ALS. Diflo showed in 1988 that GVHD could be chronically tolerated in fully allogeneic rat intestinal recipients if cyclosporine therapy was maintained chronically (80).

Using a different approach, Mayoral (Minnesota) reported in 1988 that the F_1 hybrid rat recipient could be protected from GVHD by prior conditioning with small doses of parental lymphoid cells or short segments of parental intestine (81). The clinical implications of the foregoing body of work, with its emphasis on graft lymphoid depletion or host preconditioning, is now being reassessed in light of discoveries about cell migration and its relation to tolerance.

Transplantation Immunology

Immunosuppression. When cyclosporine was introduced and its use with prednisone standardized in 1978-1980, the most dramatic impact was on liver and other extrarenal transplants. This was widely known by the end of 1980 and was a prime, if not the principal, reason for the drug's rapid approval by the Food and Drug Administration (FDA) in November 1983. For the first time, the nonrenal organs (liver and heart) had shared primary responsibility with the kidney in immunosuppressive drug

development. However, the subject of cyclosporine in the context of liver transplantation was not brought to an ASTS meeting until 1983 (9) in a clinical study of dose weaning over the first 12 months. Iwatsuki (Pittsburgh) and Shaw (Pittsburgh) reported that cyclosporine upgraded the prognosis after liver retransplantation (8). Similarly, Cosimi's report (82) on the use of OKT3 in liver recipients (Harvard-Massachusetts General Hospital, 1986) and a subsequent one by Millis (UCLA, 1988) (83) were almost afterthoughts to a long story in which the liver had played a key developmental role.

In contrast, ASTS received early notification about FK506, the most recent drug to sail through the FDA, this time with wings mounted almost exclusively on the liver. The lag between the first published report in *The Lancet* of this drug's clinical use (October 1989) and presentations at the European Society of Organ Transplantation (October 1989), American Surgical Association (April 1990), ASTS (May 1990) (84), and Transplantation Society (August 1990, San Francisco) was numbered in days to months. At all 3 transplantation meetings, culminating with a prize for the highest graded clinical paper at the Transplantation Society, John Fung (Pittsburgh) described the rescue with FK506 of liver recipients with intractable rejection despite conventional therapy. Also at the San Francisco meeting, a profusion of data on safety, efficacy, toxicity, pharmacokinetics, and dose control was documented from an already extensive experience with primary transplantation of the liver, kidney, and thoracic organs. The subsequent ASTS programs between 1991 and 1993 revealed a continuing high interest in this drug.

Fung returned in 1991 with a report of its favorable performance in a randomized liver trial (85). McMillan (Dallas) was scheduled in 1992 for presentation of a second single-center study (86), and in 1993 the results were given separately from the American (Klintmalm) (87) and European randomized trials (Neuhaus, Berlin) (88). Single-center toxicity (Stock) and efficacy reports (Esquivel) were given in 1992 and 1993, respectively, from the 2 San Francisco liver teams (89,90). Five months after the 1993 ASTS meeting, FK506 completed its "fast track" journey through the FDA with a polished final profile of efficacy and safety for liver transplantation—much the same as had been presented verbally year by year to the Transplantation Society and ASTS.

Tolerance. The mechanism of this process and means of inducing it with inert antigen or live immunocytes have been pursued at ASTS meeting along multiple lines of sophisticated in vivo and in vitro inquiry. Liver and intestinal transplantation cast a clarifying beam on these efforts—the liver because it has been long known to be naturally tolerogenic and the intestine because it is heavily endowed with the T and B lymphocytes and natural killer cells associated with graft-versus-host disease (GVHD).

Hepatic tolerogenicity was defined as the liver's ability to induce its own permanent drug-free acceptance in dogs, aided by a 4-month postoperative course of azathioprine (Denver, 1965), sometimes without immunosuppression in pigs (Paris, Bristol, Cambridge, and Denver, 1966-1968) and predictably in several strain combinations of rats (Cambridge, Tokyo, and Pittsburgh, 1975-1985) and almost all mouse combinations (Pittsburgh, 1993). The additional demonstration by Calne (1969) and

others at Cambridge that pig and rat liver recipients could freely accept other tissues and organs from the same donor created a model for investigation that resisted efforts at explanation until recently. In an Upjohn Prize-winning paper in 1988, Yamaguchi (with Bollinger, Duke) presented evidence of the central role of Class I MHC antigens in hepatic tolerogenicity (91), seemingly congruent with the documentation in Cambridge (discussed by Bruce Roser, invited speaker, 1988) that new circulating soluble Class I antigens of donor specificity could be found promptly and permanently in human liver recipients (92).

Although the putatively tolerogenic soluble antigens were widely assumed to be of hepatocyte origin, they actually are from the donor nonparenchymal cells (NPCs) that are in all tissues and organs ("passenger leukocytes") but are unusually well represented in the liver. Thus, the persistence of the new soluble Class I antigens was evidence (largely unheeded by investigators) that the NPCs remained viable. In 1992, Campos and Naji (University of Pennsylvania) demonstrated in rats that thymic injection of donor bone marrow greatly increased natural hepatic tolerogenicity, allowing long or permanent liver allograft survival in an otherwise strongly rejecting strain combination (93). Interestingly, a hepatocyte suspension (which presumably contained NPCs) had a similar but much weaker effect.

This special example of donor passenger leukocyte augmentation with delivery to an immunologically important target had been reported 2 years earlier by Naji with pancreatic islets. The work generated numerous derivative studies that included 12 presented at the 1992 Transplantation Society in Paris. However, this was only the tip of a previously undetected iceberg that drifted without warning into the postgraduate course of the 1992 ASTS meeting. In his invited lecture on cell transplantation (94), Camillo Ricordi (Pittsburgh) described to an incredulous audience the recent invariable detection, with sensitive immunocytochemical and molecular (PCR) techniques, of ubiquitous donor leukocyte chimerism in human organ recipients—as long as 3 decades postoperatively, most prominently in patients with liver allografts. These observations—plus the prior knowledge that the NPCs of liver (Colorado, 1969) and other allografts (Pittsburgh 1991-1992) are replaced by recipient cells of the same lineages—implied a bidirectional migration of immunocytes after transplantation. The dynamics were promptly worked out by Demetris, Murase, and Qian (Pittsburgh), first in rats and then in mice (1991-1993) after intestinal and liver transplantation.

Clinical success was defined as the body-wide David and Goliath engagement of the cells of the donor mini-immune system (the passenger leukocyte component of the allograft) with those of the recipient immune system, and an immunologic truce reached by these mixed leukocytes was postulated to define clinical success. The inability to achieve such a resolution was tantamount to clinical failure, defined most commonly by the familiar host-versus-graft reaction (rejection), but less commonly by an imbalance in the other direction leading to GVHD (which, in the past, has not been commonly recognized). Both HVG and GVHD reactions may occur simultaneously. In addition to the inherent immune reactivity of the host immune system, the outcome was thought to be strongly influenced by the leukocyte mass and lineage

constituency of the organ transplanted. Both of these quantitative and qualitative factors of the NPCs are especially favorable with the liver.

In this new paradigm, the appearance of suppressor cells, veto cells, cytokines, and other immunobiologic changes that had long dominated ASTS programs were seen as epiphenomena —secondary to the seminal event of cell migration and microchimerism. In nonrejecting chimeric mouse liver recipients never exposed to immunosuppression, Dahmen (Pittsburgh, 1993) (95) demonstrated "split tolerance" after one month or much longer. This was defined by these animals' acceptance of donor strain hearts or skin (but not third-party allografts) at the same time as in vitro antidonor activity measurable with MLR and CML. An implication of these clinical and experimental discoveries was that many long-surviving human liver recipients were being maintained on protocol immunosuppression that was no longer necessary. This was strongly supported at the 1993 ASTS meeting by Reyes' report of 23 liver recipients whose treatment had been stopped 6 months to 20 years posttransplant, with subsequent rejection-free intervals of 1 to 18 years (96).

Because the chimeric leukocytes dispersed from the allograft are of bone marrow origin, a therapeutic corollary was that acceptance of less favored organs such as the heart and kidney (or even the liver itself) could be facilitated by the infusion of unaltered donor bone marrow perioperatively. Donor leukocyte infusion to induce tolerance was the most ancient therapeutic strategy of transplantation immunology but perhaps the least well understood. It was first used by Prehn and Main (NIH, 1955) and Trentin (Houston, 1956), who showed that lethally irradiated adult mice reconstituted with allogeneic bone marrow could accept skin from the same donor strain but no other. These were efforts to mimic the 2 conditions (inoculation of mature donor immunocytes and immunologic nonreactivity of recipients) which had allowed Billingham, Brent, and Medawar (1953) to induce acquired tolerance of neonatally or perinatally injected mice. Thousands of similar experiments, as well as the treatment policy in the clinical field of bone marrow transplantation, have assumed the need for either a natural or an imposed state of host nonreactivity. The consequent risk of GVHD was described by Billingham and Brent (1956). The dimensions of the GVHD problem proved to be so great clinically that a dozen years passed before Robert Good (1968, Minnesota) and Donnall Thomas (1969, Seattle) were able to report the first successful examples of human bone marrow transplantation, and then only with perfect donor-recipient HLA matching.

In attempts to induce tolerance to whole organs while avoiding the GVHD trap, Good, Kelly, Lillehei, and their associates gave leukocyte membranes prepared from donor white cell pack to renal transplant recipients preoperatively. This was a preamble to the widespread current practice of pretransplant donor-specific blood transfusion reported by Salvatierra (American Surgical Association, 1980; ASTS, 1985) (97). Monaco reported at the 1975 ASTS meeting (98) that he had given cryopreserved intravenous donor bone marrow to a patient 25 days after cadaver kidney transplantation, with a good clinical result, until death 8 months later from a colonic perforation. The treatment schedule of induction immunosuppression with ALS (or ALG) plus conventional agents, with delayed infusion of bone marrow, has been called the

"Monaco model," developed systematically by Monaco, Wood, and Russell in mice (1966) and in dogs (1973), and then by Thomas (1985) in subhuman primates. More than 10 years passed before marrow augmentation was tried again in trials of cadaver renal transplantation in Alabama, presented by Barber at the 1988 (99) and the l990 (100) ASTS meetings. The clinical results were promising but inconclusive, possibly because of uncertainty about cell viability and because of the timing in the protocols.

In some of these historically important initiatives, the cells were deliberately killed. In others, it was assumed they had a short life span in the recipient environment. It may be suggested now that, in the Minnesota and California trials, the augmenting antigen or leukocytes were given too early—causing sensitization of some of their patients. In the Alabama trials (based on the Monaco model), they may have been given too late (20 days after renal transplantation) for optimal effect. Armed with the discoveries that natural chimerism from the graft itself begins within minutes of organ revascularization and persists, it was possible during 1993 to simulate this timing in unconditioned patients whose transplanted organ, immunosuppression, and adjuvant bone marrow all arrived perioperatively. At the 1993 ASTS postgraduate session (101) the uncomplicated courses were described of the first dozen kidney and liver recipients who had been given 3×10^8 unaltered bone marrow cells/kg intraoperatively and then were treated with routine FK506-prednisone immunosuppression. All recipients had 0.8% to 15% circulating donor leukocytes 1 to 8 months later, and all had good function of their whole organ allografts. None developed GVHD, which was consistent with earlier observation in rodents by Slavin and Strober (1977) and by Ildstad and Sachs (1984) on the safety of mixed chimerism.

Such cell augmentation for intestinal transplantation would have been inconceivable with the previous understanding of transplantation immunology. However, the freedom from GVHD of human intestinal recipients reported by Todo and Tzakis (74,75) could now be explained by the canceling interactions of the coexisting cell populations. Lymphoid depletion of the graft, as suggested by the research of the Harvard-Northeastern group (77-80), appeared to be unnecessary. In fact, it was probably contraindicated because it was associated in earlier cases with a high incidence of B cell lymphomas. However, T cell depletion of the infused cells may be needed if the bone marrow is to be used safely in potentially GVHD-prone intestinal recipients.

The same questions about immunologic balance must be addressed in strategies to induce the acceptance of organ xenografts. These organs have been shown in animals and humans (Pittsburgh, 1992) (57) to generate bidirectional migration patterns similar to allografts, if they survive antibody and complement activation whose effect is to devascularize the organ by occluding its microvasculature. As discussed by Ricordi, the individual free cells of a xenograft have less jeopardy than the whole organ.

HLA Matching. During the last 5 years, groups from Cambridge and Pittsburgh have reported an inverse correlation between HLA matching and clinical liver transplant results. These reports have added to questions about the enigmatic inability of HLA technology to accurately predict the outcome with any organ. The new paradigm of graft acceptance implies a postoperative dwindling of an MHC effect beginning short-

ly after the transplantation of all organs, an effect that is proportional to the load of donor migratory cells introduced by the specific kind of allograft. This explanation is compatible with the mouse liver transplant experiments of Dahmen and Qian (95), in which the effect of MHC Class I, II, and minor incompatibility was diminished or lost, even without immunosuppression.

Discussion

It is tempting in reviewing our meetings to indulge in mutual congratulations, but this would militate against course correction if indicated. Scientific and clinical specialties develop a formidable collective wisdom that safeguards their integrity and prevents the irresponsible dissemination of false information. However, the resulting conservatism can itself impede progress, perpetuate dogma, and inhibit creative movement. With 19 years of annual ASTS programs before us, we can objectively assess the extent to which we have avoided such self-entrapment by asking 4 questions: (1) Did the selected abstracts and invited lectures announce major advances in the field? (2) Were the ideas valid in retrospect? (3) Did they germinate further developments? and (4) Were manuscripts provided by the authors and, if so, what became of them?

By these criteria, ASTS cannot receive an "honors" grade for liver and intestinal transplantation, in part because so many of the presentations were late reflections of earlier work. Whether this was due to failure to submit abstracts or to their culling by program committees is not possible to determine. Such concern about program development is inevitable in all societies that conduct popular congresses, but perhaps more frequently expressed in ours because of the vast intellectual range of interest of its membership. However, at either side of the resulting gap, we should find ways to air unconfirmed scientific observations, innovations, new drug initiatives, and management strategies that have not yet met format-restricted standards (which are more attuned to verification and detail than to original discovery).

In addition, it must be noted for the benefit of future archivists how far the written record of our meetings has fallen short of the real content. Of the 95 presentations on the liver and intestine given between 1977 and 1993, only 61 (64%) appeared in or have been accepted for our designated outlet, the journal *Transplantation* (see bibliography). Failure to achieve this final step is rare at the international Transplantation Society congresses, and almost unheard-of in some of the most distinguished and pluralistic professional organizations, such as the American Surgical Association (which selects only 35 abstracts from more than 400, but then publishes them all in the *Annals of Surgery).* ASTS (and probably also ASTP) should explore arrangements that will allow the membership to review its own proceedings in an orderly way ex post facto. This could be accomplished with a supplemental issue containing extended abstracts, leaving the option open of full manuscript submission to *Transplantation* and other journals for their normal avenues of peer review.

With the discarded papers on the liver and intestine, the floor discussions of the verbal presentations also have been lost to posterity. This whittling away of program

substance could have been due to an unsatisfactory caliber of manuscripts, the failure to submit them, or an unrealistically critical editorial process reflecting a different purpose than that of the selection and program committees. Any of these factors, if uncorrected, will ultimately weaken our society by undermining its main purpose of unfettered communication.

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Pancreas and Islets

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Introduction

Transplantation for diabetes can have two objectives: 1) replacement of an organ (kidney) secondarily damaged by the effects of dysmetabolism; or 2) correction of the metabolic defect (insulin insufficiency) by providing the insulin-producing beta cells that were destroyed by the original disease process.

Both of these endeavors—kidney transplantation to treat end-stage diabetic nephropathy and total endocrine replacement therapy for diabetes by islet transplantation (either as an intact immediately vascularized pancreas, or as a free graft of dispersed or isolated tissue)—preceded the advent of ASTS, clinically as well as experimentally. This is also true in general, not only for the kidney but for all organs routinely grafted today, including the liver, heart, lung, and intestine, not to mention bone marrow (mainly used only as an adjunct for immunologic manipulation by ASTS members).

