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HLA matching and the point system

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The present format for kidney distribution begs for reform, as Halasz has said (1). What is in place now is a profound distortion of the so-called "Starzl point system" (2) which was based on three principles of which the most pervasive operationally was regional primacy; the two others were the right of the responsible physician to exercise medical judgement in any given case, and the right of the recipient to choose his/her health care center and physician. Points toward selection as a recipient were given for time waiting, antigen matching, antibody analyses, medical urgency, and logistic practicality.

The original point system (2) ensured that, with the exception of those organs with 6-antigen matches, the kidneys would be used for the population from which they came (in other words locally). Lesser degrees of matching gave points, but because of the regional primacy a higher total matching score (short of perfect) did not catapult a kidney from its procurement area. The consequence was that waiting time was far more important and therefore more equitable than the 21% of potential points cited by Halasz. Rather than increasing the value of waiting to 31% as Halasz believes, the revised rules of 1989 which increased the credit for matching seriously eroded the value of waiting (3); we agree with him that the most recent change has all but eliminated credit for waiting time. In addition, the rule changes of 1989 imposed a bias against minority (particularly black) populations (3) that has become even more naked since then with the subsequent increased emphasis on HLA matching. We do not see merit in Halasz's proposal of adding other prejudicial factors: age, presensitization, previous transplantation, or specific diseases.

In fairness to Halasz, he concedes, at least in part, that he is recommending a restoration of the original point system. However, far from "failing to update the system" as Halasz has asserted, the problem has been over-modification. From the beginning, the use of local and regional variances and more importantly the decisions taken by the UNOS Board of Directors have practically elimin-

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ated all factors except HLA matching. The original point system acknowledged tacitly that the HLA matching had inconsequential significance unless it was perfect; therefore it sharply restricted the use of matching beyond HLA identity, and gave modest but significant credit for presensitization which would be amplified to the extent that mismatching really was a factor in causing or perpetuating sensitization (2).

The increasing emphasis on tissue matching that wrecked the point system was the product of policy discussions at the UNOS Board of Directors and at lower levels of organization. These degenerated into debating and lobbying contests between the advocates of tissue matching (who for the most part were those managing or supplying the testing laboratories) and the transplant surgeons, who had realized for a long time that tissue matching did not accurately predict the outcome of kidney transplantation (4–6) or for that matter the transplantation of any other organ (7, 8). Perhaps the remonstrances of transplant surgeons went unheeded because they lacked the passion generated by a direct vested interest.

More likely, many could not understand why HLA, a genetically controlled and therefore presumably immutable biologic system, should not predict the outcome. Certainly, a correlation was expected by the senior author (TES) when in 1964 he began with Terasaki the first prospective tissue matching trials in the world at the University of Colorado (9, 10). After 5 years of effort and analysis, no advantage could be demonstrated except when there was a perfect match (11). This experience has been repeated and reported hundreds of times, invariably followed by a riposte from a multicenter registry, to the bewilderment of those in the contributing programs who cannot in their individual experience identify the favorable trends from matching that are being claimed from the data pool to which they have sent their results. In the meanwhile, even proponents of matching have delivered hammer blows to its credibility, such as Terasaki's report at the 1992 Transplantation Society Congress that the use of one-haplotype matched (parent to offspring) kidney allografts gave no better results than those with kidneys from completely mismatched living non-relatives (12). This meant that the frequently cited difference in outcome between mismatched cadaver and parent to offspring transplantation (3-antigen matched) kidneys reflected primarily the preservation injury of the former versus the latter kidneys. When the physiologic quality of the mismatched unrelated organ was equivalent to that of the related kidney, there was no matching advantage.

The most nagging intellectual concern to kidney transplant surgeons and others who wanted to, but could not, see an influence of HLA matching in their own practice was the knowledge that a perfect or near perfect match was universally conceded to be a supreme determinant of success with bone marrow transplantation (13, 14). It was hard to see why HLA matching was so critical in the bone marrow, but did not apply equally for whole organ transplantation field. Now, a plausible explanation for this dichotomy has been provided with the recent discovery that leukocytes migrate perioperatively from transplanted whole organs to widely distributed recipient tissues where they can be identified many years later (15–18).

