TRANSPLANTATION PROCEEDINGS

Proceedings of the

FOURTH INTERNATIONAL SYMPOSIUM ON SMALL BOWEL TRANSPLANTATION

Pittsburgh, Pennsylvania

1948
1949

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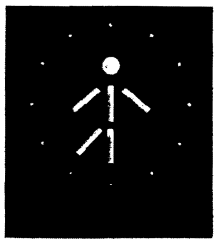

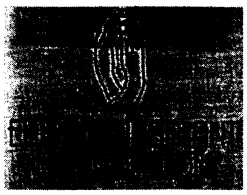

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INTRODUCTION

Current Perspectives of Transplantation Immunology Via The Intestine

T.E. Starzl

THE RECORDED history of intestinal transplantation is a long one, stretching back to the beginning of this century and Alexis Carrel. However, the line of continuity contained long blanks, even after Richard Lillehei's presentation of experimental bowel replacement in dogs at the American Surgical Association in 1959,[1] and his unsuccessful first clinical trials 7 years later. Here, I will focus on the shifting perceptions of the immunologic barrier to this operation since the symposium held in London, England, in September 1988.

By this time, the first two successful examples of transplantation of a functional human bowel had already been recorded but not yet published. The complete small intestine and half of the colon were parts of a multivisceral graft transplanted in Pittsburgh in November 1987 to a child who lived more than 6 months before dying of a B-cell lymphoma.[2] A small intestinal segment was transferred from a living donor in the case of Deltz et al of Kiel during August 1988[3]; the patient ate during most of the 56 months survival. Now the pace quickened. During the 15 months following the London conference, Grant et al from London, Ontario[4] and Margreiter et al of Innsbruck[5] added more long-surviving intestine-containing grafts, and Goulet et al[6] performed an isolated complete cadaveric intestinal transplantation in a child. Goulet et al's patient is the only one still alive, but the two Canadian recipients survived for 5 years.

At the 1988 meeting in London, the general perception of intestinal transplantation was still defined by the classical rat study of Monchik and Russell,[7] using a parent-to-offspring F_1 hybrid model in which the recipient could not reject the graft, but was vulnerable to graft-versus-host disease (GVHD). When the recipients died of GVHD, the unchallenged impression for many subsequent years was that GVHD was going to be a critical management problem in clinical cases. Lurking also in the background was concern about transplanting a sac of gastrointestinal contents. If the sac became permeable to bacteria, uncontrolled sepsis was expected to follow. The widespread pessimism about clinical application of intestinal transplantation was understandable.

One of the main themes of the 1988 London meeting was how to eliminate the lymphoid tissue in the grafts by irradiation, antilymphocyte globulin (ALG), or even surgical lymphadenectomy. However, there also was a breeze blowing in a different direction. Arnaud-Battandier et al[8] from France (working with Goulet and Ricour), had shown in pigs as early as 1985 that the donor leukocytes in bowel began migrating to the spleen and elsewhere within a few minutes after revascularization. The departed cells were replaced in the intestine by leukocytes of the recipient, seemingly without injury to the graft. Incongruously, the French team had not cited these results in their subsequent publications and did not mention them in London. Some of the histopathologic rat studies presented at that meeting by Clark and co-workers were consistent with the earlier French results. However, the important conclusion that the intestinal allograft had a dual cell construction was neither the point nor the interpretation of the English workers.[9,10]

Meanwhile, armed with the new drug FK 506 (now tacrolimus), Murase et al[11] reported at the 1989 European Society of Organ Transplantation (ESOT) meeting in Barcelona that rat bowel alone, or as part of a multivisceral complex, could be transplanted with routine success. A second article,[12] describing the pathology of these grafts, was controversial, requiring extensive editorial negotiations that held up publication for more than a year. The most important pathologic observation (by Anthony J. [Jake] Demetris) was that the grafts had become genetic composites within 14 days. The leukocytes of the lamina propria and elsewhere, including in the donor mesenteric lymphocytes, were those of the recipient. This conclusion was made possible by the development in Pittsburgh of an antibody (L-21-6) that failed to stain the class II cells of Brown Norway recipients because of a defect in their invariant chain, but did so in essentially all other strains.

Meanwhile, Satoru Todo and Andreas Tzakis had begun in early 1990 their now large clinical series of a whole range of inter-related visceral grafts and intestine alone using FK 506 (tacrolimus)-based immunosuppression.[13] These procedures were construed to be variations of a multivisceral transplant operation described in 1960 in dogs[14]; used clinically by us,[2] in Innsbruck,[5] and in Canada[4]; and exploited by Murase et al in rat studies.[11,12] The organs were envisioned as grapes on an anatomic stem (Fig 1)—to be left intact, picked off and discarded, or transplanted sepa-

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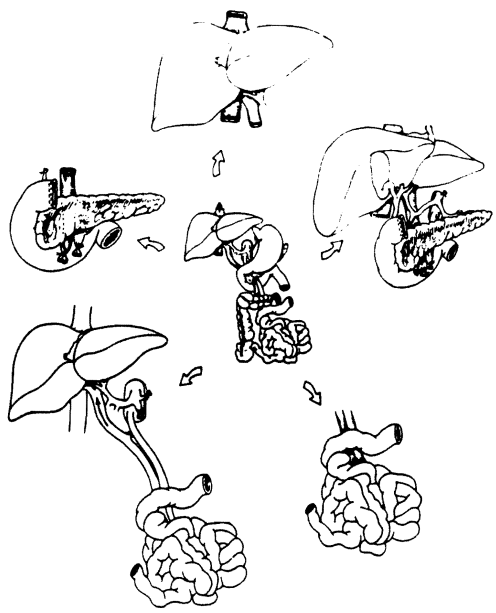

Fig 1. The complex of intraabdominal viscera (center) from which come liver-pancreas, intestine, pancreas, or liver grafts (periphery).

rately.[15] When the intestine was included in the allograft, it always was the Achilles' heel of the operation.