In this historical review, transplantation for diabetes has been divided into two periods: before and during the first 19 years of ASTS. Advances in the second period are characterized by whether they were initially presented at or elaborated on at the annual ASTS meetings (referenced numerically), or whether they were primarily publicized outside of the ASTS format (annotated in the text).

The first clinical pancreas transplant, done in conjunction with a kidney at the University of Minnesota in 1966 (*Surgery* 61:827,1967), preceded the initial ASTS meeting by 9 years. Free grafting of xenogenic or allogenic pancreatic islet tissue had been sporadically attempted since the turn of the century (see review in *Cell Transplant* 2:269,1993). But there was no sustained effort at islet transplants until 9 were done in 1974 at the University of Minnesota (*Transplant Proc* 7:611,1975), the year before ASTS was founded. It is uncertain when the first patient with end-stage diabetic nephropathy received a kidney transplant, but Minnesota began to do kidney transplants alone as routine treatment for this disease in 1968 (for history, see *Am J Surg* 166:456, 1993).

The three procedures—kidney transplants for diabetic nephropathy and either pancreas or islet transplants to correct the metabolic defect—were controversial at the time ASTS was formed, but did not stay that way. Kidney transplants for diabetic nephropathy became routine across the U.S. by the end of the 1970s, and were strongly advocated as proper treatment by the ASTS Standards Committee at the beginning of the 1980s (*JAMA* 236:1330,1981).

Only 2 papers (7,11) on clinical pancreas transplantation were presented to ASTS in the 1970s (Table 1). However, since the mid-1980s, such papers have appeared on all of the programs. By the end of the 1980s, pancreas transplantation had become routine (at least in conjunction with a kidney) at many centers.

Islet transplantation has remained developmental. Not until 1990 did a clinical islet paper appear on the ASTS program (Table 1). Papers on experimental islet transplantation were presented at the first meeting in 1975, and at all but 3 (1978, 1979, 1980) of the subsequent 18 meetings.

Of the 851 papers presented at the first 19 ASTS meetings, 93 (11%) were relevant to kidney, pancreas, or islet transplantation for diabetes. Eight focused on kidney transplants for diabetic patients, 45 on pancreas transplants (32 clinical, 13 experimental), and 40 on islet transplants (4 clinical, 36 animal or in vitro). The number of clinical pancreas papers exceeds the number of clinical islet papers, and the number of experimental islet papers exceeds the number of experimental pancreas papers. These disparities reflect the fact that although pancreas transplantation has had a relatively high success rate, it has also had a high morbidity rate; while islet transplantation has had a low morbidity rate, but a relatively low success rate.

All of the papers presented at the first 19 meetings had the potential to be published in the journal dedicated to the proceedings (*Surgery* for 1975 and 1976; *Transplantation* thereafter). Virtually all papers from annual meetings of major surgical societies are published in the journal linked to that society. However, of the 93 ASTS papers on diabetes and transplantation presented between 1975 and 1993, only 62 (67%) were published or are in press (3) in the official journal (75% of clinical kidney, 69% of experimental pancreas, 53% of clinical pancreas, 75% of experimental islet, and 75% of clinical islet papers). Of the remaining 31 papers, publications in other journals that correspond to the abstract were found by literature search for 20 (67%), 1 of 2 clinical kidney, 2 of 3 experimental pancreas, 11 of 15 clinical pancreas, 5 of 10 experimental islet, and 1 of 1 clinical islet. Thus, 82 of 93 (88%) of the papers presented on diabetes and transplantation at the first 18 ASTS meetings were ultimately published or are in press. I did not do a count for other topics presented at ASTS meetings, but I suspect the publication record is similar. Undoubtedly, many of the abstracts that were submitted but not accepted for presentation at the ASTS annual meetings found their way into print, including some cited as part of the story. It is uncertain how many of the papers were submitted for publication at the time of the meeting, and it is uncertain how many that were submitted passed the peer review process. Only what was printed in ASTS abstract booklets and what was later published can be assessed.

The first 4 papers presented at the initial ASTS meeting in 1975 were diabetes-

Table 1
Number of Papers on Kidney, Pancreas, and Islet Transplants for Diabetes (ASTS, 1975–1993)

Mtg No.	Year Diabetes	Clinical Kd Tx for Px Tx	Experimental Px Tx	Clinical Islet Tx	Experimental Islet Tx	Clinical	TOTAL
1	1975	2			2		4/24
2	1976				1		1/28
3	1977		1	1	1		3/36
4	1978	1					1/34
5	1979		1	1			2/32
6	1980		1				1/36
7	1981	2			1		3/32
8	1982	2	1/2	1	1/2		4/32
9	1983				2		2/30
10	1984		1	1	2		4/36
11	1985		1	1	1		3/30
12	1986		1	3	2		6/40
13*	1987		2	1	2		5/40
14	1988	1		3	2		6/44
15	1989		1	4	4		9/64
16#	1990		3 1/2	4	5 1/2	1	14/72
17	1991			4	3	2	9/70
18	1992			4	2	1	7/70
19	1993			4	5		9/101
TOTAL		8 (1%)	13 (1.5%)	32 (3.5%)	36 (4%)	4 (0.5%)	93/851 (11%)

* The invited lecture was on pancreas transplantation
\# The Upjohn Symposium was on pancreas transplantation

related: 2 on clinical kidney transplantation in diabetic recipients (1,2) and 2 on islet transplantation in animal models of diabetes (3,4). Of the 4, 3 were published in the official proceedings of ASTS (1,3,4) and 1 elsewhere (2).

Although the applications of kidney, pancreas, and islet transplantation for diabetes were intertwined, for ease of discussion, ASTS abstracts and papers on each topic are reviewed in separate sections. Some papers are relevant not just to diabetes, but also to transplant surgery, organ preservation, and immunology in general.

Diabetic Nephropathy and Kidney Transplantation

At the time of the first ASTS meeting in 1975, kidney transplantation for diabetic patients was not routine at most transplant centers in North America, let alone the world—but it was routine at the University of Minnesota (*Ann Surg* 178:477,1973). There was, however, widespread interest in the topic. The first papers on the very first ASTS program addressed aspects of kidney transplantation for patients with end-stage diabetic nephropathy. Both were from Minnesota.

The first, presented by Arthur Matas, was on a specific problem associated with kidney transplantation in diabetic patients—differential diagnosis of the cause of an elevation in serum creatinine in the face of hyperglycemia (1). Hyperglycemia per se

could be responsible, not because high glucose levels interfered with the assay for creatinine but because of renal dysfunction induced by secondary dehydration. Rather than perform a kidney biopsy, and treat for rejection, one simply had to correct hyperglycemia and recheck the creatinine. At the time, the number of diabetic patients who had received kidney transplants at other centers was very small, and any information on experience caring for diabetic recipients was helpful.

The second paper, presented by Carl Kjellstrand, was on the overall experience with kidney transplantation in diabetic patients at the University of Minnesota, at the time over 100 cases (2). This presentation was part of a steady stream from Minnesota describing the evolving application of renal transplantation for treatment of diabetic nephropathy (*Lancet* 2:48,1973; *Kid Int* 6(Suppl. 1):515,1975). Kjellstrand and colleagues showed very clearly that uremic diabetic patients who received a kidney transplant had a much better course than those waiting on dialysis. Retinopathy tended to stabilize posttransplant, while vision declined for those on dialysis, probably because hypertension was much better controlled by a kidney transplant than by the drugs available at the time. The survival rate of diabetic patients who received kidney transplants was also much higher compared with diabetic patients who remained on dialysis.

The evolution of kidney transplantation as a treatment by itself for diabetic nephropathy at Minnesota was intertwined with that of pancreas transplantation. The first kidney transplant in a diabetic patient was done at Minnesota in December 1966, in conjunction with a pancreas (*Surgery* 61:827,1967). The following year (1967), John Najarian came to the University of Minnesota from California; in 1968 he was joined by Kjellstrand and Richard Simmons. The results with kidney-pancreas transplants (*Ann Surg* 172:405,1970) prompted them to challenge the perception that the endocrine defect in uremic diabetic patients had to be totally corrected in order to succeed with a kidney graft. They began to accept referrals of uremic diabetic patients for kidney transplants alone (*Transplant Proc* 5:799,1973). At the time of the ASTS presentation, Minnesota experience with kidney transplantation for treatment of patients with diabetic nephropathy exceeded that of all other ASTS members combined.

In the mid-1970s, diabetic patients were often termed "high-risk" for a kidney transplantation by other institutions. What this really meant was that transplanting diabetic patients was a high risk for an institution's image based on results (see *Transplant Proc* 14:191,1982 for a full discussion of the inappropriate use of the term high-risk). Although patient survival rates of diabetic recipients were lower than those of nondiabetic recipients, they were higher than those of diabetic patients who remained on dialysis. Thus, it would have been more accurate to say that a kidney transplant was a low-risk treatment for diabetic patients with uremia as compared to dialysis treatment alone. Ironically, it would have been more accurate to say that nondiabetic patients were high-risk kidney transplant candidates: at the time, patient survival rates were actually higher for nondiabetics maintained on dialysis than for those who received a transplant, while just the opposite was true for diabetic patients (National Dialysis Registry Report, AK-8-7-1387-F. Bethesda, NIAMD, NIH, 1976). If treating

individual patients had been emphasized rather than getting good results at the expense of patients in need, many more diabetic patients would have been transplanted in this early era.

After the 2 papers in 1975 by Matas and Kjellstrand, there was a 2-year hiatus before another paper relevant to kidney transplantation for diabetic patients was presented at an ASTS meeting. In 1978, Bruce Sommer gave a paper from the Minnesota group that defined risk factors for kidney transplantation, diabetes among them (9). They compared outcome according to recipient age, presence or absence of diabetes and other systemic diseases in the recipients, donor source, and HLA match; risk was defined only relative to these categories of kidney transplant recipients, not to the alternative therapy of dialysis. Again, the potential for the term "risk factor" to be misused was inherent. Although diabetic recipients tended to have lower patient and kidney graft survival rates than nondiabetic recipients, donor source and HLA match had a greater impact on outcome than presence or absence of diabetes. Nevertheless, there was a clear challenge to improve the results in diabetic recipients relative to nondiabetic recipients (not relative to dialysis, where transplantation was the clear winner for diabetic patients).

After a second 2-year hiatus, the topic of kidney transplantation in diabetic patients again made the 1981 ASTS program—this time with 2 abstracts, as at the first meeting. The first, presented by Charles Peters (transplant fellow), was the fourth consecutive one from Minnesota on renal transplantation in diabetic patients. The series involved about 400 diabetic recipients by that time, and Peters gave the patient and graft functional survival rates in those who did and did not require amputations over time (17% incidence at >2 years posttransplant) (13). Uremic diabetic patients were now being kept alive by kidney transplants (instead of dying without treatment or dying early on dialysis), allowing diabetic complications to advance beyond the stages that would otherwise have occurred. Those who required amputations had lower patient and graft survival rates than those who did not. Interestingly, those who did not have amputations had survival rates (patient and graft) nearly identical to nondiabetic recipients.

1981 also marked the first paper on kidney transplantation for diabetic recipients from a group other than Minnesota. Nicholas Feduska, from the University of California in San Francisco (UCSF), presented a paper confirming that diabetic recipients had higher patient and graft survival rates with living related donor (LRD) than with cadaver donor kidneys (14). Indeed, LRD outcomes were similar for diabetic and nondiabetic recipients treated by the donor-specific blood transfusion protocol employed by the UCSF group (*Ann Surg* 192:543,1980). The living donor approach had been advocated by Kjellstrand at the 1975 meeting, and was taken up by the UCSF group as well as by other ASTS members (*Transplant Proc* 11:55,1979; *JAMA* 246:133).

The following year, 1982, Feduska presented again (17). The UCSF program had a better outcome for uremic diabetic patients transplanted before versus after dialysis was necessary. Again, early transplantation for diabetic patients had been advocated by Kjellstrand in 1975 (2).

The Minnesota group also had another paper on kidney transplants for diabetic

nephropathy in 1982 (19). This one showed how patient and renal graft survival rates for uremic diabetic recipients had improved over the past 13 years, particularly after the first decade of experience. The cases in this analysis preceded the cyclosporine era. Multiple factors were responsible for improved results since the earlier experience reported by Sommer (9), including deliberate pretransplant blood transfusions, intensive insulin therapy posttransplant, and judicious treatment of rejection episodes. Indeed, with living donors, patient and graft survival rates were even slightly higher for diabetic than for nondiabetic recipients; with cadaver grafts they were similar for the first two years for diabetic and nondiabetic recipients, after which they declined in diabetic recipients. The conclusion of the 1982 paper was that diabetic patients should no longer be considered high-risk for transplantation in any sense of the word, and that diabetes was just another cause of renal failure to be treated by a kidney transplant.

That was not to say that other diabetic complications did not have a significant impact on rehabilitation, since they did. Thus, many of the patients in the Minnesota series were also receiving pancreas transplants after the kidney (18). But it was apparent that kidney transplants in the early 1980s were just as successful for diabetic as for nondiabetic recipients using the non-cyclosporine Minnesota protocol of antilymphocyte globulin (ALG) for induction immunosuppression (*Ann Surg* 184:352,1976).

Steady improvements in outcome had occurred before the introduction of cyclosporine. Further improvements in diabetic kidney transplant outcome were yet to come (see *Amer J Surg* 166:456, 1993), perhaps due, in part, to the use of cyclosporine in combination with other drugs (*Transplant Proc* 18:76, 1986).

The final ASTS paper of the 8 that focused on clinical kidney transplantation for diabetic patients was presented to ASTS 6 years later, in 1988, by John Najarian (45). This paper was the culmination of 20 years of kidney transplantation for diabetic nephropathy at the University of Minnesota. It detailed the long-term course of 100 Type I diabetic patients who had survived more than 10 years with a functioning renal allograft. Interestingly, some of the graft losses after 10 years were due to recurrence of diabetic nephropathy—a consequence of remaining diabetic and escaping rejection. The series of 100 also included patients who had a pancreas transplant after their kidney transplant. None of these patients had lost a kidney due to recurrence of diabetic nephropathy. At the time of Najarian's presentation, one patient who had a kidney transplant 16 years earlier and a pancreas transplant 10 years earlier, with both grafts functioning normally. More patients with an LRD (n=75) than with a cadaver (n=25) kidney had survived 10 years. But once they made it that long, patient and kidney survival rates thereafter were similar, regardless of donor source; about half survived at least another 5 years, and some are still alive with a functioning kidney graft at 20 years.

After the 1988 Minnesota paper (45), either none were submitted or none were accepted on the topic of kidney transplants alone for treating diabetic nephropathy. By the late 1980s, kidney transplants for diabetic nephropathy were routine at virtually all centers, and perhaps a mundane subject for presentation. The focus in the late 1980s was on the improved results with pancreas and kidney transplants in diabetic

patients. The continued quest to succeed with islet transplants to treat diabetes was also given its due in papers selected for ASTS meetings.

Pancreas Transplantation to Treat Diabetes

Of the extrarenal organs commonly transplanted today, the pancreas was done the least in the years preceding the formation of ASTS in 1975. The American College of Surgeons (ACS) maintained an Organ Transplant Registry under contract with the National Institutes of Health (NIH) until 1976, the year after ASTS was born. Records from the ACS/NIH registry were transferred to the International Pancreas and Islet Transplant Registry (formed under the auspices of the Scientific Studies Committee of ASTS) in 1980 (*Transplant Proc* 12[No.4, Suppl. 2]: 229, 1980).

During the 8 years from the first pancreas transplant in December, 1966 to the birth of ASTS in 1975, only 43 pancreas transplants were done—28 in North America and 15 elsewhere—and never more than 9 in any one year (*Diabetalogia* 20:435,1981). The level of activity remained low during the first few years of the existence of ASTS, with only 6 reported in 1975, 7 in 1976, and 8 in 1977.

