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2244

Immunosuppressive Therapy and Tolerance of Organ Allografts

Thomas E. Starzl, M.D., Ph.D.

In this issue of the *Journal*, three articles describe several organ-transplant recipients in whom allografts have maintained good function for up to 5 years without immunosuppressive treatment.¹⁻³ In two articles concerning combined kidney and hematopoietic stem-cell transplantation, the authors attributed the successful outcome in their patients to the cotransplantation of donor stem cells.^{1,2}

The third report, by Alexander et al., concerns a young girl who received a completely HLA-mismatched liver from a deceased male donor but did not receive a donor stem-cell infusion.³ The cause of the fulminant hepatic failure with which the patient presented was never firmly established. However, a viral infection was thought to have caused lymphopenia that was noted at the initial hospital admission and persisted for a half year after liver transplantation. During the post-transplantation phase, passenger leukocytes from the graft largely replaced the recipient's leukocytes. In addition to the presence of male chromosomes in leukocytes from the girl's blood, the recipient's RhD-negative blood subgroup switched to the RhD-positive blood sub-

group of the donor. Severe hemolytic anemia, which developed 10 months after transplantation, was attributed to anti-RhD antibodies produced against the donor's RhD-positive erythrocytes by residual B cells in the recipient. This condition prompted the patient's physicians to discontinue all immunosuppressive therapy so that the donor's hematopoietic cells might eliminate all of the recipient's residual B cells. The net effects of this action were resolution of the patient's hemolytic anemia and retention of the graft without immunosuppression.

In one article concerning combined kidney and hematopoietic stem-cell transplantation, reported by Scandling et al.,¹ tolerance was thought to be due to the stem-cell cotransplantation. The recipient of a kidney from an HLA-matched brother began to receive cyclosporine at the time of renal transplantation. During the next 2 weeks, he received 10 doses of total lymphoid irradiation, 5 doses of antithymocyte globulin, and a 10-day course of prednisone. On postoperative day 14, he received an infusion of donor hematopoietic stem cells, and a 1-month course of mycophenolate mofetil was initiated. Within

1 month after transplantation and consistently thereafter, the proportions of donor and recipient cells in the recipient's blood were about equal; however, there was a wide range (5 to 85%) in lineage subgroups. The finding of T-cell-receptor excision circles — an indication of newly minted T cells — suggested that donor-type lymphocytes in the recipient were of thymic origin. Immunosuppressive therapy was discontinued 6 months after transplantation, with maintenance of good renal function 34 months after transplantation.

In the other article related to cotransplantation, Kawai et al.² performed simultaneous kidney and stem-cell-enriched leukocyte transplantations from five HLA single-haplotype mismatched living related donors (three parents and two siblings) into recipients who had received a conditioning regimen with multiple agents.⁴ One patient rejected the kidney. The other four patients had undefined spontaneously reversible or corticosteroid-responsive “capillary leak” phenomena, which presumably were rejection episodes; nevertheless, immunosuppressive therapy was discontinued in the four recipients 9 to 14 months after transplantation, without deterioration in the function of the grafts during 2.0 to 5.3 years of follow-up. There was no evidence of leukocyte chimerism in any patient for more than 21 days. Since only blood samples were studied, assessment of the presence of small numbers of donor leukocytes (microchimerism) outside the blood circulation was not possible. The presence of suppressor T cells could explain the results, but no direct evidence of regulatory T cells with immunosuppressive activity was reported.

The explanation that links the three articles begins with the description of blood-cell chimerism in freemartin cattle that inspired Burnet's⁵ clonal selection theory and led to the demonstration of the induction of immunologic tolerance in chimeric neonatal mice by Billingham, Brent, and Medawar.⁶ These kinds of experiments, and others performed in irradiated adult mice, showed that allogeneic leukocytes that persist in the recipient because they cannot be rejected by a weak, or deliberately weakened, immune system are associated with donor-specific immune tolerance. The seminal requirement for the leukocyte en-

graftment is enfeeblement of the recipient's immune system before transplantation.