In the human recipients, the bowel allografts showed the same transformation[16] as had been observed by Arnaud-Battandier et al[8] and in rats.[12] It had been known for nearly 20 years that this leukocyte replacement was characteristic of human hepatic allografts,[17] but it was assumed to be a special quality of liver transplants. Now it was realized that leukocyte replacement must be a generic phenomenon with the acceptance of all kinds of whole organ allografts.[16]

Although the fate of the departed donor cells was not known and would not be for another year, we understood the folly of deliberate donor leukocyte depletion[15] and realized that doing so generated the B-cell lymphomas that crippled the clinical trials between 1987 and 1989.[2,4,18] The management philosophies that had dominated the 1988 transplant meeting took a sharp turn away from these practices by the time of the Second International Small Bowel Symposium hosted in October 1991 by David Grant, William Wall, and Calvin Stiller in London, Ontario.

The observations of leukocyte migration and replacement that were made in the course of research in intestinal transplantation eventually matured to the concept depicted in Figure 2 (lower panels). Before this time, transplantation had been defined largely in terms of a unidirectional immune reaction (Fig 2, upper panels): host versus defenseless graft following organ transplantation (upper left) and graft versus defenseless host (GVH) after bone marrow transplantation (upper right). With either direction, this one-way paradigm had failed to elucidate numerous enigmatic observations including the surprising clinical success of these procedures. However, it now appeared that the events following both varieties of transplantation might be explained by the previously unsuspected persistence of a trace population of immune cells. This was proved in organ transplant recipients in 1992 when donor leukocytes (microchimerism) were found in the skin, lymph nodes, blood,

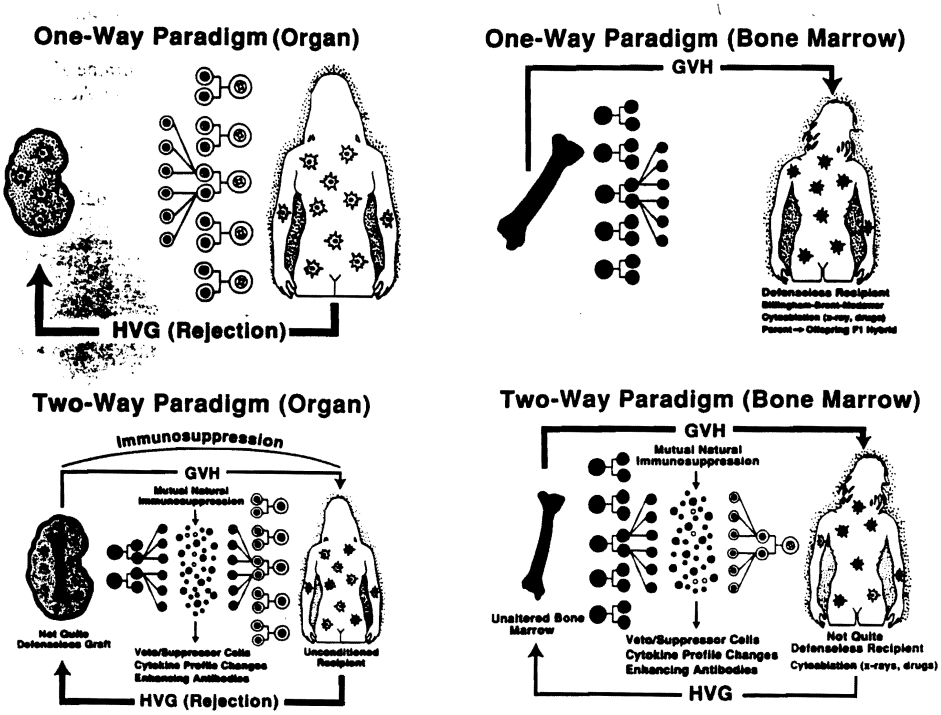

Fig 2. The one- and two-way paradigms of immune interaction following organ or bone marrow transplantation.

and other locations in patients whose kidney or liver allografts had been functioning for up to 30 years.[19–23] The implication was that donor stem cells present in the transplanted organ had migrated and survived in the recipient[24–26] (Fig 2, lower left).

In the mirror image condition that evolves after conventional clinical bone marrow transplantation,[19,26] the trace population consists of leukocytes of host origin (Fig 2, lower right), meaning that recipient stem cells survive and persist despite patient preconditioning with supralethal cytoablation.[27,28] With either conventional organ or bone marrow transplantation, the quantitative disproportion of the coexisting donor and recipient leukocytes is enormous. Nevertheless, there is much circumstantial and direct evidence that the two cell populations reciprocally modulate immune responsiveness, including the induction of mutual nonreactivity (the two-way paradigm).

The implications of this concept at virtually every level of transplantation immunology have been discussed elsewhere.[19,20,26,29–32] The duality of the immune reaction following organ transplantation (HVG and GVH) is obvious after intestinal transplantation and was a dominant theme in the research and clinical presentations of this year's splendid program. It was appropriate that the program was organized by Satoru Todo, a genuine pioneer in the visceral transplantation field.

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