Beginning with 15 cases in 1978, sustained growth occurred (Figure 1). By the end of 1993, more than 5500 had been reported to the International Pancreas Transplant Registry, including more than 3500 from North America (*Clinical Transplants*—1993). Thus, 99% of the pancreas transplants reported to the Registry by the 20th anniversary of ASTS were done during its existence.

Nevertheless, pancreas transplantation was begun by individuals who were founding members of ASTS, and their contributions during the years before 1975 must be mentioned. The first two pancreas transplants were done in December 1966 by Richard Lillehei and William Kelly at the University of Minnesota (*Surgery* 61:827,1167). Both were done with a simultaneous kidney transplant. The first pancreas transplant was a segmental duct-ligated graft and the second was a whole pancreaticoduodenal graft with a cutaneous duodenostomy (*Surgery* 61:827, 1967). Three more cases were done at Minnesota (in 1967 and 1968) before any were done elsewhere (*Ann Surg* 172:405,1970). In North America, the first pancreas transplant outside of Minnesota was done at the University of Colorado in 1969, by Frederick Merkel. John Connally did another case at the University of California, Irvine, in 1969, using enteric drainage. In 1970, Wesley Alexander did a duct-ligated pancreas transplant at the University of Cincinnati. 1970 was also the year the first urinary drained pancreas graft was transplanted by Marvin Gliedman at Montefiore Hospital in New York, with the duct of a segmental graft anastomosed to the ureter of the recipient (*Amer J Surg* 125:242, 1973). Although devised to circumvent technical problems associated with whole organ grafts or with anastomosis of a segment to the bowel,Gliedman also noted that rejection was associated with a decline in urine amylase activity generated by graft exocrine secretions discharged directly into the urinary tract. Later, the urinary drainage technique was made simpler by the innovation of Hans Sollinger, with direct anastomosis to the bladder (*Transplant Proc* 16:749, 1984).

Thus, by 1975, the year ASTS was formed, 14 pancreas transplants had been done

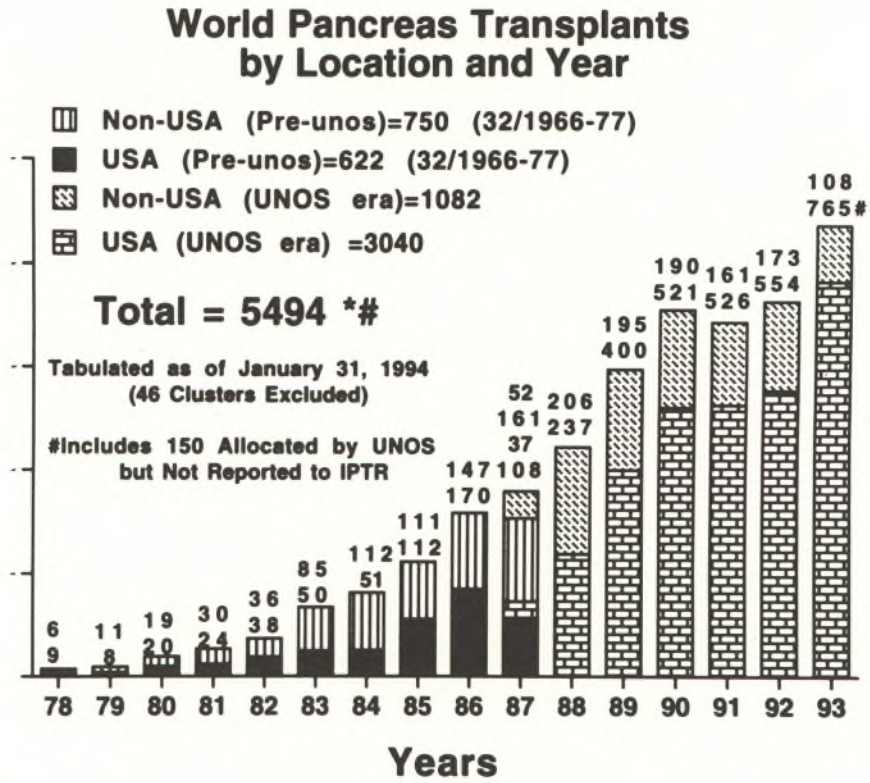

Figure 1. Number of Pancreas Transplants tabulated by the International Pancreas Transplant Registry (IPTR), 1966-1993 before and after the United Network for Organ Sharing (UNOS). The reporting for 1993 is incomplete. The total number of U.S. cases was 3662 (45 clusters); non-U.S. 1832 (1 cluster). The world total with cluster cases included was 5540 (in Terasaki, Clinical Transplants—1993).

at the University of Minnesota (*Acta Endoc* 83(Suppl.205):303, 1976); 1 at the University of Colorado (unpublished); 3 at the University of California, Irvine (*Arch Surg* 106:489, 1973); 1 at the University of Cincinnati (unpublished); 7 at Montefiore Hospital, New York (*Surgery* 74:191, 1973); and 2 in Chicago by Frederick Merkel, 1 at Northwestern University (*Arch Surg* 103:205, 1971), and 1 at Rush-Presbyterian Hospital (*Ill Med J* 144:477, 1973). During 1975, the year ASTS was formed, only 6 pancreas transplants were done worldwide and just 1 in the U.S. (Montefiore Hospital, New York).

The results with these pioneering cases were less than good. Only 2 patients had pancreas grafts function at >1 year, 1 transplanted by Lillehei at Minnesota, the other by Gliedman in New York. However, these cases showed that a normoglycemic,

insulin-independent state could be maintained long-term. The potential of transplantation to treat diabetes was obvious, even if some viewed the initial results as discouraging. The technical complication rate was initially extremely high, with at least half of the transplants done before 1975 failing for surgical reasons (*Diabetalogia* 20:435,1981). Most of the others failed because of rejection unless the recipients died first with a functioning graft. Most recipients were very sick uremic diabetic patients, and most would probably have been better off with a kidney transplant alone.

No pancreas transplant abstracts were presented at the first ASTS meeting in 1975. There were 2 on islet transplants (3,4), the approach most perceived would be the future. The prevailing attitude was negative. In 1977 Felix Largadier, a protégé of Lillehei and himself one of the pioneers, wrote an article entitled "Farewell to Pancreatic Organ Transplantation?" (*Euro Surg Res* 9:399, 1977)—an article I never failed to cite as things got better in the years to come (*Diabetalogia* 20:435, 1981). However, that same year (1977), for the first time, papers on pancreas transplantation were presented at the ASTS meeting, 1 clinical (7) and 1 experimental (8). Gleidman presented the series of 10 cases from Montefiore Hospital, New York (7). One long-term pancreas-kidney recipient was alive and insulin-independent at 4 years. The patient continued to suffer the ravages of vascular disease, but a kidney graft biopsy was normal. There was no evidence of recurrence of diabetic nephropathy in the transplanted kidney (7). In contrast, the year before (1976), the Minnesota group had reported that microscopic lesions of diabetic nephropathy uniformly recurred after 4 years in diabetic recipients of kidney transplants alone (*NEJM* 295:916, 1976).

The 1977 experimental paper was presented by George Kyriakides, from the Veterans Administration Hospital component of the University of Minnesota program (8). Long-term function of pancreas allografts occurred in pigs given ALG for induction immunosuppression. The paper by Kyriakides was important in that it also addressed the technical aspects of transplantation (8). In the late 1970s, debates over endocrine replacement therapy by transplantation revolved around whether pancreas transplants should be abandoned altogether and islet transplants pursued, or, if not, which surgical technique should be used to manage the graft duct or exocrine secretions if an intact pancreas was transplanted. Kyriakides used a very simple technique—leaving the duct open, thus allowing the pancreatic secretions to drain freely into the peritoneal cavity of recipient pigs—and it worked (8).

The debate over pancreas and islet transplants continued for many years and persists to this day. But by the late 1970s, it should have been obvious that islet transplants were not as simple as initially perceived. No islet allograft recipients were insulin-independent (at the time *Surg Clin N Amer* 58:365, 1978).

Meanwhile, a few investigators persevered with pancreas transplants, both experimentally and clinically. They mainly used segmental grafts, since the donor duodenum that accompanied whole pancreas transplants (as used by Lillehei and others) was thought to be the source of many complications. The use of the duodenum was resurrected in the 1980s (*Surg Gynecol & Obstet* 159:265,1984), but from the mid-1970s until the early 1980s, partial pancreas transplants without the duodenum were the mode. Europeans were active in advancing the field. In Stockholm, Carl Groth

used enteric drainage for segmental grafts (*Lancet* 2:522, 1982). In Lyon, France, Jean-Michael Dubernard introduced duct injection of segmental grafts with a synthetic polymer—a safe, new technique with a low complication rate (*Surgery*, 84:633, 1978).

Dubernard's work was a stimulus to the transplant group at Minnesota. In the laboratory the duct-injection technique was compared to the open-duct technique, both in dogs at the University of Minnesota (*Transplantation* 28:485, 1979) and in pigs at the Minneapolis VA Hospital (*Surgery* 85:154, 1979). The open-duct technique worked very well in both models, and began to be used clinically at the University of Minnesota in 1978, the first year that more than 10 transplants were done worldwide (*Transplant Proc* 12 (No.4, Suppl 1):229, 1980).

The focus on the surgical aspects of pancreas transplantation was appropriate, because until the technical problems were solved (as best they could be; surgical complications still occur), experience in diagnosing and preventing rejection could not be gained. Cyclosporine was introduced by Roy Calne in England (*Lancet* 2:1033, 1979) while the debate on surgical techniques was ongoing. Only a few recipients of pancreas grafts before the cyclosporine era enjoyed long-term function (some still are functioning, *Am J Surg* 167:456, 1993). But it is doubtful that cyclosporine would have had the impact it has had on solitary pancreas transplants, without the application of surgical techniques allowing exocrine graft function to be monitored for each diagnosis of rejection. From 1979, the evolution of pancreas transplantation can be traced nearly completely by a chronology of the papers presented at the ASTS meeting.

A clinical series of 5 open-duct pancreas-after-kidney transplants from Minnesota was reported to ASTS in 1979 (11). At the time, 3 pancreas grafts were functioning, one for 1 year (still functioning 16 years later, *Am J Surg* 167:456, 1993). At the same meeting in 1979, Luis Toledo-Pereyra from Detroit presented a paper on autotransplantation of duct-ligated segmental pancreas in dogs (10). The complication rate was less with open-duct grafts, and the duct-ligation technique has basically been defined clinically.

The 1979 Minnesota paper on the open-duct technique in humans and dogs (11) was followed in 1980 by an experimental paper by Kyriakides and associates on long-term functional studies in open-duct grafts in dogs (12). Serum amylase levels were initially high, but gradually declined as the duct closed from fibrosis. Gradual closure was not associated with the acute problems precipitated by duct ligation. Clinically, however, not all patients tolerated the open-duct technique. Of 15 done at the University of Minnesota in the late 1970s and early 1980s, a third had technical problems such as ascites (*Surgery* 90:159, 1981). For this reason, the Minnesota group adapted the duct-injection technique of Dubernard (*Surgery* 84:633, 1978) for a comparison with the enteric drainage technique as modified by Groth (*Lancet* 2:522, 1982), and reported on a series of 49 cases—in which all techniques were compared—at the 1982 ASTS meeting (18).

The 1982 paper basically was the first clinical series with a sufficient number of cases to calculate pancreas graft functional survival probabilities (18). At the time of the 1982 ASTS meeting, about 200 pancreas transplant cases had been reported to the International Pancreas Transplant Registry (IPTR), of which one-fifth were from

Minnesota. Most transplants in the registry were simultaneous pancreas-kidney (SPK) transplants, but there were none of this type in the new Minnesota series. The Minnesota group took a different tack in 1978. Perceiving that the complication rate might be lowered by lessening the magnitude of the surgical procedure, they performed solitary pancreas transplants. After initial success with pancreas after kidneys, the group began to do pancreas transplants alone in nonuremic diabetic patients. Not until the mid 1980s did Minnesota resume SPK transplants.

At the time of the 1982 ASTS meeting, there were no SPK transplants in the Minnesota series. About two-thirds were pancreas-after-kidney (PAK) and one-third pancreas transplants alone (PTA). Another unique feature of the Minnesota series was the use of living donors for segmental pancreas transplantation (*Surgery* 90:159, 1981), the first having been done in 1979 (*Transplant Proc* 12 (No.4)(S1):19, 1980). LRDs comprised about 40% of the series at the time of the 1982 report (18). About one-fourth of the cases were open-duct, one-half duct-injected, and one-fourth enteric-drained. With each technique, some grafts were functioning, but most from cadaver donors were rejected. The main drawback of the duct management methods was the inability to diagnose rejection early, since exocrine function could not be monitored long-term with any of the techniques. In the absence of a kidney graft from the same donor, rejection episodes of the pancreas could not be diagnosed by surrogate monitoring of serum creatinine. Rejection was not diagnosed until hyperglycemia occurred, which was usually too late to allow for reversal. Thus, the graft survival rate at 1 year in the 49 cases reported in 1982 was only 40%. The series also included the first pancreas transplant patients in North America treated with cyclosporine (*Surgery* 90:159, 1981), beginning a year after Calne's report in England where 2 of 34 organ transplant recipients initially given cyclosporine had a pancreas graft (*Lancet* 2:1033, 1979).

Cyclosporine was undoubtedly a critical advance in the development of all extrarenal organ transplantation, including the pancreas (*Diabetes* 31:92,1982). There were, however, recipients of pancreas grafts transplanted before cyclosporine was available that were functioning for 2 to 4 years at the time of the 1982 presentations (18), and some are still functioning, the longest for 16 years (*Am J Surg* 166:456, 1993). Nevertheless, the proportion of recipients who enjoyed sustained function was higher in those treated with cyclosporine. Later, when cyclosporine was combined with other drugs, the results improved even further (*Ann Surg* 200:414, 1984).

In retrospect, the most notable aspect of the 1982 Minnesota paper was the first description (with histology) of recurrence of Type I diabetes (selective destruction of beta cells with occurrence of hyperglycemia in the absence of rejection) in the pancreas graft (18). This patient received an enteric-drained segmental pancreas graft alone from her HLA-identical sibling. She was only immunosuppressed with cyclosporine (no prednisone or azathioprine, and no ALG for induction—perceived as unnecessary with such a good match), but after being normoglycemic and insulin-independent for 3 months, she became hyperglycemic. She was treated for presumed rejection with improvement, but at 6 months was fully hyperglycemic and did not improve with further immunosuppression. A biopsy at that time showed a normal

pancreas (no features of rejection) except for the complete absence of beta cells. This was reported as recurrence of disease, but the isletitis phase was missed because of the late timing of the biopsy (18). Subsequently, isletitis and recurrence of disease identified in nonimmunosuppressed recipients of segmental pancreas grafts from their nondiabetic identical twin donors (*Trans Amer Assoc of Physicians* 97:80, 1984; *Laboratory Invest* 53:132, 1985), a process that could be prevented by adequate immunosuppression (*Diabetes* 38 (Suppl.1):85, 1988).

Also of note in the 1982 Minnesota paper (18) was the finding that histologic lesions due to recurrence of diabetic nephropathy in a kidney transplanted 6 years before the pancreas had resolved by the time of a 4-year follow-up biopsy. This complemented the earlier observation of Gliedman (18) that recurrence of diabetic nephropathy could be prevented by a successful pancreas transplant (later confirmed in a large series by the Stockholm group) (*Diabetes* 34:306, 1987). The 1982 paper (18) included the index cases of series showing that a successful pancreas transplant could ameliorate early lesions of diabetic nephropathy in a previously transplanted kidney (*NEJM* 321:80, 1989).

Thus, the 1982 Minnesota paper (18) described the patients with the longest fully functioning pancreas grafts at that time from both cadaver (>4 years) and related (>2 years) donors; showed that recurrence of disease the pancreas graft from preexisting autoimmunity was a risk, but could be prevented by adequate immunosuppression; and demonstrated that at least one secondary complication of diabetes (nephropathy) could be ameliorated.

