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Matching and the Black Recipient

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WE WILL TRY to show how new insight into the mechanism of graft acceptance makes possible the reexamination of the UNOS policy of cadaver kidney allocation primarily by tissue matching criteria. Because matching is only marginally relevant to outcome, the present practices are prejudicial to the minority recipients of this country without a quantum gain in efficient organ use.

A successful transplant was long envisioned as an alien patch in a homogeneous hostile sea. This changed for the liver in 1969 when karyotyping studies in human female recipients of male hepatic allografts showed that the entire macrophage system, including the Kupffer cells, was replaced with recipient female cells within 100 days.[1,2] This graft chimerism was assumed to be a special feature of the liver for more than 20 years. The illusion of the liver's uniqueness was dispelled in 1991 with the demonstration that transplanted intestines in rats[3] and humans[4] became permanently chimeric within a few weeks; the same findings were soon verified in other transplanted organs.

Between 1991 and now, it was discovered what happened to the donor leukocytes replaced in the liver, intestinal, and other grafts. A combination of clinical and experimental observations (summarized in ref 5) showed that these donor cells leave the graft within minutes and pass into the lymphoid organs including the thymus. Under effective immunosuppression in rats (and probably somewhat later in humans), they disperse ubiquitously after 2 to 4 weeks and thereafter can be found in the heart, skin, and elsewhere.

With organs vascularized by surgical anastomosis, the primary cell migration is vascular, with prompt secondary inclusion of the lymphatic circulation. Multiple lineages of chimeric cells home to areas of lymphoid organs where syngeneic cells of the same lineages normally traffic.[6] For example, in the thymus, macrophages and dendritic cells show up in the medulla with T and B cells in the follicles. At first, the thymic cortex is donor cell free. In the lymph nodes, B cells are home to follicles, T cells to the T-lymphocyte-rich paracortex, and macrophages and dendritic cells to both medulla and paracortex. The spleen traffic conforms to the substructure of the periarterial sheath anatomy. After the cells break out of the lymphoid organs, they spread ubiquitously and, in human cases, can be found 20 and 30 years later in the skin, lymph nodes, and elsewhere.

Under immunosuppression, these events apparently lead to a body-wide mutual engagement, activation, and ultimately clonal "silencing" of both donor and recipient immunocytes.[5,7] These cell interactions are thought to play a crucial role in the "acceptance" of allo- and xenografts under immunosuppression and to participate in the first step of the induction of donor specific nonreactivity. The nonreactivity which resembles the "infectious" tolerance described in a recent *Science* article by Waldmann[8] also develops the other way round, explaining the rarity of graft-versus-host disease (GVHD) in human recipients of both intestinal and liver grafts that contain a dense migratory leukocyte component.

Systemic chimerism has been most extensively studied after liver transplantation.[9] It was demonstrated in all 25 liver recipients studied in 1992, 2 to 22 years after liver transplantation, either by finding donor cells in peripheral tissue with immunostaining by donor-specific HLA antibodies or by identifying donor DNA by polymerase chain reaction (PCR); and in nine female recipients of male livers by the presence of the Y chromosome in these tissues with cytostaining or PCR technologies.

Relevant to today's discussion, the same systemic chimerism was demonstrated in five patients studied after they had borne their continuously well-functioning kidney transplants for nearly 30 years posttransplantation.[10] All were HLA *mis*matched and thus could be studied (along with their donors) by finding the HLA alleles in peripheral tissues with immunostaining or PCR. Viable donor cells that appeared to be dendritic cells were found in the lymph nodes and skin of all of these kidney recipients and then confirmed with PCR.

Under the conditions of clinical whole organ transplantation, we have postulated and obtained evidence of cellular interactions (graft-versus-host and host-versus-graft) that we have called mutual natural immunosuppression. These are envisioned as occurring on a sliding scale in which each further level of histo*in*compatibility provokes countervailing increases in the initial immune response. This initial response is genetically controlled. However, if the acute storm can be weathered long enough to allow a rapprochement under the protective umbrella of modern day immunosuppression, the anticipated typing effect rapidly dwindles. We think that this explains the poor correlation of tissue matching with outcome after all kinds of

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whole organ cadaver transplantation, short of a perfect match.[5,7,9]

As to matching, it has been 27 years since the first prospective trials of HLA matching in kidney transplantation were begun by our team at the University of Colorado in collaboration with Dr Paul Terasaki of UCLA.[11] The logical assumption was made that this kind of donor–recipient pairing would be a definitive way of improving the results. The anticipated results were obtained with perfectly matched siblings, but not with other donor–recipient pairings.[12]

However, the power of anticipation that the same thing would apply in unrelated cases with lesser degrees of matching has been so great that it has not been shaken, in spite of the fact that thousands of conflicting reports have not allowed this question to come to scientific closure. A matching effect either has not been found or even in the most optimistically presented large collections has been confined to a few percentage points mounted on the successes without matching that have become greater and greater over the years.

Matching as a guide for organ deployment has been thought by many to endow little or no advantage to the cadaveric-kidney recipient except when there is a perfect match and to have become an instrument of social injustice, specifically affecting the black patient whose chances of obtaining a good match and therefore a kidney are diminished.[13,14] Armed with the paradigm shift in understanding of matching that derives from the mechanisms we have described, the time has come to address this issue with a different approach than the usual fiery debate between those lined up on one side or the other side of the matching issue.

There is more at stake than matching per se. The naturally occurring postoperative cell migration and repopulation responsible for graft acceptance can be augmented perioperatively by infusion of donor bone marrow, blood (donor specific transfusion), and presumably other donor leukocyte sources including the spleen. This could build up the conditions for leukocyte-poor organs (like the kidney and heart) to the immunologic advantage enjoyed by the tolerogenic liver.[5,7,9,10] It is ironic that the present HLA-dominated UNOS distribution scheme with its quasi-legal status, emphasis on matching, and necessity for kidney transport is the single greatest logistic impediment to the exploitation of this next and much needed phase of development.

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