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Liver and Intestine

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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 PGE1—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 ABO-mismatched kidney recipients (Denver) and in recipients with positive lymphocytotoxic 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 1990 (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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