By contrast, after 1962, the protocols for organ transplantation in humans called for weakening of the recipient's immune system by immunosuppressive drugs after rather than before transplantation. There was an implied commitment to lifetime immunosuppressive therapy. Almost all of the experimental and clinical observations in the fields of bone marrow and organ transplantation since 1962 that involved drug immunosuppression were presaged by the discoveries of Schwartz and Dameshek in 1958⁷ and 1959.⁸ Their research showed that in rabbits, 6-mercaptopurine inhibited the immune response to a foreign albumin, and second and third albumin injections given without further 6-mercaptopurine treatment did not induce a typical anamnestic response.

These simple experiments yielded the first evidence of the importance of dose, type, and timing of immunosuppressive therapy, and they provided insight into the importance of the dose, type, timing, route, and localization of foreign antigens. Consistent with the albumin experiments, lifetime tolerance in transplantation models was later accomplished with a judiciously timed short course of immunosuppressive therapy, and it was accomplished in selected models without any treatment.⁹⁻¹³

Such experimental results, and the occasional examples of human organ recipients who have successfully discontinued immunosuppressive treatment,⁹⁻¹³ have not been viewed as tolerance,⁴ because engraftment was accomplished without a leukocyte infusion or cytotoxic treatment of the recipient. The theory that organ engraftment occurs by means of mechanisms that are independent of chimerism remained unchallenged until 1992.

In 1992, all 30 recipients of long-surviving human kidney and liver allografts were observed to have multilineage donor-leukocyte microchimerism (<1% donor cells). The sparse donor cells were detected less frequently (in 20 to 25% of patients) in blood than in tissues. It was postulated that the microchimerism observed in these patients, in some cases 30 years after transplantation, was a prerequisite for maintaining the