The Minnesota group also presented an experimental paper on the combined use of cyclosporine and azathioprine in pancreas, islet, heart, and kidney allograft animal models (16). Jean-Paul Squifflet showed that graft survival in 3 of the 4 models was extended significantly longer with combination therapy rather than cyclosporine alone. The experimental results prompted the clinical use of triple-drug maintenance immunosuppression (cyclosporine and azathioprine, in addition to prednisone), initially for cadaver pancreas graft recipients (*Ann of Surg* 200:414, 1984), and later for recipients of living donor grafts as well (24). Cyclosporine and azathioprine in combination was subsequently used for heart transplant recipients (*J Heart Transplant* 4:315,1985), and was widely adapted for organ transplant recipients in general by the end of the 1980s (*NEJM* 310:1217, 1988).

The next paper on pancreas transplantation presented at an ASTS meeting (1984) was on the Minnesota experience with LRD pancreas transplants (24). The pancreas was the first extrarenal organ for which an LRD transplant was used (*Transplant Proc* 12, No. 4, (Suppl. 1):19, 1980). It was a prelude of what was to come with the liver (*Adv Surg* 26:209, 1993) and lung (*J Thorac Cardiovasc Surg* 104:1060, 1992).

At the time of the 1984 ASTS meeting, the number of pancreas transplants in the total series at Minnesota since 1978 was 89, including 36 segmental grafts from LRDs (17 HLA-identical siblings, 6 identical twins, 13 HLA-mismatched), 12 who had previously received a kidney from the same donor. The latter group had the highest success rate, with all technically successful (TS) grafts functioning at the time of report (24). All of the cases (LRD and cadaver) were solitary pancreas transplants. Since

none were urinary drained, rejection episodes could only be diagnosed after elevation of blood sugar had occurred. The results clearly showed the benefits of a genetic match. In the absence of the ability to diagnose rejection episodes early, graft survival rates for LRD pancreas transplants were double those for cadaver donor transplants. In years to come, the gap in results between LRD and cadaver transplants narrowed (*Surgery* 104:453, 1988). The urinary drainage technique allowed rejection episodes to be diagnosed earlier because urine amylase declines before hyperglycemia occurs (*Surgery* 102:680, 1987). The advantage of LRD pancreas transplants is partially offset by the higher technical failure rate. But for technically successful grafts, LRD functional survival continues to be higher, as is the case for kidney transplants (*Am J Surg* 166:456, 1993).

The Minnesota ASTS paper on LRD pancreas transplants (24) also included an update on the observation made earlier, i.e., that pancreas grafts from at least identical twin or HLA-identical siblings donors in non- or minimally immunosuppressed recipients were susceptible to autoimmune isletitis and recurrence of disease (see *Trans Am Assoc of Phys* 97:80, 1984; and *Lab Invest* 53:132, 1985 for a complete description). The first 3 recipients of pancreas isografts from identical twin donors were not given prophylactic immunosuppression (because they could not reject). All had recurrence of hyperglycemia between 6 and 10 weeks posttransplant; graft biopsies showed insulitis and selective reduction of beta cells, with no other histologic abnormalities. With the immunologic basis for recurrence of disease proved, the fourth identical twin recipient was immunosuppressed (ALG for induction, azathioprine for maintenance); at the time of the report to ASTS, she had been insulin-independent and normoglycemic for about a year (24). That immediate autoimmune recurrence of disease could be prevented by immunosuppression was confirmed in subsequent identical twin donor pancreas transplants (*Diabetes* 38:S1; 85, 1989). The etiology of Type I diabetes mellitus was also being studied by other ASTS members using animal models (*Transplantation* 36:355, 1983), and their experimental findings in conjunction with the Minnesota clinical observations were linchpins in confirming the autoimmune hypothesis.

The other pancreas transplant abstract on the 1984 ASTS program was on experimental organ preservation, presented by George Kyriakides for the University of Miami group (22). They confirmed that machine perfusion could preserve canine pancreas grafts for 24 hours. By that time, others had found simple cold storage in plasma-based solutions to be superior, allowing preservation of canine pancreases for up to 48 hours (*J Surg Res* 34:493, 1983). In fact, the Minnesota group was successfully preserving human pancreases for up to 24 hours in plasma-based solutions (*Transplant Proc* 16:153, 1984). Several papers on pancreas preservation were presented at subsequent meetings (32,36,55), including the initial report on the use of the University of Wisconsin (UW) solution. UW solution eliminated the risk of disease transmission since it was entirely synthetic (32), and at the same time, gave results equivalent to or better than those achieved with plasma-based solutions.

In the interim, technical aspects were the focus of presentations on pancreas transplantation. The 1985 ASTS meeting had 2, 1 in an experimental model (26) and

1 clinical (27). Donald Dafoe of the University of Michigan reported that inclusion of the donor spleen with the pancreaticoduodenal allograft in pigs increased the propensity for rejection (26). This paper added to the damper on including the donor spleen with human pancreas transplants. This approach had been tried by a few groups to see if the thrombosis rate could be decreased or if there would be an immunologic advantage, but the results were disastrous. The thrombosis rate was actually higher (*Clinical Transplants*—1987, p. 63), and some recipients developed graft-vs.-host disease (*Transplantation* 54:190,1992).

A highlight of the 1985 ASTS meeting was the presentation by Hans Sollinger of the University of Wisconsin on his series of pancreas transplants using the bladder drainage technique (27). He reported a relatively low complication rate, and his approach caught the imagination of all Americans working in the field. Since the late 1980s, more than 95% of pancreas transplants in the US reported to the registry have been bladder-drained (*Clinical Transplants* —1993). European groups were much slower to adapt this technique. Of about 1,000 European cases reported to the registry between 1987 and 1993, only 60% were bladder-drained (the others were equally split between enteric drainage and duct injection). The proportion of bladder-drained cases that were did increase over time.

Sollinger hinted in his 1985 address that urine amylase might be useful to monitor for rejection. But nearly all of his cases were SPK transplants from the same donor, and monitoring of the kidney appeared to be sufficient (27). Since most of the pancreas transplants in Europe were SPK, surgeons there had no compelling reason to adapt the bladder drainage technique for monitoring. Except at Minnesota, SPK transplants predominated in the U.S. as well (*Clinical Transplants* 1:3,1987). However, the relatively low technical failure rate reported by Sollinger prompted its adaptation by most U.S. centers. The potential to use urine amylase to monitor for rejection episodes of solitary pancreas grafts was an impetus for the Minnesota group to do so as well (29). No randomized prospective trials of bladder drainage versus the other techniques were done in the U.S.. Dubernard in Lyon, France, conducted two randomized studies in SPK recipients, one of duct injection versus bladder drainage (*Transplant Proc* 25:1182,1993) and one of duct injection versus enteric drainage (*Transplant Proc* 19:2285,1987). They found no differences in pancreas graft survival rates. Nevertheless, bladder drainage is relatively simple, and remains the most popular technique for all pancreas transplants. In the year after Sollinger's presentation (27), bladder drainage was shown by the Minnesota group to be a major advantage for solitary pancreas transplant recipients because of the ability to monitor urine amylase for clinical diagnosis of rejection, making a kidney from the same donor unnecessary (29).

1986 marked the first year that more than 1 clinical paper on pancreas transplantation was presented—3 in all (29-31). In 1986, there also was one landmark experimental paper on pancreas preservation (32).

The first clinical paper was presented by Mikel Prieto of the Minnesota group, detailing their experimental and clinical experiences with urinary amylase monitoring for early diagnosis of rejection of bladder-drained pancreas transplants (29).

Observations in dogs and humans clearly showed that a decline in urinary amylase activity preceded an increase in blood sugar levels as a manifestation of rejection. Although urine amylase levels varied from day to day, endocrine dysfunction never preceded exocrine dysfunction [29}, and this was true in subsequent follow-up studies as well (*Surgery* 102:680, 1987). After adaptation of the bladder drainage technique, the results with solitary pancreas transplants from cadaver donors began to approach the success rate achieved with SPK transplants (*Surgery* 104:453, 1988).

That the advantages of bladder drainage outweigh the disadvantages is reflected by its frequent use. But there are several unique complications of this method, and papers on some of them have been on ASTS programs. The first was presented by Rino Munda of the University of Cincinnati group in 1986 (30). They had a few recipients whose urinary tract was irritated by the pancreas graft exocrine enzymes, including 1 with severe balanitis that resolved after conversion to enteric drainage (*Surgery* 102:99,1987). Munda showed that some patients with this problem had a urine capable of activating pancreas exocrine proenzymes (30). Later, several groups accumulated series of patients treated by conversion from bladder to enteric drainage (*Transplant Proc* 22:651, 1990; *Ann Surg* 216:668, 1992; *Surgery* 112:842,1992; *Transplant Proc* 25:1179, 199.)

The perturbations that occur with bladder drainage were further emphasized at the 1986 meeting in a paper presented by Dai Nghiem of the University of Iowa (31). Whereas Munda had focused on the local effects of the pancreatic enzymes, Nghiem emphasized the metabolic abnormalities, including metabolic acidosis. These abnormalities could occur secondary to bicarbonate wasting from lack of absorption of the large amount contained in the pancreas and duodenal graft secretions excreted directly into the urine. The Iowa group also showed that a denervated, ectopic pancreas graft would respond physiologically to stimulation by exogenously administered secretin, with increased enzyme and electrolyte output.

Nghiem should also be cited for describing a modification of a bladder drainage technique in which a segment of duodenum was anastomosed side-to-side to the recipient bladder (*Am J Surg* 153:405, 1987). The graft was prepared similarly to what had been described earlier for enteric drainage by Lillehei (*Acta Endocrinol* 83(S205):303, 1976) and Starzl (*Surg, Gynecol & Obstet* 154:265,1984). This technique was used for bladder drainage by other groups as well (*Surgery* 102:680, 1987), and was formally compared to the duodenal patch technique by the Wisconsin group in 1988 (42); they concluded that the duodenal segment technique was associated with a lower complication rate (42).

Perhaps the most important paper on the 1986 ASTS program was the one presented by Jan Wahlberg of the University of Wisconsin (32). They showed that the solution (UW) bearing the institution's name (also called Belzer's solution) could preserve canine pancreas grafts for up to 72 hours. UW solution is basically an intracellular electrolyte solution, with raffinose added as an osmotic agent and with chloride replaced by lactobionate (a large anion that does not cross cell membranes by passive diffusion, thus preventing exchange for intracellular phosphorus). These changes in

formulation (compared with other solutions) are probably responsible for UW's ability to preserve the liver much longer than is possible with Collins solution.

Plasma solutions had previously been used for pancreas preservation for up to 48 hours in dogs (*Surgery* 92:260,1982) and up to 24 hourse in humans by the Minnesota group (*Transplant Proc* 16:153, 1984), but had the disadvantage of being biological, entailing a risk of disease transmission. UW solution clearly obviated this risk, and appeared to be superior to the other solutions in the canine model (32). A paper presented by the Minnesota group at the 1989 ASTS meeting did not show any difference in clinical outcome for pancreas grafts stored in UW or plasma-based solutions for up to 30 hours (55). But the advantage of UW solution was considerable, not only in eliminating transmissible disease risk but in being made commercially available (*Transplantation* 45:673, 1988). It gained ascendancy over all other preservation solutions for intraabdominal organs (*Transplantation* 47:1097, 1989). The logistics of extrarenal organ transplantation have been greatly simplified by this advance. The impact of UW solution on kidney transplant logistics is less, since for more than a decade it had been possible to preserve kidneys for 48 hours or longer by either cold storage in Collins solution or by machine perfusion. There is no doubt, however, that UW solution was a huge advance for extrarenal organ transplantation. The Wahlberg paper testing its efficacy for storage of canine pancreas grafts is a landmark (31).

In 1987, ASTS president Robert Corry (from the University of Iowa) was one of the leaders in promoting expansion of pancreas transplantation in the 1980s (*Surg Gynecol & Obstet* 162:547,1986). He invited Walter Land, director of transplantation at the University of Munich and the 1987 president of the European Society of Transplantation, to give the plenary lecture on pancreatic transplantation in Europe (35). Land had been as active in Europe as Corry had been in the U.S. in advancing the field, and Munich was one of the European big three (the others were Stockholm and Lyon) in pancreas transplant volume. However, 1987 was also the year when the United Network for Organ Sharing (UNOS) Registry began to coordinate transplant activity in the U.S.; in the years to come, the number of pancreas transplants in Europe remained stationary, while expansion was rapid in the U.S. (Figure 1). Before October 1987, more than half of about 1,400 pancreas transplants reported to the registry had been done outside the U.S. In contrast, from October 1987 through December 1993, more than three-fourths of the 4,000 pancreas transplants reported to the registry were done in the U.S. (Figure 1). More than 88 institutions have done pancreas transplants in the U.S. since 1987, while in Europe the procedure is still done at only a few academic centers (*Clinical Transplants*—1993).

The 1987 ASTS meeting included 3 pancreas transplant papers: 2 experimental (36,39), and 1 clinical (38). George Abouna showed that unmodified commercial plasmanate could preserve canine pancreas grafts for up to 48 hours (36). But by this time the impetus to use the nonbiological UW solution clinically was well underway. Frank Thomas attempted to use urinary insulin levels as a method to diagnose pancreatic allograft rejection early in dogs (39), but was unable to show any advantage over urinary amylase, which remains the standard.

The clinical paper by J. Van der Vliet at the 1987 ASTS meeting was another in the

Minnesota series on the effect of pancreas transplantation on secondary complications, in this case on neuropathy (38). Basically, after successful pancreas transplants, the recipients had significant increases in motor nerve conduction velocities and evoked muscle action potentials at 1 or more years posttransplant. In later papers from the Minnesota group, improvements in autonomic as well as somatic nerve function were demonstrated as well (*NEJM* 322:1031, 1987; *Surgery* 104: 453, 1988; *Diabetes* 39:862, 1990).

Since 1987, there have been no fewer than 3 clinical pancreas transplant papers on each ASTS program. The 3 in 1988 were technically oriented. First, Ngheim reviewed the use of pediatric donors for SPK transplants in the University of Iowa series (41), and confirmed that results equivalent to those with adult donors could be obtained. Second, Anthony D'Alessandro presented a prospective study from the University of Wisconsin, comparing the duodenal (segment) bubble technique versus the duodenal patch technique for bladder drainage of whole pancreas transplants; they concluded that use of a duodenal segment was associated with the lowest complication rate (42). The segment technique had already been adopted by most groups, as with enteric-drained grafts (*Surg Gynecol & Obstet* 159:265,1984; *Surgery* 102:680, 1987). Third, Christopher Marsh of the Mayo Clinic showed that bladder-drained pancreases could be easily accessed transcystoscopically for graft biopsies, to differentiate between rejection and other causes of dysfunction (43). The transcystoscopic biopsy technique was adopted by others; 4 years later, a large series correlating pancreas graft histology with clinical parameters was presented by the University of Minnesota group (72). After the Mayo Clinic paper, Richard Allen of Australia developed a percutaneous technique for pancreas graft biopsies (*Transplantation* 51:1213, 1991). The techniques complement each other, since the transcystoscopic approach can always be used if the percutaneous technique fails. Both represent important advances in pancreas transplant recipient care.

1989 was the first of 5 consecutive years in which 4 clinical pancreas transplant papers were on the ASTS program (Table I). Two from the Mayo Clinic (49,51) addressed laboratory parameters that could be used to differentiate causes of dysfunction in bladder-drained pancreas grafts. James Perkins showed data suggesting that Interleukin-2 receptor levels increased before other manifestations of rejection (49). Steven Munn found that hypoamylasuria usually signaled a rejection episode, but cytomegalovirus infection or pancreatitis could also be responsible (51).

