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PRESIDENTIAL ADDRESS

Cell Migration and Chimerism—A Unifying Concept in Transplantation—With Particular Reference to HLA Matching and Tolerance Induction

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WE recently reported that the acceptance of whole-organ transplants connotes (and requires) a special kind of mixed chimerism involving an exchange between organ and recipient of lymphodendritic leukocytes (Fig 1).¹ The consequence in five of five patients studied 27 to 29½ years after kidney transplantation from HLA-mismatched donors was the diffuse presence of donor dendritic cells in the lymph nodes and skin of the recipient.² Chronically surviving liver recipients have even more prominent evidence of systemic and graft chimerism,^{1,3} which can be shown with immunocytochemical techniques and confirmed with polymerase chain reaction (PCR) technology. Chimerism has been particularly easy to study after intestinal transplantation.^{4,5}

With the thesis that this cell migration, repopulation, and consequent chimerism is the basis of graft acceptance, no matter what the organ transplanted,¹ we are able to reexamine some controversies in transplantation immunology, including why HLA tissue matching to govern the distribution of cadaveric organs has been so nonpredictive of outcome. To understand these controversies, we must turn back the pages 50 years, when Peter Medawar planted the seed of our specialty.

FOUNDATION OF TRANSPLANTATION

If rejection was an immunologic response, as Medawar claimed,⁶ what could be more logical in preventing it than to weaken the immune system? By 1951, Medawar (with Billingham and Krohn)⁷ and the American Morgan⁸ had taken this crucial step and had shown that skin graft survival was prolonged with cortisone acetate and adrenocorticotrophic hormone, the first immunosuppressive drugs. The year before, Dempster of Hammersmith showed mitigation of skin graft rejection with total body irradiation.⁹

These were seemingly small steps, but then Billingham, Brent, and Medawar¹⁰ raised expectations to a new level by showing the possibility of acquiring immunologic tolerance, albeit only under the special circumstance of inoculation of immunocompetent adult spleen cells into fetal and perinatal mice. Main and Prehn¹¹ were able to mimic these conditions of ontogenesis in adult mice using supralethal total body irradiation and bone marrow alloconstitution. When the reconstituted mice were shown to be tolerant to

donor strain skin, the clinical possibility of creating radiation bone marrow chimeras as a means to the end of solid organ transplantation seemed obvious. These hopes were promptly dashed when the concept of graft-versus-host disease (GVHD) and runt disease was delineated by Billingham and Brent.¹²

However what was not clearly recognized then or later was that these whole-animal models and the subsequently exploited F₁ hybrid model were almost artifacts in that the interactions of the two-way cell migration and repopulation shown in Fig 1 were precluded (1) by the immature state of one party (the Billingham, Brent, Medawar model), (2) by the cytoablation used by Main and Prehn (and later bone marrow transplanters), or (3) by genetic manipulation (the F₁ hybrid model). These were whole animal analogues of the one-way, mixed-lymphocyte reaction (MLR) introduced much later by Bain, Vas, and Lowenstein et al¹³ and Bach and Hirschhorn.¹⁴

The precision of the one-way systems allowed easy interpretation of the results and invariably showed an almost perfect correlation between histocompatibility and the immune reaction of the target lymphocytes, whether these were in vitro or in vivo. Now that we know about cell migration and repopulation, it seems likely that the relevant in vitro (or surrogate) model of clinical transplantation for at least some purposes should be the two-way MLR, in which the effect of two cell populations—each on the other—can be studied.