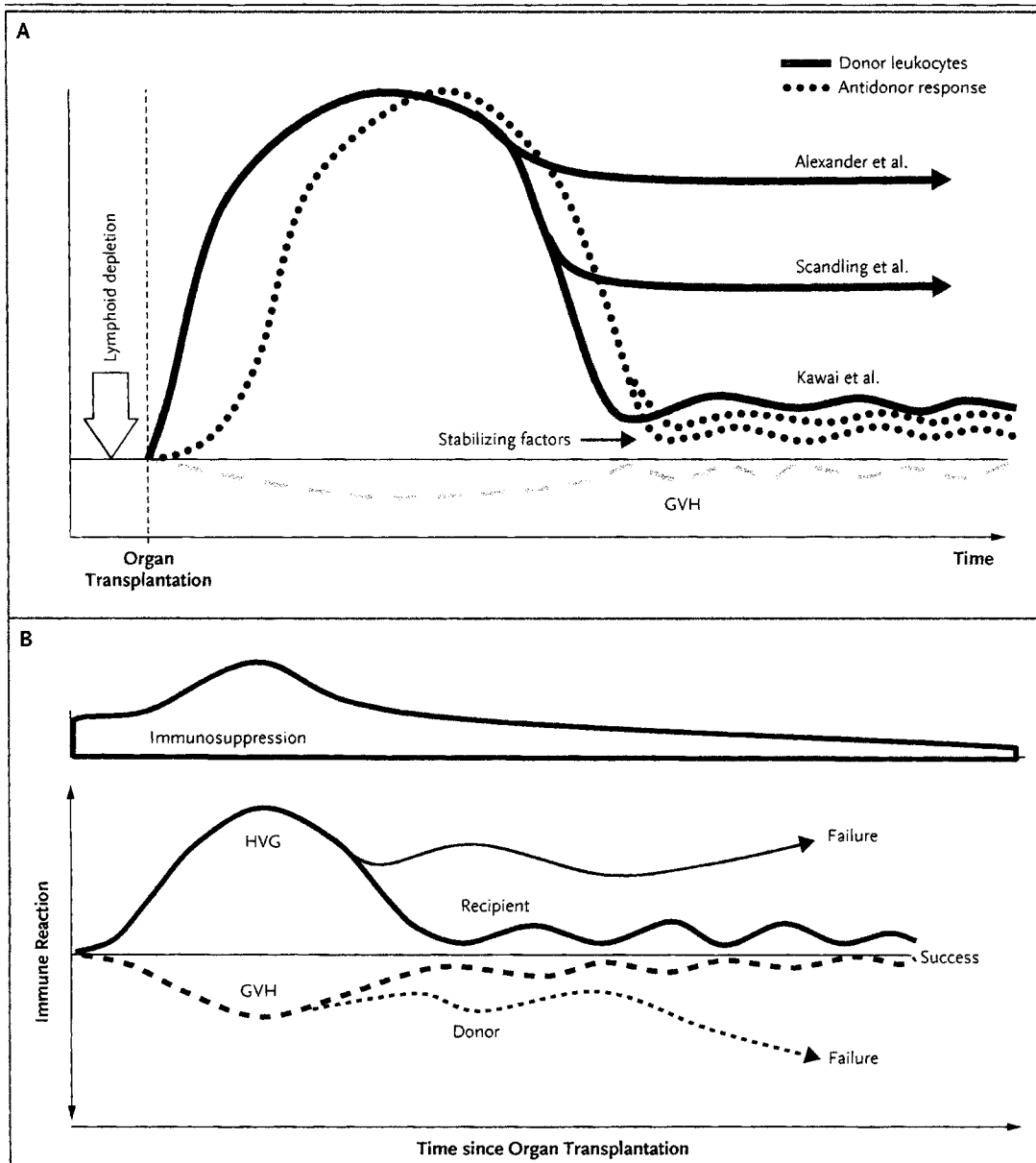


Figure 1. Schematic of the Kinetics of the Development of Variable Donor-Specific Tolerance.

Panel A shows the development of different stable balances between the quantity of persisting donor leukocytes that migrate to host lymphoid organs and the number of antidonor T cells produced at these sites in the organ recipients described in this issue of the *Journal*.¹⁻³ The greatest opportunity for clonal exhaustion—deletion of the antidonor response is during the first few days or weeks of maximal leukocyte migration. The gray dashed curve depicts the graft-versus-host (GVH) reaction mounted by immune-competent donor cells that also must be exhausted and deleted. Stabilizing factors may include immunoregulatory cells, antibodies, endogenous molecules, or ongoing maintenance immunosuppressive therapy. Panel B shows the immune responses that occur simultaneously after transplantation. To the extent that reciprocal clonal exhaustion—deletion is not accomplished, one cell population will destroy the other. Solid lines depict the host-versus-graft (HVG) reactions, and dashed lines the GVH reactions. Failure to achieve engraftment with the aid of immunosuppressive therapy implies the inability to control one or both of these responses. Adverse immune events occurred in the patients, but they were reversible.

state of clonal exhaustion–deletion that was achieved at the time of transplantation.⁹⁻¹¹ Findings from experiments that provide strong support for this concept have recently been published.^{13,14}

Zinkernagel and I have proposed that all outcomes of organ or bone marrow transplantation are determined by the balance between the number of leukocytes that travel to lymphoid organs and the number of donor-specific T cells produced at those sites.¹⁰ The movement of donor leukocytes between lymphoid and nonlymphoid compartments in the recipient governs both responsiveness and unresponsiveness to the allograft.¹⁰ I believe that in the four patients with surviving allografts described by Kawai et al., there is persistent microchimerism just above the threshold required to maintain the clonal exhaustion–deletion that occurred in the first few weeks, when within the recipient there was massive migration of passenger leukocytes derived from the graft plus the infused hematopoietic stem cells (Fig. 1A). More donor cells (macrochimerism) were evident in the recipients described by Scandling et al. and by Alexander and colleagues (Fig. 1A).

Recipients of organ allografts usually receive large doses of immunosuppressive therapy during the early period of maximal leukocyte migration. These large doses may erode the mechanism of tolerance by clonal exhaustion–deletion, and they may preclude the goal of minimal dependence on (or independence from) long-term immunosuppressive treatment.¹¹ To avoid this consequence, two principles have been advocated for application singly or in combination: pretreatment of the recipient and the administration of the least possible amount of immunosuppressive medication after transplantation. One or both principles were applied in the care of the patients described in the three articles in this issue of the *Journal*, either fortuitously or as a planned component or components of treatment.