The other 1989 clinical papers addressed the technical and logistic issues of pancreas procurement and preservation (54,55). Ngheim demonstrated that, in procurement of the pancreas and liver, excessive intravascular flushing to cool the organs could injure the pancreas (54). Philippe Morel of the University of Minnesota analyzed the effect of preservation time and solution on the function of bladder-drained pancreas grafts (55). He found that preservation for up to 30 hours was successful with either UW solution or silica gel fractionated (SGF) plasma. Only a few grafts had been preserved for >30 hours in either solution, the longest in SGF (55).

There was 1 abstract on pancreas transplantation in animals on the ASTS program in 1989 (48), and 4 in 1990 (59,62,64), the last year experimental papers on the

topic were presented. The one in 1989 was by Corry's group at the University of Iowa. They showed that inclusion of the donor spleen with a pancreas allograft in certain strains of transfused, cyclosporine-treated rats prolonged functional survival (48). This phenomenon in rats had been described earlier by Bitter-Suerman (*Transplantation* 26:28, 1978), but found to be strain-specific by Squifflet (*Transplantation* 34:302, 1983).

The 1990 experimental papers on pancreas transplantation included one by James Perkins of the Mayo Clinic on the use of somatostatin to decrease the incidence of graft pancreatitis in pigs (59); one by Tanai Zheng of the V.A. Wadsworth in Los Angeles on modifying UW solution with polyetheleneglycol to prolong pancreas preservation in rats (63); and one by Rainer Gruessner of the University of Minnesota asking whether single versus combined pancreas and renal allografts differed in their susceptibility to rejection in pigs (64). The Minnesota paper confirmed the clinical impression that pancreas grafts transplanted simultaneously with a kidney had delayed or less severe rejection than those transplanted alone (64).

The 4 clinical pancreas transplant abstracts on the 1990 ASTS program were diverse (61,64,65,69). Charles Rosen described the morbidity associated with pancreas transplantation at the Mayo Clinic (61). Hans Sollinger gave lessons from 100 consecutive simultaneous kidney-pancreas transplants with bladder drainage at Wisconsin (65). Morel of Minnesota, gave the long-term results of metabolic function in pancreas transplant recipients after reversal of rejection episodes, and found that normal endocrine function was usually retained (66). David Dunn presented the Minnesota group's experience with combined procurement of pancreas and liver grafts (a routine procedure by this group since the early 1980s): it did not affect pancreas or liver transplant outcome (19). Dunn also found no difference in outcome according to pancreas reconstruction techniques or to whether the procurement was done by the Minnesota team or by another team who then sent the organs to Minnesota(69). This and other papers made it readily apparent that all viable organs should always be procured from all cadaver donors (*Surg Gynecol & Obstet* 168:254,1989; *Surgery* 105:718,1989).

In 1990, the annual joint ASTS/ASTP Scientific Symposium (sponsored by Upjohn) had as its topic "Pancreas Transplantation as a Treatment of Type I Diabetes Mellitus." By that time, the consensus was that pancreas as well as kidney transplants should be offered to most uremic diabetic patients, to make them insulin-independent and normoglycemic as well as dialysis-free. More controversial was when to do a pancreas transplant alone. It was noted that the expansion of pancreas transplantation indications would be linked to advances in immunosuppression.

At the 1991 ASTS meeting, 3 of the 4 clinical pancreas transplant papers focused on a topic that had been of continuing interest—how to assess the meaning of graft dysfunction and how to diagnose rejection episodes early. William Marks presented the Yale experience with measurement of serum anodal trypsinogen as a possible marker for rejection in pancreas allografts (70). An increase was observed in association with a clinical diagnosis of rejection, but the assay is not available in most hospitals. Thus, urine amylase continues to be the standard for solitary bladder-drained

pancreas transplants, and serum creatinine and urine amylase for combined kidney and bladder-drained pancreas transplants.

Robert Stratta presented the Omaha experience with cellular, cytokine, and cytologic monitoring of urine to detect rejection after combined pancreas and kidney transplants (73). These tests are not generally available, and have yet to replace either serum creatinine for monitoring in combined kidney-pancreas transplants or urine amylase in solitary pancreas transplants, especially if the recipients are at home in locations distant to the transplant center (73).

Kenneth Brayman presented the Minnesota experience with transcystoscopic techniques to evaluate pancreas graft biopsies with exocrine dysfunction (72). He found that when a decline in urine amylase occurred, rejection was confirmed in about 50% of the cases. Not treating for rejection based on a decline in urinary amylase would risk graft loss, particularly for solitary pancreas transplants.

As in the previous year, one 1991 paper emphasized the complications that can occur after pancreas transplants (71). The Ohio State group gave the incidence of infections in their series of SPK transplants, and found it higher than after kidney transplants alone in diabetic recipients.

The Ohio State paper on infections was followed by a similar paper from the University of Iowa the next year, 1992 (81). But as in 1991, the themes of the other 1992 papers were on the benefits of pancreas transplants (79,80,85). Mark Stegall of the Wisconsin group presented an analysis indicating that graft survival rates of cadaver kidneys transplanted with a pancreas were as high as for LRD kidney transplants alone in diabetic recipients (79). No other center has reported cadaver kidney graft survival rates to be as high as with LRD donors long-term, but of course, this is everyone's goal, and Wisconsin seems to have achieved it. Robert Stratta analyzed the benefits and risks of combined pancreas-kidney versus kidney transplants alone in diabetic patients, and concluded that establishing insulin independence and normoglycemia improved the quality of life sufficiently to justify the morbidity of a pancreas transplant (low in the Omaha series) (85). Finally, a group from the University of California, Davis, presented preliminary data showing that diabetic recipients of simultaneous pancreas-kidney transplants experienced reversal of microangiopathy (80).

The beneficial effect of pancreas transplants on secondary complications was further emphasized at the 1993 ASTS. Osama Gaber of Memphis showed that autonomic neuropathy and gastroparesis was improved in diabetic recipients of pancreas-kidney transplants (87). The favorable impact of insulin independence on quality of life was also emphasized by Gaber.

How to diagnose pancreas allograft rejection episodes early was a recurring question in papers presented over the years. At the 1993 ASTS meeting, R. Ploeg of Wisconsin reported that a rise in serum anodal trypsinogen (SAT) levels usually occurred concomitant with a rise in serum creatinine levels during rejection episodes of SPK transplants (92). The Wisconsin group hypothesized that SAT would be a useful marker in solitary pancreas transplants, where creatinine cannot be used. The Omaha group presented an abstract at the 1993 meeting on pancreas grafts undergoing chronic rejection; the histology of the results was similar to that seen in other organ

transplants (88). Interestingly, good endocrine function can continue in pancreas grafts undergoing chronic rejection; islets appear capable of surviving chronic rejection if the ischemia induced is not too severe (*Transplant Proc* 26:in press, 1994).

Of the 31 papers on clinical pancreas transplants presented during 19 years of ASTS meetings, the last was from the University of Minnesota (93). Rainer Gruessner defined the probability of success or failure of pancreas grafts according to recipient risk factors in a multivariate analysis of the entire Minnesota series of bladder-drained pancreas grafts. Age and cardiac disease were the only significant risk factors. The highest probability of long-term graft function occurred in young patients without cardiac disease who had SPK transplants. The Minnesota series included a large number of non-uremic recipients of pancreas transplants alone, and a high-risk subgroup could not be identified in this category (93). Gruessner emphasized that the future of pancreas transplants lies in earlier application to prevent the occurrence of renal failure and other secondary complications.

In the 20th year of ASTS, most centers continue to limit their application of pancreas transplants to diabetic patients with renal failure who also have a kidney graft. As less toxic immunosuppression becomes available, it is anticipated that more pancreas transplants alone will be done (immunosuppression and new antirejection strategies are reviewed elsewhere in this monograph).

During the first 19 meetings of ASTS, virtually every significant advance in pancreas transplantation was presented. As with all progress, pancreas transplants got off the ground because of persistence in the face of initially high failure rates. Now it is routine, and all pancreases from all donors should be used for transplantation, either as an intact organ or as a free islet graft. Whether islet transplants will supersede pancreas transplants is still an open question, but if not, it will not be for lack of effort.

Islet Transplantation for Diabetes

Four islet transplant abstracts were presented at the first 3 ASTS meetings (3,6) before 1 on pancreas transplants appeared (7). Back in 1976, islet transplantation was felt to be just around the corner (*Med World News* Jan. 13,1975). But clinical success with islets was slow (*Diabetes Forecast*, Jan. 1984). Pancreas transplantation never fell by the wayside. Twenty years later, it is a common and effective transplant procedure, while islet transplantation is just beginning to have some clinical success (*Cell Transplant* 2:229, 1993). Nevertheless, the fact that there is any success at all is a tribute to the enormous effort that has gone into islet transplantation research over the last two decades, as reflected by the papers presented to ASTS.

The islet transplant papers will not be summarized as completely as the kidney and pancreas transplant papers in the preceding sections, since Camillo Ricordi has included many of the details in his chapter on Cell Transplants. Rather, major contributions will be highlighted.

As with the pancreas, transplantation (both clinical and experimental) of islets preceded the founding ASTS. Most of the islet pioneers have become ASTS members, but not all, since nonsurgeons have also been active in the field.

The history of islet transplantation begins in the 1960s. The year before the first clinical pancreas transplant was done, Moskelewski, a Polish anatomist, used collagenase to disperse animal pancreases. He was able to hand-pick islets through a dissecting microscope (*General Comprehensive Endocrinology* 5:342, 1965). Purification on a large scale was made possible a few years later when Arnold Lindall of the Department of Anatomy at the University of Minnesota used discontinuous Ficoll density gradients to separate islets (lighter) from exocrine (heavier) tissue (*Endocrinology* 85:218,1969). Shortly thereafter, one of Lindall's graduate students, Raouf Younoszai, transplanted isolated allogenic islets into rats with alloxan diabetes, achieved transient amelioration, and presented the results at the annual meeting of the American Diabetes Association in 1970 (*Diabetes* 19(Suppl.1):406, 1970).

Younoszai's work was the first indication that islets could function in an ectopic site and cure diabetes. Two years later, Walter Ballinger and Paul Lacy of Washington University, St. Louis, ameliorated diabetes long-term with isogenic islet transplants in rats (*Surgery* 72:175,1972). Other groups around the world were, virtually simultaneously, initiating islet transplant research. They published their initial results before the formation of ASTS. The most active groups were at the University of Minnesota (*J Surg Res* 16:102, 1974; *Diabetes* 23:748, 1974); the University of Pennsylvania Hospital, Philadelphia (*J Surg Res* 16:575, 1974; *Surgery* 74:91, 1973); Columbia University, New York (*Transplantation* 19:42, 1975); and Washington University, St. Louis (*Transplantation* 16:686, 1973; *In Vitro* 9:364, 1974; *Surgery* 77:100, 1975).

The third and fourth papers presented at the first ASTS meeting were on islet transplants, one from the Minnesota group (3) and one from the Columbia group (4). The Minnesota paper, presented by Ernest Lampe, described the use of unpurified dispersed pancreatic islet tissue in totally pancreatectomized pigs. It demonstrated intraperitoneal engraftment and the ability to sustain life after total pancreatectomy. At that time, most groups believed it was essential to purify islet tissue. The debate over whether purification should or should not be done continues to this day: each approach has advantages, but at least it is now clear that purification is not essential (*Amer J Surg* 166:538,1993).

Collin Weber of Columbia presented islet papers at each of the first three ASTS meetings (4-6). Except for the one from Minnesota in 1975 (3), he was the only member with islet abstracts on the program during this early period. After 1977, no islet paper appeared on the ASTS program until 1981. Weber's papers dealt with different subjects (4-6). In 1975, he compared the survival of islet isografts, allografts, and xenografts in rats. Isografts functioned indefinitely, allografts at best only transiently, and very discordant xenografts virtually not at all (4). The extreme susceptibility of islet allografts to rejection in rats was described by the Pennsylvania group (*J Surg Res* 16:575, 1974) and many others (see review in *Diabetes* 25:785,1976). In 1976 Weber presented a paper on in vitro function of isolated human islets, confirming viability of the preparation (also shown by others, *J Surg Res* 16:102,1974). No transplants were done of human islets isolated by the Columbia group, but other centers were clinically active at this time (*Transplant Proc* 9:233,1977). In 1977 Weber confirmed the obser-

vations by the Minnesota group in rats (*Diabetes* 23:748,1974) that successful islet transplants could prevent the development of diabetic lesions in kidneys (6).

From 1977 to 1981, no islet abstracts were presented at the ASTS meetings. But many groups published results of islet transplant experiments and presented at other meetings, especially the International Congresses of the Transplantation Society (see review in *Diabetalogia* 20:161,1981). Clinical trials were also conducted during this period. Intraportal human islet autografts after total pancreatectomy were successful in establishing insulin independence (*Surg Clin North Amer* 58:365,1978), but human islet allografts were not (*Diabetes* 29 (Suppl.1):31,1980). Naturally, interest in pancreas transplantation was renewed (*Diabetologia* 20:435,1981). However, even though pancreas transplant outcome continuously improved during the 1980s, there was an irreducible morbidity, and islet transplants never lost their allure. Thus, papers on experimental islet transplantation were presented at every ASTS meeting during the remainder of the decade (16,20,21,23,25,28,33,34,37,40,44,46). In the 1990s clinical islet transplant papers began to appear (67,75,76,82), along with an increasing number of papers on experimental islet transplantation (47,50,52,53,56-58,60,62, 68,74,77,78,83,84,89-91,94).

During the late 1970s and early 1980s, several advances were made in experimental islet transplantation that were not necessarily presented to ASTS: diabetes could be completely ameliorated in dogs with unpurified islet tissue transplanted in the spleen (*Transplantation* 101:265,1976; *Surgery* 82:74,1977) and with purified islets in the portal vein (*Diabetes* 30:455,1981); islets could be cryopreserved (*Cryobiology* 14:116, 1977); cultured islets were less susceptible to rejection in rodents (*Science* 204:312,1979); and rejection was prevented in mouse islets depleted of passenger leukocytes by antibodies against the MHC class II antigens (not expressed in parenchymal cells) (*Proc Nat Acad Sci* 78:515,1981).

In spite of the spectacular achievements with islet allografts in rodents, preventing of rejection of islet allografts in large animals continued to be difficult (*Diabetalogia* 20:161,1981). The rodent work was not generalizable. Indeed, the culture or passenger leukocyte depletion effects (*Transplant Proc* 15:1366,1983) depended on the animal strain and transplant (*J Immunol* 137:1482,1986).

Nevertheless, the dominate theme of islet papers presented in the 1980s was on manipulations to reduce islet immunogenicity (20,21,25,47,56,58,60,89,94). Papers on islet allografts in large animal models were much less frequent, probably because it was so difficult to get positive results (15,16,23,60,62,84). In addition, ASTS members continued to present and publish very important islet transplant work outside of ASTS (see reviews in *Transplantation* 43:321,1987 and *Diabetes Reviews* 1:76,1993). One of the most notable recent examples is the discovery by the Pennsylvania group that intrathymic injection of allogenic islets could induce donor-specific tolerance in adult rodents (*Science* 249:1248,1990).

The difficulties with preventing islet allograft rejection by conventional or nonspecific immunosuppression are epitomized in the first islet paper (16) to be published after presentation at an ASTS meeting (1982) since Weber's mid-1970s trilogy (4-6): Squifflet of Minnesota showed that cyclosporine and azathioprine in combina-

tion was more effective than monotherapy in preventing rejection in 3 of 4 (dog kidney; rat heart, pancreas, and islet) experimental allograft models. But the model in which rejection was not delayed was with islets (16).

The following year, 1983, Steve Bartlett of the Pennsylvania group found that even culturing islets would not necessarily prevent rejection (20). Only when the recipient strain differed at the MHC was culture effective. When there were only minor antigen differences, cultured and uncultured islets had similar survival. This is consistent with the hypothesis that direct presentation of alloantigens by passenger leukocytes was the predominant stimulus of the rejection response. At later meetings, evidence that indirect presentation of alloantigens on islets was sufficient to initiate a rejection response was presented by Peter Stock of Minnesota (68)). But at that time the passenger leukocyte hypothesis was nearly dogma (*Ann Rev Immunol* 1:143,1983). However, even if rejection of islet allografts was prevented, tolerance was not established, according to a report by the Minnesota group in 1983 (21): skin grafts could be rejected by mice bearing nonrejected islet allografts, and rejection could be induced by injection of donor strain spleen cells (21).