DIVISION OF THE FIELD

Of course, this is hindsight 33 years later. Between 1959 and 1963—and without really knowing why—the intellectual root that came from Medawar's seed divided into two branches that soon looked like separate trees (Fig 2). The differences between the branches actually reflected divergent therapeutic dogmas. The bone marrow tree with its precondition of cytoablation mimicked the Billingham,

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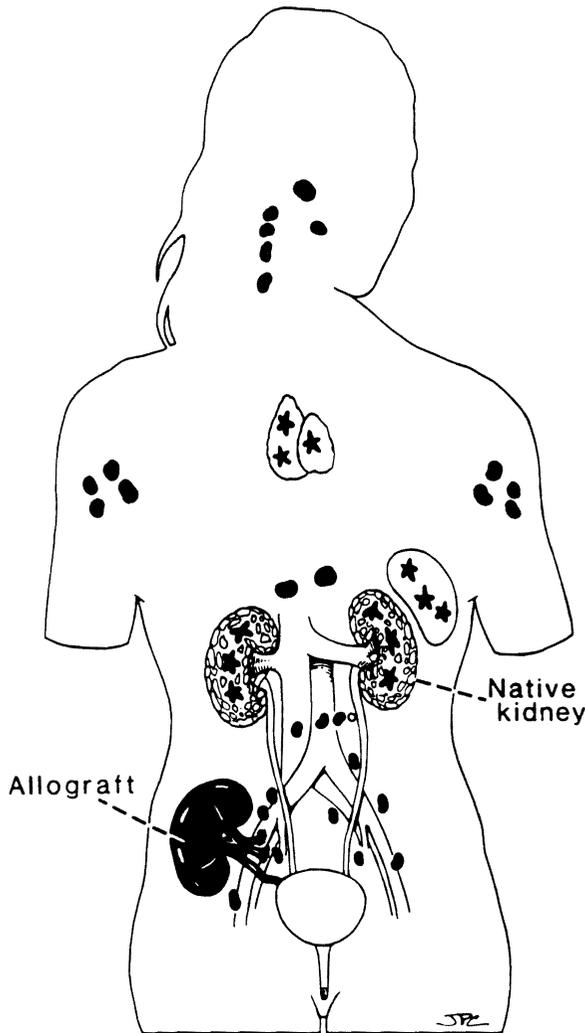


Fig 1. Systemic and graft chimerism after kidney transplantation.

Brent, and Medawar model and was the in vivo version of a one-way MLR. HLA matching was crucial. Engraftment in a drug-free state (called tolerance) was a realizable objective with perfect matching, although this was not achieved clinically until 1968.^{15,16} However, even with MHC compatibility, GVHD was a constant threat.

The reason for the virulence of GVHD with an HLA mismatch was the complete removal of a counterweight to the transplanted immunocytes, as shown in Fig 3 in which each of the six antigens (two each at the A, B, and D loci) has been given equal importance. With perfect matching, immune modulation usually could control non-MHC reactions responsible for GVHD and/or rejection and keep the donor–recipient immunologic teeter-totter in balance. This was not possible with significantly mismatched donors.

The whole-organ transplanters who had broken ranks with their bone marrow colleagues (Fig 2) empirically developed long-term immunosuppression with which suc-

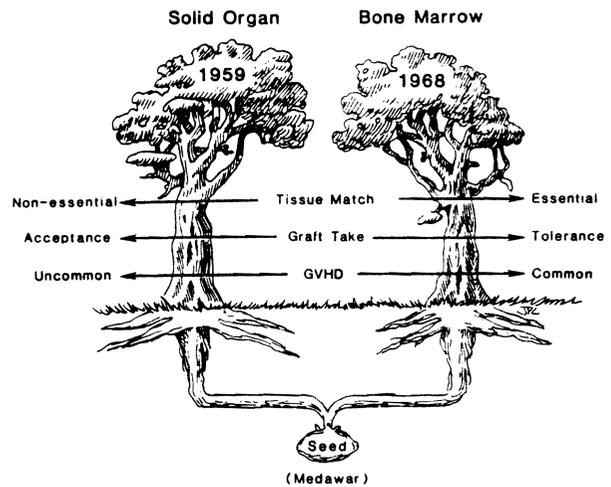


Fig 2. Division of transplantation into whole-organ and bone marrow camps.

cess (called graft acceptance, not tolerance) did not depend on matching and could be accomplished without GVHD, even after the transplantation of lymphoid-rich organs such as the intestine and liver.^{17,18}