Zinkernagel and I have proposed that mechanisms of immune reactivity and nonreactivity, their regulation by leukocyte migration and localization, and potential means of therapeutic manipulation can be generalized.^{10,11} The relationship of transplantation to the immunologic aspects of infection, oncology, and other fields has been obscured, however, by the characteristic double-immune reaction of transplantation. In this reaction, the responses of donor and re-

ipient immune cells, each to the other, result in reciprocal clonal expansion followed by mutual clonal deletion (Fig. 1B).⁹⁻¹³ If this process does not occur, the result is rejection or graft-versus-host disease.¹⁰⁻¹² The recipient of an HLA-identical kidney reported by Scandling et al. reached the kind of stable coexistence of nearly equal donor and recipient leukocyte populations that has been very difficult to achieve while avoiding the risk of graft-versus-host disease with any donor other than those who are histocompatible.

The results reported in all three articles are consistent with the axiom that organ engraftment is a form of variable tolerance, the completeness of which can be crudely estimated by the need for maintenance immunosuppressive therapy.¹³ In all six patients, this need reached zero. The presumed balance between donor cells and antidonor T cells in the patients described by Kawai et al. is extremely close. It resembles the balance in recipients with partial tolerance or those who are not receiving immunosuppressive therapy; this balance can be produced with pretreatment with anti-T-cell antibodies and minimal post-transplantation immunosuppressive therapy.¹¹⁻¹³ It appears that all six recipients are analogous to asymptomatic carriers of intracellular (noncytopathic) microbes.^{10,11} Perhaps it will be possible to systematically achieve stable organ engraftment with very low dependence on — or in some cases complete freedom from — long-term treatment. To do so will require just the right dose and timing of immunosuppressive therapy with or without the aid of adjunct hematopoietic stem cells.

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Cost Sharing for Health Care — Whose Skin? Which Game?

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In this issue of the *Journal*, Trivedi and colleagues¹ examine the effect of cost sharing on the use of screening mammography among women enrolled in Medicare managed-care plans from 2001 to 2004. Focusing on more than 350,000 women between the ages of 65 and 69 years, the authors show that cost sharing — either in the form of copayments (in which patients pay flat fees when they receive services) or coinsurance (in which patients pay a fixed percentage of the cost of those services) — reduces the number of women who undergo mammography. The effects are large relative to the modest cost burdens the plans impose. The authors estimate that cost sharing on the order of \$10 to \$20 reduces by 8% the proportion of women who undergo mammography.

Their findings are robust, with similar findings in unadjusted analyses and in multivariable analyses adjusted for potential demographic and regional confounders. Likewise, they are consistent between their cross-sectional comparisons (i.e., between plans) and longitudinal comparisons (i.e., the change over time within a plan before and after cost sharing was instituted). Their findings are also broadly consistent with other analyses of cost sharing for cancer screening.² The authors conclude that cost sharing should be waived for mammography, essentially because mammography is beneficial, and therefore reducing its use by imposing out-of-pocket costs is against the interest of public health.³

Their conclusion raises a challenging health policy question: How, if at all, should cost sharing be incorporated into the design of health insurance? Specifically, what is the best way to structure financial incentives so that patients use health care services wisely but not excessively

— or, in colloquial terms, what kind of “skin in the game” best serves the interest of patients within the fiscal constraints of the health care system?⁴

At the extremes, approaches to cost sharing differ in many respects. At one end are high-deductible plans that are linked to savings accounts, such as health savings accounts. In these plans, patients are placed in the same position as consumers of other goods or services. The expectation that patients will consume health care services wisely and sparingly because they are using their own money, rather than funds from insurers or taxpayers, is a key assumption of high-deductible plans. Other anticipated benefits are that patients will take more responsibility for their own health and will seek high-quality and efficient providers, in both cases because they will save money by doing so.⁵ Because of these expected benefits, economists and policymakers who believe in market-based solutions often champion high-deductible plans.⁶

At the other end of the spectrum is “value-based insurance” design, in which third-party insurers use cost sharing to induce patients to seek higher-value services in preference to lower-value services. To encourage the use of beneficial services, insurers lower cost sharing. Conversely, insurers increase cost sharing when they want to discourage the use of undesirable services or those that provide little benefit. For instance, the proposal to eliminate copayments for angiotensin-converting-enzyme inhibitors for Medicare patients with diabetes is a “value-based” proposition. A recent study showed that when copayments are waived, adherence increases, resulting in both reduced total costs for diabetes care and improved diabetes outcomes.⁷ The RAND Health Insurance