The emphasis on altering islet immunogenicity continued in 1984. The Columbia group had previously introduced the concept of ultraviolet irradiation of islets. Henry Lau of this group showed that pretreatment could facilitate graft acceptance in rodents (25). A later presentation (1990) by Mark Stegall of the same group showed that immunogenicity could be altered by gamma irradiation as well (47).

In 1985, questions on autoimmunity to beta cells and its implications for islet transplants were addressed by the Pennsylvania group (28). The BB rat model of autoimmune diabetes became available around 1980 (*Diabetalogia* 22:225, 1982). The Pennsylvania group led the way in exploiting it for transplant experiments (*Science* 213:1390,1981). They showed that perturbations of the immune system, rather than abnormalities of the beta cell per se, led to selective beta cell destruction (28).

A new approach to rejection was presented by Gotoh et al. of Deaconess Hospital, Boston, in 1986 (34). They transplanted islets from multiple donor strains. The immunogenicity of a small number of islets was minimal. By using multiple different strains, the total islet mass was sufficient to correct diabetes without rejection (34). (Unfortunately, when this approach was tried in dogs, it was not successful, *Transplantation* 45:1036,1988). In 1987, the Boston group found that specific unresponsiveness to pancreatic islet allografts could be induced in mice by antilymphocyte serum (37). Again, whether this approach would work in large animal models was doubtful. Indeed, when tested in dogs by Dixon Kaufman of Minnesota in 1990, ALG could not induce permanent survival of islet allografts (62). The Boston group presented again in 1988 (46), expanding on their 1986 observations. In sequential transplants, small numbers of allogenic islets from multiple donors were able to ameliorate diabetes long-term without the need for immunosuppression (46).

The 1988 meeting also marked the first presentation on the critical problem of cold storage preservation of the pancreas before islet isolation (44). Stephen Munn, of University of Minnesota showed that, when collagenase was injected into the pancreatic duct before storage, a sufficient number of viable islets to reverse diabetes post-

transplant could be obtained. But when the collagenase digestion process was started after storage, the islets were inadequate.

Immunoisolation of allogenic tissue is an old concept (*Science* 20:908,1980). Its application to islets was presented to ASTS in 1989 by Collin Weber of Columbia (50). Other groups had successfully prevented rejection of islet allografts and of rat islet xenografts by encapsulation in mice with chemically induced diabetes. But in NOD mice with autoimmune diabetes, destruction still occurred (50).

On an entirely different theme, the 1989 meeting included a presentation from Patrick Soon-Shiong's group in Los Angeles on steps to improve the efficiency of islet purification. They used magnetic microspheres coated with anti-acinar cell monoclonal antibodies (52). A variety of methods to improve the islet purification process have been tried over the years, emphasizing the inherent difficulty of the process.

The 1990 meeting continued with the potpourri of islet themes, including a continuation of the immunoisolation approach (60) broached in 1989 (50). Takashi Maki of the Deaconess group in Boston reported on their success with ameliorating diabetes in pancreatectomized dogs. They implanted an islet-containing device in the vascular system. In 1992, Maki presented again, this time reporting success for more than 1 year (84).

The 1990 meeting also included fresh looks at the role of passenger leukocytes (56,68) and at the expression of MHC antigens on allogenic islets (58). The University of Chicago group showed that depletion of passenger leukocytes had a stronger effect on promoting survival of islets than of immediately vascularized pancreas grafts (56). Conversely, Peter Stock of Minnesota showed that, at least in some strains of mice, the indirect pathway of antigen presentation could generate an allo-immune response against pancreatic islets (68). On a more practical note, Dixon Kaufman of Minnesota showed a transient beneficial effect of antilymphocyte globulin on islet allograft survival in dogs, but he also found that prednisone was profoundly detrimental to islet function (62).

The most notable islet paper at the 1990 meeting was by David Scharp ofWashington University, St. Louis. For the first time, the results of clinical islet allotransplantationwere presented to ASTS (67). The St. Louis group had previously published a brief report on achievement of transient insulin independence in a Type I diabetic recipient of a multiple donor islet allograft (*Diabetes* 39:515,1990). This and other cases were included in a review of the results of their first 9 intraportal islet allografts. Most had some evidence of function for weeks or months, but long-term insulin independence was not achieved, presumably because of rejection (67).

Clinical islet transplant presentations continued in 1991 (75,76). Camillo Ricordi of the Pittsburgh group, described their experience with 22 islet allografts—some in patients with Type I diabetes, others in patients with surgical diabetes induced by total pancreatectomy and hepatectomy for malignancy (75). The latter patients received islet allografts in conjunction with a liver transplant (*Science* 336:402,1990), and some of them achieved insulin-independence. However, long-term islet allograft function is also possible in patients with Type I diabetes, as shown by the Edmonton group (76). They described insulin independence for more than 1 year in a patient who received

islet allografts from multiple donors after a kidney transplant (76). The need for multiple donors—demonstrated by the St. Louis, Pittsburgh, and Edmonton group—may be due to their use of purified islets, an approach that does not allow a sufficient number to be prepared from a single donor. Without purification, a single donor is sufficient, as shown by the Minnesota group in 2 recipients of simultaneous islet-kidney transplants (*Lancet* 241:19, 1993).

The 1991 meeting featured 2 other important islet papers, both experimental (77,78). Dixon Kaufman of Minnesota showed that 15-deoxyspergualin could prevent primary nonfunction of islet allografts in mice (77). Kaufman had previously described the phenomenon of primary nonfunction of islet allografts, defined as failure to achieve even transient normoglycemia in the recipient with an islet mass that would be sufficient to do so as an isograft (*J Exp Med* 172:291,1990). This was hypothesized to be the result of cytokines toxic to beta cells generated during the early phases of the alloimmune response (over and above those generated by the trauma of the transplant itself). In a 1993 presentation by Brian Stevens of Minnesota, cytokine-induced nitric oxide production was shown to be the dominant mechanism of primary nonfunction (90). Interestingly, 15-deoxyspergualin was used in the subsequent successful transplantation of human islet allografts by the Minnesota group (*Lancet* 341:19, 1993).

1991 also continued the theme of immunoisolation of islet allografts (78). Patrick Soon-Shiong of Los Angeles reported that spontaneous diabetes in dogs could be ameliorated long-term by intraperitoneal microencapsulated allogenic islets (78). It remains unknown whether the encapsulation process will be equally or consistently effective in preventing rejection of islet allografts in dogs with pancreatectomy-induced diabetes. But undoubtedly the immunoisolation approach will continue to be the focus of experiments because of the attractiveness of eliminating immunosuppression.

In 1992 the Boston Deaconess Hospital group updated their results with a vascularized hybrid artificial endocrine pancreas device (84). They reported preliminary results using xenogenic islets and achieved transient function of pig islets (84).

The importance of thwarting the rejection process when islet allografts are retransplanted was reemphasized by the Pittsburgh group at the 1992 ASTS meeting (82). Even when purified, islets are immunogenic: the frequency of kidney rejection in diabetic patients undergoing simultaneous kidney-islet cell transplants was higher than in kidney transplant alone recipients (82).

The frustration inherent in the islet transplant field is apparent from a glance at the 1993 ASTS program. After 3 consecutive years of clinical islet papers, none were presented, and the emphasis was on experimental phenomena. The relevance of some of the xenograft models was addressed by Brayman of Minnesota (86). Most islet xenograft experiments have been in mice, a species with a low tendency to reject. In contrast, Brayman found that in rats, function with canine islets was nearly impossible (86). The disparity between mice and rats remains to be explained. Mice may not be discordant with the species (dogs and humans) used as donors, while rats may be

highly discordant. However, rats have also been found to be excessive nitric oxide producers (90).

New approaches to prevent rejection of islet allografts are continuously being tried. Some were presented at the 1993 meeting. Stock of UCSF showed that modulation of MHC class I antigens could prolong islet allograft survival in mice (94). Emphasis seems to be shifting from the passenger leukocyte depletion approach, particularly with the recent finding that the persistence of donor leukocytes in the host is associated with long-term graft survival (*Lancet* 340:617,1992).

The islet story is one of continual promise in the face of continuing frustration. Clinical success has been rare, at least in the sense of establishing insulin independence in diabetic recipients. But the potential to eliminate surgical complications and immunosuppression is a dream that has kept ASTS members, and others, in the field for a full two decades (*Diabetes Reviews* 1:76,1993). ASTS is still young. Hopefully, consistent success with clinical islet transplantation will be achieved before old age sets in.

Summary

In the first decade of ASTS, kidney transplantation for diabetic nephropathy became routine. By the end of the second decade, pancreas transplants were routine as well. Nearly all the advances that allowed successful kidney and pancreas transplants were presented at one ASTS meeting or another. Clinical islet transplants have also succeeded in a few patients cared for by ASTS members, but consistent success remains elusive. A legitimate questions is whether routine prevention of diabetes will be achieved (*Diabetes Rev* 1:15,1993) before consistent cure with islets is routine. Pancreas transplantation will undoubtedly be employed with increasing frequency over the next decade, Yet it is difficult to see how surgical complication rates can be reduced any further. My guess is that islet transplants will eventually supersede pancreas transplants and that ASTS members will lead the way.

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Heart and Heart-Lung

BRUCE REITZ

At the time ASTS was established in 1974, transplantation of the heart and the heart-lung block was only rarely attempted. Clinical heart transplantation had been initiated in December 1967 by Barnard in South Africa, and Kantrowitz and Shumway soon thereafter in the U.S. However, after the first two years of worldwide interest and enthusiasm, heart transplantation had essentially disappeared. The exceptions were Stanford University Medical Center in California and the Medical College of Virginia in Richmond. Thus, it was not unexpected that only a few heart transplant surgeons became ASTS members during the 1970s. These surgeons were Norman E. Shumway (1974), Donald R. Kahn (1974), Edward B. Stinson (1975), Eugene Dong (1976), and Keith Reemtsma (1976).

With improving clinical results demonstrated by the Stanford and Medical College of Virginia programs, additional centers began heart transplant programs in the late 1970s, and additional heart transplant surgeons Baumgartner, Jamieson, Losman, and Reitz joined ASTS during the early 1980s. With the advent of cyclosporine-based immunosuppression—introduced clinically in 1981 at Stanford and the University of Pittsburgh and then widely after FDA approval in 1983—a number of other heart transplant surgeons were admitted to ASTS during the late 1980s and early 1990s. By 1993, a total of 41 surgeons with primary interest in heart transplantation had been admitted for membership out of a total of 584, or 7% of the membership at that time. The growing importance of heart transplantation was further emphasized by the Ad Hoc Committee on Heart Transplantation, formed in 1982 as an advisor to the council. This committee became permanent in 1984, and changed its name to the Committee on Thoracic Organ Transplantation in 1991. The papers relating to heart and heart-lung transplantation that have been presented at annual meetings reflect the significant developments in this field during the past 20 years.

It is most fitting that Norman E. Shumway was among the founding members of ASTS, given his major contributions to the attainment of successful heart transplantation. Together with Richard Lower, later chief of Cardiac Surgery at the Medical College of Virginia, Shumway established a workable model for performing heart trans-

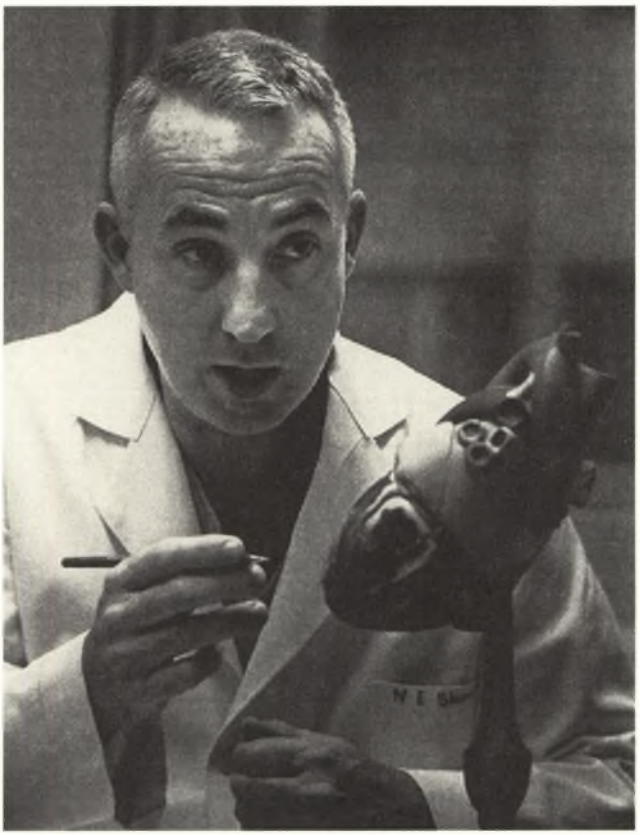

Figure 1.
Norman Shumway

plantation in dogs. A report of this work was presented at the Surgical Forum of the American College of Surgeons in 1959. Later, the group of surgeons working in Shumway's department at Stanford made a number of contributions to experimental heart transplantation throughout the 1960s, culminating in successful clinical application. The Stanford group has been the longest continually active heart transplantation program in the world. Perhaps not unexpectedly, successful transplantation of the heart and lung together was first accomplished by this group in 1981, with the availability of cyclosporine immunosuppression. A number of ASTS members have come from the group of surgeons trained by Shumway at Stanford. A picture of Shumway as he appeared in 1968 at the time of the first adult heart transplant in the U.S. is shown in Figure 1.

The first ASTS paper relating to heart transplantation appropriately came from the Stanford group and concerned control of graft arteriosclerosis in human heart transplant recipients. The paper was presented by Griepp, Stinson, Reitz, Copeland, Oyer, Bieber, and Shumway. It demonstrated that coronary artery disease developing in the transplanted heart was related to a mismatch of the HLA-A2 antigen and the increasing age of the donor. This paper, presented in 1976, emphasized the growing awareness that chronic rejection might limit the long-term success of heart transplants.

The next ASTS paper relevant to heart transplantation did not appear until 1980. A clinical study, again from the Stanford group, was reported by Watson, Reitz, Oyer, Stinson, and Shumway. It described the results of sequential orthotopic heart transplantation in humans. This was the largest series of retransplantations of the heart, primarily for graft atherosclerosis, but also for early acute failure of the graft due to pulmonary hypertension or inadequate preservation. A second experimental paper at that meeting by Corry and Kelley reported prolongation, achieved by transfusion of third-party blood, of heart transplant survival in a mouse model. This paper, extending the observations about pretransplant transfusion, was the sole experimental study on heart transplantation before the cyclosporine era.

The ASTS meeting in 1981 included work from Stanford on survival of primates, after orthotopic cardiac transplantation, treated with total lymphoid irradiation and chemical immunosuppression. This paper, by Pennock et al., made the important observation that total lymphoid irradiation for chronic immunosuppression of the heart, particularly when combined with antithymocyte globulin, could be quite effective. This extended their earlier observations that heart transplants in rats could be greatly prolonged, although the tolerance shown in the rat model could not be applied to primates.

The next paper, from Stanford on heart and lung transplantation, was presented in 1983 by Jamieson. It outlined the results of heart-lung transplants in the first dozen patients at Stanford. The Stanford series had started in March 1981, using cyclosporine and resulting in survival and rehabilitation of a 45-year-old woman with primary pulmonary hypertension. Later, patients with Eisenmenger's syndrome also underwent successful transplants.

The next year, a second report from Stanford, presented by McGregor, concerned late studies of ventilation, perfusion, and pulmonary alveolar capillary function in primates after heart-lung transplantation. The good function of the transplanted heart and lung several years posttransplant in these primates preceded the same observations in human patients.