The explanation for the GVHD resistance with whole organs is envisioned as the interaction of cells coming out from the allograft with the immunocytes of the recipient (a two-way MLR) (Fig 4). However, if this whole-organ

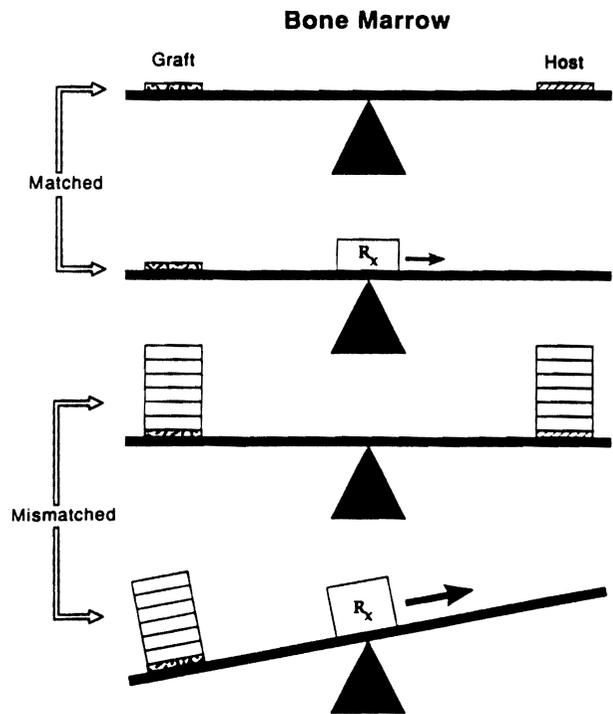


Fig 3. In vivo one-way MLR with recipient cytoablation or with the F₁ hybrid experimental model.

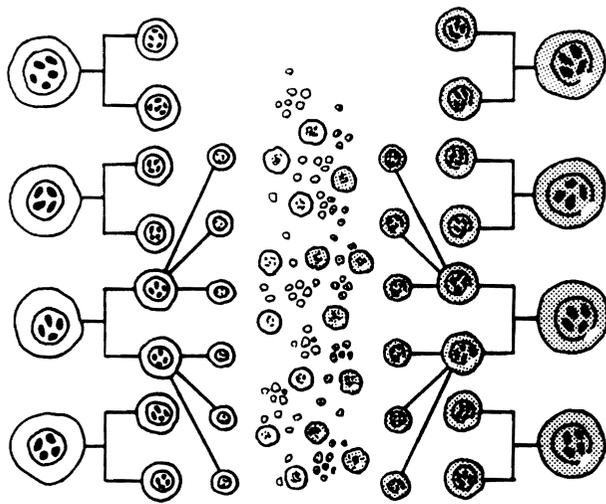


Fig 4. Donor–recipient cell interaction with two-way MLR in vitro or in vivo.

system is immunologically unbalanced by cytoablation or, as in the cross-back F₁ hybrid model, used in the classical intestinal transplant studies of Monchik and Russell,¹⁹ a lymphoid-rich graft, such as the intestine, will eat the recipient alive with an uncontrolled GVHD (Fig 5).

With bone marrow transplantation also, avoidance of GVHD when the recipient system is left at least partially intact was recognized (and strongly emphasized) by Slavin and Strober in the 1970s,²⁰ and demonstrated even more clearly in the brilliant studies of Ildstad and Sachs,²¹ who concocted various mixtures of donor and recipient bone marrow cells ex vivo and then systematically created mixed allogeneic chimeras by infusing the mixtures into cytoablated recipients who did not develop GVHD.