The leukocytes leaving the graft are replaced by recipient cells moving in the opposite direction. The events under immunosuppression leading eventually to the chimerism in the graft as well as ubiquitously in its recipient imply that there is a mutual engagement, activation, and ultimately clonal "silencing" of the immunocytes of both parties. The cell mixture can be seen as an *in vivo* two-way mixed lymphocyte reaction (MLR) (Fig. 1). Such a cell interaction cannot transpire after bone marrow transplantation because the conditioning cytoablation of the recipient with irradiation or myelotoxic drugs eliminates host hematopoietic cells. Thus, the conditions in the bone marrow patient who can stimulate but not respond immunologically resemble a one-way MLR.

The cells that persist long after the exchange between an organ allograft and the tissues of the recipient have the appearance of the dendritic leukocyte (antigen-presenting cells) shown by Steinman and Cohn (19, 20) to be of bone marrow origin. Although highly antigenic under normal conditions, these leukocytes appear to play a paradoxical role in the "acceptance" of allo- and xenografts under immunosuppression and to participate in the first step of the induction of the donor-specific non-reactivity that often has been noted in long surviving whole organ recipients (15–18). We have asked if the elusive "tolerance producing" veto and suppressor cells are the products of these interactions and further if they are altered dendritic cells (18) rather than changed T cells or other lineages as usually has been assumed.

In the delivery of the antigenic signal to the T cell, the dendritic cell (the most prominent chimeric cell in the patient tissues by morphologic criteria) is critical because it can modify the expression of cell interaction molecules, major histocompatibility complex (MHC) molecules, and adhesion molecules – all of which modify how antigen signals are heeded by T cells (20). The mechanism by which mixed chimerism causes co-existing cell

populations to view each other in a progressively revised light is unknown, but that this occurs has been confirmed many times since it was first clearly described in bone marrow transplant models by Slavin and Strober (21) and even more clearly by Ildstad and Sachs (22).

The ultimate non-reactivity which may or may not require continued immunosuppression in the circumstances of whole organ transplantation (15–18) is not only of the recipient immunocytes in respect to the donor antigens, but also the other way round as exemplified by the rarity of graft versus host disease (GvHD) in chimeric recipients of intestinal (23) and liver grafts (17) that contain a dense migratory leukocyte component. It is clear that the requisite seeding and intermingling of chimeric cells begin immediately after revascularization (17).

With each additional day under the protective umbrella of effective immunosuppression, a corollary expectation is that the responsible donor-recipient interactions, that are governed initially by rules of histocompatibility, are influenced by a kind of "mutual natural immunosuppression". Here, each further level of incompatibility provokes countervailing increases in the variably cancelling donor versus recipient and recipient versus donor cell reactivity. If the initial storm can be weathered, as has been increasingly possible with modern immunosuppression, the anticipated typing effect dwindles.

In the aftermath, the number of peripheralized donor cells is small compared to the recipient leukocyte population but the sustained effect may be large as has been suggested in another context by the apparent absorption of storage deposits in chimeric liver recipients with inborn errors of metabolism caused by pancellular enzyme deficiencies (24). The metabolic amelioration by presumed transmission of enzymes in these cases from a small normal cell population to a large abnormal one raises intriguing questions about a potential cell to cell effect of other molecules directly involved in immunologic processes including tolerance induction.

It has been 27 years since the first prospective trials of HLA matching in kidney transplantation were begun (9) with the logical assumption that this kind of donor-recipient pairing would be a definitive way of improving the results. The power of expectation was so great that it has not been shaken in those doing the testing procedures in spite of the fact that thousands of conflicting reports have not settled the issue beyond a consensus that there is an advantage with the uncommon perfect HLA match (25). Matching under all other circumstances has been thought by many to have little or no merit and to have become an instrument of social injustice (3, 26).

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