In 1985, for the first time, two papers on clinical cardiac transplantation appeared on the same ASTS program. The first, by Brasile et al. was on the identification of antibody to vascular endothelial cell antigens (VEC) in patients undergoing cardiac transplantation. The second, presented by Zeevi, from Pittsburgh, characterized the lymphocytes grown from heart biopsies to monitor for rejection. By now, rapid growth in the number of heart transplant centers was occurring throughout the U.S. and abroad. This meeting also featured the first heart transplant surgeon moderator for a session at the annual meeting, with Reitz chairing the session on immunosuppression.

Reflecting the greatly increased cardiac transplant activity, the first session in 1986 was dedicated to the topic of cardiac transplantation and immunosuppression. Moderated by Reitz and Light, this session featured five papers on clinical cardiac transplantation. Frazier et al. from the Texas Heart Institute showed successful cardiac transplantation in patients over age 55. Zeevi et al. from Pittsburgh analyzed the lymphoid cells from bronchoalveolar lavage obtained from heart-lung recipients.

In 1987, four additional papers on clinical cardiac transplantation were presented. Melvin et al. from Cincinnati demonstrated success with less than optimal cardiac donors, at least as defined at that time. Bolman et al. from Washington University presented an important analysis of the changing face of cardiac transplantation, emphasizing the increasing severity of illness of candidates. The effectiveness of triple-drug therapy for cardiac transplantation was demonstrated by the important paper of Ring et al. from Minnesota. Before that time, double-therapy (either cyclosporine-prednisone or cyclosporine-azathioprine) was considered appropriate. Triple-drug immunosuppression allowed lower levels of cyclosporine with less renal toxicity.

In 1988, papers relevant to cardiac transplantation were limited. An experimental study of heterotopic heart transplantation by Stepkowski et al. from the University of Texas showed that local delivery of continuous low-dose cyclosporine could be effective. In another experimental and clinical study, Baumgartner et al. from Johns Hopkins showed that cardiopulmonary bypass with profound hyperthermia, compared with other multiorgan procurement methods, led to very satisfactory function of the heart and lung; total body cooling by cardiopulmonary bypass could perhaps facilitate and improve preservation of all of the solid organs.

The 1989 ASTS meeting had an expanded program. A special scientific session reflected renewed interest in accelerated rejection in xenografts. Another session on hearts and perfusion, moderated by Baldwin, demonstrated the great interest in heart preservation at that time. Storage of the heart for up to 24 hours with a simplified University of Wisconsin (UW) solution containing polyethylene glycol was described by Wicomb et al. from. Presbyterian Medical Center in San Francisco. Additional improvement in transplanted heart function after treating both donor and recipient with triiodothyronine was described by Novitzky et al. from Baptist Medical Center in Oklahoma City. An experimental study in rats by Aziz from Minnesota showed less coronary arteriosclerosis when PGE_1 was used in combination with Cyclosporin A.

By 1990, the next generation of immunosuppressive molecules was being reported in patients undergoing thoracic organ transplantation. Armitage et al. from Pittsburgh described their experience with heart and heart-lung transplantation using FK506. A total of 8 papers were presented in the session on heart-lung transplantation, a new record for excellent manuscripts involved with this aspect of transplantation. Among the papers presented was a randomized prospective comparison, by Deeb et al. from Michigan, of Minnesota ALG versus OKT_3 for rescue therapy of acute cardiac rejection. An interesting paper by Letsou et al. from Yale discussed the predictors of survival in patients with end-stage cystic fibrosis awaiting heart-lung transplantation. Keenan et al. from Pittsburgh compared pulmonary rejection patterns among heart-lung and double-lung transplant recipients. The greatly increased number and quality of manuscripts received for consideration reflected the explosion of workers involved with this area of transplantation.

The heart-lung scientific session in 1991 featured two studies of pulmonary vasoconstriction after heart-lung preservation and after lung transplantation by Kontos from the University of Alabama and Wagner from the University of California at San Diego. Another lung preservation study, by Bresticker et al. from Northwestern Uni-

versity, showed the remarkable ability of UW solution to extend cold ischemic time. Two other papers demonstrated that mild diffuse acute rejection, when unaccompanied by functional changes, might not require treatment. This concept was introduced by Cohnert et al. from the Berlin Heart Center. An important plenary session, intended to enhance procurement of all donor organs, examined the suitability of heart donors for lung donation; the conclusion was that this resource was greatly underused and should be expanded. This work was by Egan from the University of North Carolina.

The heart-lung scientific session in 1992 featured 8 papers. Cooper described the use of DHPG for successful prophylaxis of cytomegalovirus (CMV) infection in heart transplant recipients. The diminished efficacy of OKT3 in treating steroid-resistant heart rejection occurring more than 90 days posttransplant was demonstrated by Redmond et al. from Johns Hopkins. Leventhal from Minnesota presented a study of xenotransplantation in nonhuman primates, reflecting continued interest in this topic as the donor supply became the limiting factor in thoracic organ transplantation. This had been apparent since 1989, with no significant improvement in the number of donors available despite growing lists of waiting patients.

The heart-lung transplant session in 1993 had the most extensive number of presentations in this area of any meeting to date. A total of 12 papers regarding heart transplantation were discussed. The use of heterotopic heart transplants as a biologic left ventricular assist device was described by Kanter et al. from Emory. The application of heart transplantation in patients over age 65 was reported by Scheinin at the Texas Heart Institute and Baylor College of Medicine in Houston. The important topic of long-term results in patients transplanted after mechanical bridge devices was presented by Koerner et al. from the University of Bochum, Bad Oeynhausen, Germany. Several papers again discussed heart preservation, with excellent clinical results presented by Aziz et al. from the University of Washington using the UW solution. Finally, discordant cardiac xenograft survival in nonhuman primates was extended by the synergistic effect of combined antibody and complement depletion, described by Sakiyalak et al. from Minnesota.

The development of heart and heart-lung transplantation has been greatly facilitated in recent years by a greater role for these specialties within ASTS. The improved immunosuppression of the 1980s has resulted in about 2,300 heart transplants and about 50 to 60 heart-lung transplants in the U.S. each year. Although rarely represented in the early years of ASTS, the developments that led to this remarkable expansion of transplant activity have been chronicled through recent meetings. It is hoped that the many ASTS members whose primary interest is thoracic organ transplantation will also strongly contribute to further advancements in clinical transplantation in general.

Lung

R. MORTON BOLMAN III

Thoracic transplantation in general has been relatively underrepresented in the annual ASTS programs. But in recent years more and more thoracic transplant surgeons have embraced the ASTS meeting as a desirable forum for presenting their work.

Lung transplantation first appeared on the ASTS program 1977, when Bardin and Halasz presented "Studies in lung preservation." Interestingly, no subsequent papers in lung transplantation appeared until 1981 when Veith presented work on Cyclosporine A in experimental lung transplantation. This represented a milestone, since Veith is generally recognized as one of the pioneers of clinical lung transplantation. In 1982, Veith's group updated their work on canine lung allografts with Cyclosporine A, documenting the short- and long-term effects and the impact of cessation of therapy. Heart-lung transplant papers from the Stanford group were presented, one each in 1983 and 1984. Jamieson dealt with clinical heart and lung transplantation. McGregor et al. summarized an experimental study of late evaluation of ventilation, perfusion, and pulmonary alveolar capillary function in primates after heart-lung transplantation. Bruce Reitz, the father of heart and lung transplantation, figured prominently in both of these papers.

In 1986, the Pittsburgh group presented work on functional analysis of bronchoalveolar lavage cells obtained from heart-lung recipients. Griffith, Hardesty, Zeevi, et al. have made many contributions to thoracic transplantation immunology. Reitz and his group from Johns Hopkins presented work in 1987 on the model of the autoperfused working heart-lung preparation during cardiopulmonary preservation. This would become an important model for preservation of clinical heart-lung blocks for transplantation.

In 1989, the first clinical abstract in lung transplantation was presented by Christopher McGregor, involving work at Newcastle-upon-Tyne in the U.K. as well as at the Mayo Clinic. This was a landmark ASTS presentation. Another important paper was presented by the Cambridge group regarding bronchoalveolar lavage and transbronchial biopsy for monitoring heart-lung transplant recipients. This work would

develop into an important contribution to both heart-lung and lung-only transplantation. Terrance Higenbottam and John Wallwork were the principal authors. In 1990, John Armitage presented work on thoracic organ transplantation under FK506. This novel immunosuppressive agent, first employed at the University of Pittsburgh in thoracic organ transplantation, has shown considerable promise. An important experimental paper from Pittsburgh involved improved immunosuppression using local delivery of cyclosporine in a rat lung transplant model. Keenan and Griffith described the similarity of pulmonary rejection patterns between heart-lung and double-lung transplant recipients. This was one of the first papers to deal with the histology of pulmonary allograft rejection in humans.

1991 saw a presentation of successful extended lung preservation with University of Wisconsin (UW) solution. Peter Andreone from Minnesota presented an important review of infection after lung and heart-lung transplantation, nicely outlining the etiologies and frequencies of infection. Egan et al. presented results of a study on the suitability of heart donors for lung donation. Their paper dealt with the important issues of attempting to maximize the number of transplantable organs from currently available human donors. In 1992, Jamieson et al. from the University of California, San Diego, presented work on human lung transplantation with triple immunosuppression alone. This immunosuppressive modality, introduced by Bolman et al. at Minnesota in 1983 in heart transplantation, has been extended by many groups into lung and heart-lung transplantation with satisfactory outcomes. Griffith et al. from Pittsburgh presented work on the effect of HLA matching in lung transplantation.

In 1993, Deeb et al. from the University of Michigan presented a paper investigating pulmonary function in single-lung recipients transplanted for pulmonary fibrosis.

This completes the lineage of lung transplantation work presented at the ASTS annual meetings, highlighting the many important contributions in this field. It is anticipated that more and more thoracic transplant surgeons and physicians will use this forum for presenting their work.

Cells

CAMILLO RICORDI

It is an honor to summarize the last two decades of cell transplantation as perceived through the proceedings of the American Society of Transplant Surgeons. I remember 1975, the year of the first ASTS scientific meeting, very well. I was still in high school, anxiously waiting to reach the legal driving age. If someone had asked me about cell transplantation I probably would have said it was some activity related to the transfer of criminals in jail.

Cell transplantation has come a long way since 1975. Its evolution is very well reflected by the number of presentations at ASTS meetings: from an average of less than 2 presentations per meeting during the first five years, to more than 10 per meeting during the last five years, with 17 presentations in 1993. Due to space restrictions, I will be unable to adequately honor all the contributions; however, they are all listed in the references. Different aspects of cell transplantation have captured the interest of ASTS members: islet, hepatocyte, and hematopoietic cell transplants, and, more recently, gene therapy research. Other fields are not covered at all: neural, myoblast, and epidermal cell transplantation. Nevertheless, the abstracts over the years represent the evolution of the field from the pioneer experiments of the 1970s to the sometimes high-tech, molecular biology-oriented approaches of the 1990s.

In 1975, the year of the first ASTS scientific meeting, the same themes in cell transplantation predominated that are still of central interest today. In 1975, the Minnesota group was already addressing the problem of transplantation of porcine islets of Langerhans, demonstrating that dispersed pancreatic tissue could be successfully implanted in the peritoneal cavity of the pig(1). At the same meeting, Weber presented a pioneer study on the fate of islet allografts and xenografts in rodents. He documented one of the main advantages of nonvascularized cellular transplants across xenogeneic barriers: rejection time of cell xenografts and cell allografts was similar, indicating a delayed rejection of cell xenografts compared with vascularized organs(2).

Monaco presented another milestone study on enhancement of a human cadaver renal allograft with antilymphocyte serum (ALS) and donor bone marrow infusion (3). This was the first clinical attempt, after several studies in rodents and in dogs

showing active enhancement of allograft survival through infusion of donor-specific bone marrow cells. Monaco's study demonstrated the feasibility of donor-specific marrow harvest and administration without any serious complications such as graft-versus-host disease (GVHD). Moreover, the procedure did not precipitate graft rejection; of interest, a sensitized recipient of a multiple antigen mismatched kidney survived with completely normal renal function and no rejection episodes (3). Monaco concluded that donor marrow injection after grafting makes the system well suited for clinical cadaver transplantation.

1976 was the year of preservation and culture. Initial feelings that cell transplants could be less immunogenic than organ transplants were rapidly disproven. Efforts turned to in vitro manipulation of tissues pretransplant to decrease their immunogenicity. The ultimate goal of this line of investigation was to perform cell transplants without the requirement of continuous immunosuppression. Sollinger brilliantly demonstrated that 10 days of in vitro culture significantly prolonged thyroid xenograft survival for up to 15 days. If the culture treatment was extended to 27 days, no sign of rejection could be detected for up to 25 days posttransplant. Injection of fresh donor cells at the time of the transplant reversed the effect of long-term organ culture.

Weber, Hardy, and Reemtsma at Columbia University extended the preservation studies to collagenase-dispersed human cadaver pancreases. They found that culture techniques could be useful for both islet purification (by selective death of the exocrine component during culture) and preservation, and may even affect islet antigenicity. The work of Sollinger and Weber was representative of the general trend that was gaining consensus in the cell transplant community (at that time still a restricted club): it was felt necessary to decrease immunogenicity of the tissue pretransplant to achieve prolonged survival of allografts and xenografts.

Monaco's theory lay dormant for several years, perhaps because of the findings that adding bone marrow-derived donor cells to grafts triggered rejection. Several groups concentrated their efforts on techniques to decrease cell immunogenicity pretransplant, through either in vitro culture antibody treatment or ultraviolet (UV) irradiation.

In 1979 and 1980, hepatocyte transplantation made its ASTS debut with two presentations by Mito and Makowka. Hepatocyte transplants were proposed as an alternative to liver transplants in selected applications, such as treatment of fulminant hepatic failure, in which a transplant at the cellular level could constitute a bridge to transplantation or just allow the native liver to recover. In addition, hepatocyte transplants could be used to treat selected enzymatic deficiencies that would not require transplantation of the whole liver. Mito indicated that hepatocytes transplanted in the spleen maintained qualities proper to normal hepatocytes one year posttransplant (10). It was not known, however, whether the developed hepatized spleen could also function as an integrated ectopic liver. Makowka, who previously showed that intraperitoneal hepatocyte transplants could improve survival of rats with acute hepatic failure, extended his observations to allogeneic and xenogeneic models, indicating that improved survival was possible in an otherwise lethal rat model of hepatic failure (16).

The issue of whether blood transfusion really enhanced the possibility of a compatible transplant was first raised by Salvatierra's group in 1978 (9) and dominated the 1979 meeting with four oral presentations(12-15) in addition to the Honored Lecture by Robert Good on "Hematopoietic Transplantation in Clinic and Laboratory: A Vital Approach to Organ Transplantation." Good's lecture was the first ASTS presentation on bone marrow transplantation, a field that until then had seemed rather distant. The possibility that bone marrow-derived cells could enhance any organ transplant slowly evolved in the 1980s, resulting in an increase interest in hematopoietic cell transplant procedures. The question of blood transfusion was examined clinically in a multicenter prospective study (25) that followed the preliminary experience of Stiller and Corry, who reported improved cadaver renal allograft survival when patients received transfusions at the time of the transplant. The study known as the National Institute of Allergy and Infectious Diseases (NIAID) Kidney Transplant Histocompatibility Study indicated that perioperative transfusions had no demonstrable effect on graft survival, and that only pretransplant blood transfusions had a beneficial effect on primary cadaver or living related renal allograft outcome. By 1982, the use of fresh donor-specific transfusions for MLC reactive haploidentical living related transplants became widely accepted as a means of pretransplant conditioning (33). Since blood transfusions to transplant recipients seemed to improve renal allograft survival, the hypothesis was then raised that additional improvement in graft survival could be obtained in transfused recipients who received kidneys from transfused donors. Corry's group obtained data from a large series of patients (110 recipients who received kidneys from transfused donors), but found no beneficial effect of donor blood transfusions on graft survival. Thus, blood should not be administered to transplant donors unless medically indicated, such as for blood loss (29).