DILUTION OF HISTOCOMPATIBILITY

Of course, the fact that mixed chimerism interdicts GVHD is only half the story. The other half is that the donor–

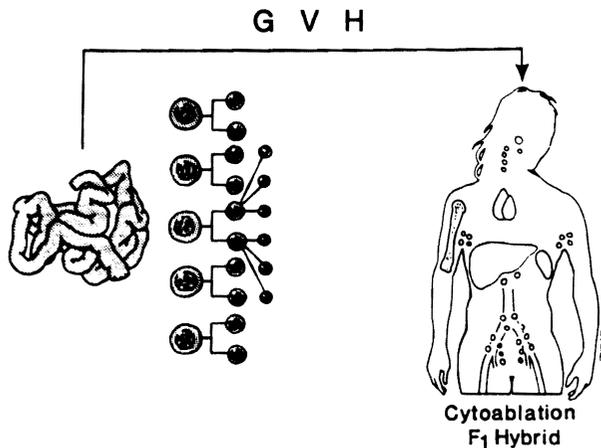


Fig 5. Inevitability of GVHD with unbalanced system.

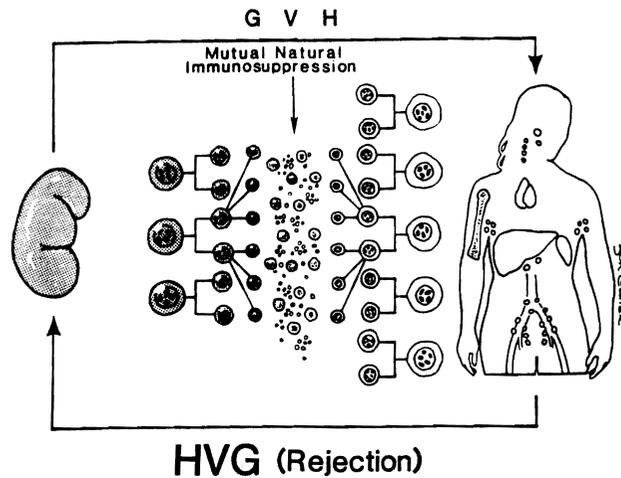


Fig 6. Natural imbalance between the lymphodendritic poor kidney and the recipient.

recipient cell interaction (which we have called mutual natural immunosuppression) also mitigates the host-versus-graft reaction (rejection). In Fig 6, we have depicted a kidney with its relatively small leukocyte army. As was recently proved in recipients examined after they had borne transplanted kidneys for nearly 30 years,² remnants of this army remain identifiable in recipient tissues for the lifetime of the graft.^{1,2} The details of this donor–recipient rapprochement are not known, but it seems clear that even organs with a poor lymphoreticular constituency have enough dendritic cells to induce for themselves the donor-specific nonreactivity that is called tolerance.

This was demonstrated in our long-surviving kidney recipients² and in studies reported from Stanford by Strober et al²² in patients treated with total lymphoid irradiation and a short course of antilymphocyte globulin. The donor–recipient interactions are envisioned as occurring on a sliding scale in which each further level of histoincompatibility provokes countervailing although not equal increases in the mutually cancelling donor-versus-recipient and recipient-versus-donor cell reactivity (Fig 7). Case by case individualization of immunosuppression for variable periods of time, or often permanently, is required to affect a harmonious balance between the cell systems.

With this concept, it becomes possible to understand why Terasaki²³ and others have shown such a small advantage even for six-antigen–matched cadaver kidney allografts and essentially none for lesser degrees of matching. Most importantly, it becomes possible to understand why so many recipients of unmatched kidneys do well even as debates rage about a few percentage points that may be gained or lost by matching or failure to do so. For livers, the strange reports from Cambridge²⁴ and Pittsburgh²⁵ become comprehensible that have shown an inverse relation between tissue matching and survival of liver recipients, but again with a matching influence that does not exceed a few percentage points.

