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Acquired Tolerance, Allograft "Acceptance," and Immune Suppression

T.E. Starzl

THE ADAPTIVE response of the immune system, leading to immunity or to nonreactivity, and frequently to gradations between these extremes, is determined primarily by antigen migration and localization, in contradistinction to antigen per se.[1] This conclusion has been determined through separate lines of evidence. The first began in 1992 with the previously overlooked finding of donor leukocyte chimerism in organ transplant recipients.[2] The second came from observations following experimental infections, with emphasis on the importance of the transport and localization of live microbial antigen (viral, bacterial, and protozoan).[3]

In both circumstances, there are two potential mechanisms of nonresponsiveness: (1) clonal exhaustion/deletion and (2) immune indifference. The kinetics of the migratory antigen leading on average to acute immune reactivity or to immune indifference at one extreme and exhaustion/deletion at the other are influenced by dose, timing, route, and localization of the migratory antigen. Although the relation between infectious and transplantation immunity is complicated by the presence of a double immune reaction after transplantation (host-versus-graft and graft-versus-host) and the additional factor of immunosuppression, the two mechanisms of acquired tolerance and the rules by which they operate are fundamentally the same.

This concept exposes the meaning of acquired immunologic tolerance as first produced in a transplant setting 44 years ago by Billingham, Brent, and Medawar, and it relates such tolerance to the "allograft acceptance" that we observe daily in practice. The enigmatic pattern of immunologic confrontation and resolution seen in organ recipients was explained by responses of co-existing donor and recipient immune cells, each to the other, causing reciprocal clonal expansion, followed by peripheral clonal deletion.[1,3] An additional role of immune indifference was suggested by the replacement of donor by recipient leukocytes in the transplanted organ (rendering the graft less antigenic) and by ubiquitous distribution of the migratory donor leukocytes in the skin, host parenchymal organs, and other nonlymphoid areas where they may be sequestered from cytotoxic T lymphocytes and neutralizing antibodies.

Increasingly potent baseline immune suppressants have allowed these changes in the host/graft relationship to be engineered more efficiently and safely. This has been reflected in a stepwise improvement of patient and graft survival—from zero to feasible but unsatisfactory with azathioprine, striking improvement with the advent of cyclosporine A (CyA), and another dramatic one with FK 506. These improvements, made possible with better drugs, have been observed with all whole organ transplantation and with bone marrow transplantation. Because FK 506 can efficiently rescue the vast majority of CyA failures, the availability of FK 506 has systematically upgraded program performance even when it has not been used from the outset as the baseline immunosuppressant.[4]

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From the Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address reprint requests to Dr Thomas E. Starzl, Department of Surgery, University of Pittsburgh, 3601 Fifth Avenue, 5C Falk Clinic, Pittsburgh, PA 15213.

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