In the 1980s, most groups involved in cell transplantation were rather cool to the concept of enhancing graft survival by infusing bone marrow-derived cells. In fact, pretransplant tissue culture for tissue allografts was a significantly more popular approach to improve survival of both allogeneic and xenogeneic tissues, such as pancreatic islets. The explanation for the beneficial effect of culture was that highly immunogenic passenger leukocytes in the transplanted tissue do not survive culture (either due to the low temperature or the presence of high oxygen tension) or become metabolically inactivated as a result of the in vitro treatment.

In 1983, Bartlett and Naji made the interesting observation that depletion of islets from passenger leukocytes benefited graft survival only if the transplant was performed across a major histocompatibility barrier. In contrast, culture grafts transplanted to MHC-compatible hosts were rejected, presumably because the recipient could provide the antigen-presenting cells since they were MHC-compatible with the donor. Clinical extension of these findings would mean that if a passenger cell-free preparation of human islets could be prepared, rejection would be avoided only if the recipient were HLA-mismatched with the donor (37).

In addition to culture procedures to decrease islet immunogenicity, the early 1980s brought Faustman's demonstration that pretreating of islets with anti-Class II antibodies and complement could prolong survival of islets across major histocom-

patibility barriers (*Proceedings of the National Academy of Sciences,* 1981). These experiments opened the way to other methods to selectively deplete passenger leukocytes from islet preparation through monoclonal antibody treatment. Whether acceptance of allogeneic islets was the result of true tolerance was still the object of controversy. Islet allografts surviving for 100 days remained susceptible to rejection if challenged with donor splenocytes. Morrow and Sutherland showed that mice bearing established anti-Ia pretreated islet allografts did not accept donor-specific skin allografts, indicating they were not tolerant in the classical sense. Their results suggested that anti-Ia treated islets have reduced immunogenicity, but are also unable to induce tolerance. Such islets retained target antigens for rejection as long as class I disparities existed (Morrow, 1983).

With progressive attempts to transfer islet transplantation from rodents to large animals and humans, it became clear that techniques developed for rodent islet isolation and purification were not easily applied to larger mammals, including humans. Nor did methods to induce islet graft acceptance transfer. Whether collagenase digestion should be used for islet preparation from the pancreas of large animals remained controversial. Sutherland and Toledo-Pereyra appeared to support transplantation of less purified islet preparations, in contrast to traditionally nonsurgical groups, such as Paul E. Lacy and colleagues at Washington University and the Miami group of Daniel H. Mintz. They concentrated their efforts on refining islet cell separation and purification methods. In 1984, Toledo-Pereyra suggested that, in dogs, the renal subcapsular region could be an alternative site for islet cell allotransplantation. The choice of site was also dictated by the relatively crude islet preparations available in those years. His method included pressing the tissue through a stainless steel screen or mincing it in a mechanical tissue chopper. The high volume of unpurified, pancreatic fragments could not be transplanted in the liver or even in the spleen because of the risk of serious complications, such as portal hypertension and disseminated intravascular coagulation (DIC).

In 1984, the use of ultraviolet (UV) irradiation to facilitate pancreatic islet allograft survival was first introduced at an ASTS meeting by Lawrence and Hardy. The results indicated that the combination of cyclosporine and UV irradiation could induce permanent islet allograft acceptance in donor-recipient combinations, whereas the single use of either agent did not produce any significant benefit (41).

The experience of almost a decade of donor-specific blood transfusions was reviewed by Salvatierra in 1985 (42). Such recipients enjoyed excellent graft survival: 94% at 1 year, 90% at 2 years, 85% at 3 years, 83% at 4 years, and 83% at 5 years. Excellent long-term graft survival was seen in l-haplotype pairs; remarkable 2-year graft survival was seen in 2-haplotype mismatched pairs.

A milestone paper was presented at the ASTS meeting in 1985 by Pierce and Watts (44) on the role of donor lymphoid cells in the transfer of allograft tolerance. Monaco et al. had previously shown (1981), in their model of allograft enhancement, that suppressor cells in the host spleen were of donor origin. Studies on transfer of neonatally induced tolerance had found evidence that donor T cells played an integral role in maintaining tolerance (Dorsch and Roser, 1982). Since the number of persistent

donor cells was too low to determine whether tolerance could be transferred with an infusion of donor cells alone, Pierce and Watts developed a model of allograft tolerance in which about 20% of spleen cells in tolerant hosts were persistently of donor origin. Tolerance was obtained by infusion of donor bone marrow cells into recipients after a sublethal 24-hour course of fractionated irradiation (250 x 3). In addition, Pierce and Watts showed that tolerance could be transferred with only 2 x 107 cells. They demonstrated that tolerance to skin allografts across a strong H-2 barrier could be transferred with lymphoid cells of donor but not of host origin (44). They also provided a possible explanation of the apparent benefit of donor-specific transfusion as well as clues for developing methods to induce specific tolerance in view of clinical transplant applications.

In 1986, the first fetal transplant work was presented at the ASTS meeting by Hullett of Sollinger's group. Results indicated that human fetal pancreases transplanted into diabetic mice differentiated and matured, normalizing blood glucose control (47). This indicated that human fetal pancreases could be suitable for transplantation into diabetic patients. Moreover, the interim host model developed by Sollinger was suitable for reduction of immunogenicity of human fetal pancreases, by allowing reduction of passenger leukocytes of human origin pretransplant into the final recipient. Unfortunately, political circumstances severely impaired the development of fetal transplant research, including the promising work of Hullett and the Madison group. The federal ban on such research has only recently been lifted.

Also in 1986, a new model for successful pancreatic islet transplantation was proposed by Gotoh of Monaco's group, indicating that transplantation of small numbers of islets from multiple donors could lead to long-term graft survival (46). The reason for these excellent results was thought to be the small number of islets from each donor strain, which generated a low-grade immune response to each specific donor strain, not sufficient to cause rejection (46).

The following year (1987), the same group presented a very stimulating hypothesis based on the fact that only highly immunogenic islet preparations were able to induce tolerance to subsequent islet allografts from the same strain. Yet highly purified, handpicked islets were unable to induce donor-specific tolerance (50) after ALS treatment of the recipient. It was then well known that pancreatic islet preparations prepared by collagenase digestion in Ficoll gradients contained highly immunogenic contaminants, which were thought to be responsible for the acute rejection frequently observed after allotransplantation in nonimmunosuppressed recipients. Gotoh's study indicated that the use of crude islets and ALS treatment of recipients induced specific unresponsiveness to a second-set transplant (50). This effect was postulated to be mediated by suppressor cells. In contrast, the prolonged allograft survival observed by other groups with purified islets was thought to be due to the reduced immunogenicity of highly purified islet preparations. Two different, potentially conflicting mechanisms for inducing prolonged graft acceptance were proposed. First, highly purified islets with reduced immunogenicity (e.g., culture, monoclonal antibodies, UVR) could achieve prolonged graft acceptance by reducing the immunogenicity of the preparation pretransplant. Second, strong immunosuppression

together with highly immunogenic preparations could induce graft acceptance, possibly because of the presence of highly immunogenic cells. Interestingly, only in the latter case was donor-specific tolerance obtained, suggesting that an "active" mechanism for tolerance induction was involved in this model as opposed to the "passive" graft acceptance of passenger leukocyte-depleted grafts.

The concept of transfusion into the recipient of viable donor bone marrow-derived cells, after an induction course of antilymphocyte serum, was brought to the clinical arena by Barber et al. In their milestone trial, cryopreserved donor bone marrow was transfused to cadaver kidney allograft recipients, after the use of antilymphocyte globulin (ALG) for 7 to 14 days posttransplant (54). The trial was first reported at the 1988 ASTS meeting (Sandoz Fellowship Award, 1987). It followed by over 10 years the first described case by Monaco (3). The trial indicated that infusion of cryopreserved donor bone marrow cells after cadaver kidney allograft transplants, was feasible and could induce donor-specific unresponsiveness. The protocol was safe and did not induce rejection episodes or graft-versus-host disease.

Also in 1988, Chester and Sachs extended the previous model of mixed chimerism (Ildstad, Sachs. *Nature*, 1984) to study the engraftment capacity of combinations containing syngeneic and more than one allogeneic source of bone marrow. Analysis of the recipients by flow provided evidence of stable multiple mixed chimerism in the majority of animals (55). All animals that exhibited multiple chimerism where also tolerant to skin grafts from allogeneic bone marrow donors and promptly rejected fourth-party skin grafts. Thus, multiple allogeneic engraftment paralleled transplantation tolerance to multiple donors—an insight of particular relevance to islet transplantation, where islets from more than one donor may be needed to produce normoglycemia in diabetic recipients.

Hepatocyte transplantation reappeared at the 1988 ASTS meeting with an elegant experiment by Chen of Ascher's group, showing how hepatocyte class I molecules alone in the absence of an allo-class II signal could still induce allospecific CTL in mixed lymphocyte hepatocyte culture. This result conflicted with the generalized assumptions that (1) donor class II positive cells (i.e., passenger leukocytes)—and not class II negative parenchymal cells—accounted for the immunogenicity of grafted tissues and (2) these cells were necessary for the generation of allo-CrL (59).

Besides "passive" and "active" methods for tolerance induction, a third line of research received increasing attention in the 1980s: encapsulation, or the introduction of physical barriers between the transplanted cells and the recipient's immune system. Weber reported on xenotransplantation of microencapsulated islets at the 1989 ASTS meeting (63). Results indicated that the reaction to microencapsulated islets in NOD mice is helper T cell dependent and that the target of this reaction is not the microcapsule itself, but the donor cells within it. In addition, a more intense reaction in diabetic versus prediabetic NOD mice suggested that anti-islet autoimmunity played a role in the failure of the microencapsulated graft. These findings put a brake on the sometimes overoptimistic world of microencapsulation.

Markman of Naji's group added more variables to the potential mechanism of prolonged cell transplant survival after culture at the 1989 ASTS meeting. His con-

vincing data supported the hypothesis that it is not just antigen-presenting cell depletion that occurs during culture but also decreased class I MHC expression. Islets cultured at 24° expressed significantly less class I MHC antigens, and—in contrast to islets cultured at 37°—were also refractory to the increased induction of MHC antigen expression mediated by lymphokine exposure. Thus, other factors in addition to antigen-presenting cell depletion could play a decisive role in graft acceptance. That same year, Chabot of Hardy's group indicated that methods used to prevent cell allograft rejection by UVB pretreatment could also be used to prevent both graft-versus-host disease and marrow rejection after rat bone marrow allotransplantation if the UVB treatment was applied to the donor bone marrow. Chimerism and donor-specific unresponsiveness were also reduced (66). Guzzetta of David Sachs' group clearly demonstrated that donor-specific tolerance could be induced by bone marrow transplantation in a large animal model: the miniature swine. Such animals retained kidney transplant function at least as well as animals without bone marrow transplants that received kidney transplants from MHC-matched donors (65).

In 1990, Barber reported the long-term results of the clinical trials of kidney transplantation after donor-specific bone marrow infusion. In 50 recipients, the use of cryopreserved donor-specific bone marrow was associated with improved allograft survival. However, Barber indicated that a more effective induction protocol was necessary to reduce the overall number of rejection episodes (80).

1990 was also the year of the islets, with several presentations reflecting the renewed interest in pancreatic islet transplantation for treating diabetes (72-75, 77, 78, 82). Monaco's group presented diabetes reversal in dogs by implantation of a biohybrid artificial pancreas (73). Results of clinical trials of human islet transplantation were reported by Scharp and Lacy, who showed it was possible to normalize glucose in the absence of exogenous insulin therapy for a few days and with islets obtained from 2 donors. Their relatively poor results were overwhelmed by news of prolonged insulin independence after islet allotransplantation just months before the 1990 ASTS meeting at several centers, including Pittsburgh, Edmonton, Milan, Miami, and St. Louis. It has been an honor for me to be associated with all of these trials, except for Edmonton. Some of these results were presented at the 1991 ASTS meeting (83, 91).

Also in 1990, Monaco characterized the spleen and lymph node cells that were capable of inducing unresponsiveness to skin allografts in ALS-treated mice. It was known that the active marrow cells had limited expression of phenotypic markers and did not appear to be mature T or B cells. Monaco characterized the active cell that induces unresponsiveness in lymph nodes and thymus, indicating it was Thy-l positive. He postulated a lack of tolerogenic cells in lymph nodes and thymus that could explain the relative inability of cells from these lymphoid organs to prolong graft survival (81). Additionally, Stock of Sutherland's group presented an elegant paper demonstrating both direct and indirect pathways in generating the early immune response against pancreatic islets (77). Generation of allo-CTLs against pancreatic islets could occur by indirect presentation of MHC class I molecules by recipient APCs or by direct presentation by MHC class II positive cells within the islets. This

indicated that alteration of the early immune response to islets may require blocking of both direct and indirect pathways (77).

It was only in 1991 that gene therapy was introduced at an ASTS meeting (94). The use of gene transfer technology allowing alteration of MHC expression enabled study of animal models of the immune response to an isolated Class I disparity within transplanted myocardial cells, which also expressed class I antigens identical to the recipient. Extension of this method could permit alteration of graft immunogenicity by genetically influencing MHC expression of transplanted tissues (94).

Even though the first successful clinical trials of pancreatic islet transplantation were reported in 1991(83,91), rejection limited its application for treating Type I diabetes. Kaufman that same year pointed out that, besides rejection, islet allograft primary nonfunction could be responsible for the failure of these grafts (93). The study detailed how macrophages could be involved in islet primary nonfunction and how 15-deoxyspergualin (an agent that also suppresses macrophage activity) prevented islet allograft primary nonfunction. This was particularly relevant, since the number of islets that successfully engraft after intraportal infusion could be the real limiting factor to successful islet transplantation—and could explain why multiple donors have been required in most of the cases of insulin independence after human islet allotransplantation. Also in 1991, Soon-Shiong reported successful long-term reversal of spontaneous diabetes in dogs by intraperitoneal implantation of microencapsulated islet allografts, demonstrating potential clinical utility (84). Deoxyspergualin was successfully used for the first time in combination with splenectomy and ATG to obtain long-term survival of pig islet xenografts in rats (89). Zeng obtained long-term survival of islet xenografts in fully xenogeneic chimeras (cat to mouse)—an interesting model, but of no clinical relevance.

1992 was the year of intrathymic transplantation. The model developed by Posselt and Naji was rapidly followed by a series of experiments with different models (100, 101, 108). The Philadelphia group discovered that transplantation tolerance in adult animals followed intrathymic inoculation of donor islets into recipients treated concomitantly with a single dose of antilymphocyte serum. This was a major breakthrough that opened the way to a series of studies to determine exactly which cells (or which antigens) are responsible for the mechanism of intrathymic tolerance induction, still the object of intensive investigation.

In 1993, a new gene therapy approach was proposed to obtain donor-specific tolerance (106). Preliminary indications were that products of the class II region of the major histocompatibility complex were of overwhelming importance in inducing transplantation tolerance toward renal allografts in miniature swine. Shimada et al. proposed a potential gene therapy approach to tolerance induction, involving the introduction of MHC antigens to potential recipients by genetic engineering. It would avoid the usual complications associated with allogeneic bone marrow transplantation. Experiments are still in progress to verify the validity of this approach. At the same meeting, Colson of Ildstad's group, showed that the morbidity and mortality associated with full myeloablation of the host cannot be justified in clinical trials. He reported a nonlethal approach to obtain mixed allogeneic chimerism and donor-spe-

cific tolerance. However, the radiation-based model still required 3 to 7 Gy of total body radiation, a dose that would still be too morbid for clinical trials.

The 1993 meeting underlined a trend in cell transplantation, with the progressive involvement of molecular biology and gene therapy applications, that will be more and more closely related to clinical organ transplants. Whether a bone marrow component approach, an intrathymic cellular transplant, or even a transplant at the molecular level, it appears that cell transplantation may become an integral part of most organ transplant procedures—or an alternative to some. Therefore, the progressive interest in this field and the involvement of an increasing number of ASTS members is fully justified.

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