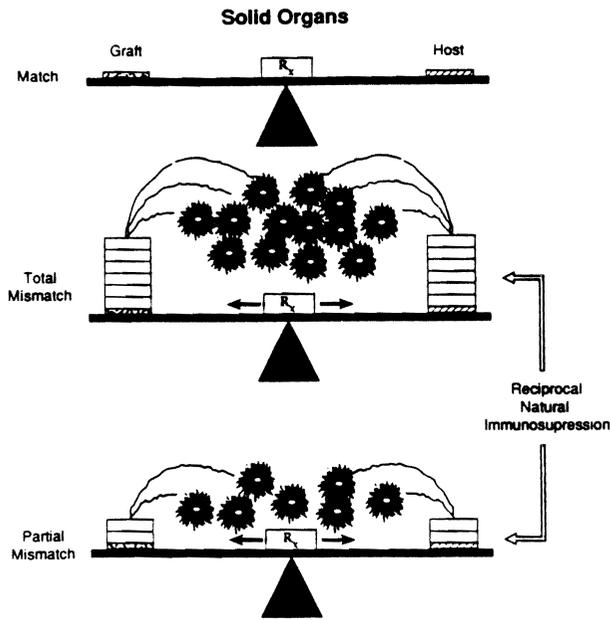


Fig 7. Cancelling of histocompatibility matching effect by donor-recipient cell interaction shown in Figs 4 and 6.

AUGMENTING TOLEROGENICITY

It seems obvious that the crucial variable distinguishing one organ from another is the lymphodendritic (not the parenchymal) component of whole-organ grafts, and that these leukocytes can be tolerogenic as well as immunogenic when effective immunosuppression is given. Be-

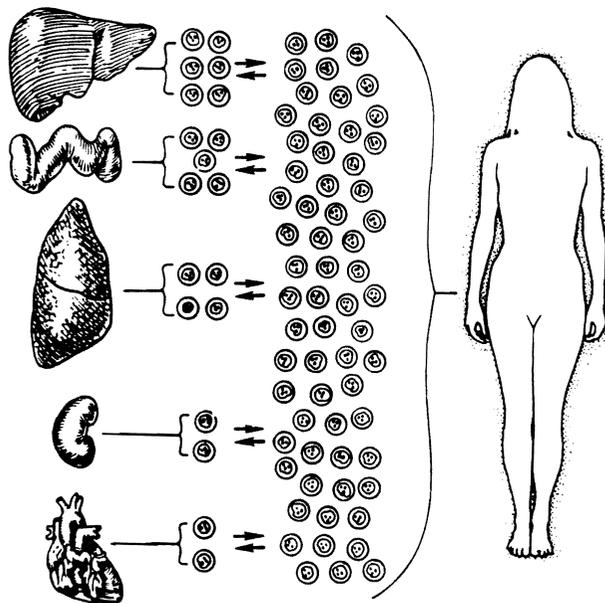


Fig 8. Rank order tolerogenicity of major organs correlates with lymphodendritic constituency.

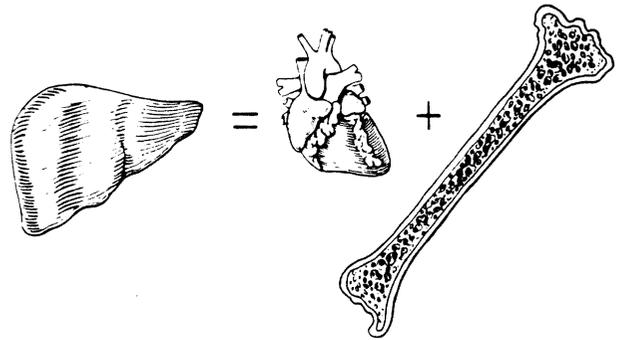


Fig 9. Augmentation of tolerogenic cells for "underprivileged" organs such as heart and kidney by concomitant bone marrow infusion.

cause of its dense constituency of these cells, the liver is high on the favorable list of tolerogenicity with the lung and intestine following and the heart and kidney bringing up the rear (Fig 8). It is self-evident that the underprivileged kidney and heart could be brought to the same level of tolerogenicity advantage as the liver by the perioperative infusion of lymphoreticular cells obtained from bone marrow of the organ donor (Fig 9) or possibly from the spleen.

Now the cycle is complete because this was the starting point for Billingham, Brent, and Medawar,¹⁰ and then Main and Prehn.¹¹ It would be particularly unjust not to mention that such cell supplementation with bone marrow for whole-organ transplantation is what our ex-President Monaco has been advocating for more than 20 years,²⁶ leading to a major clinical trial by Barber and Diethelm in Alabama.²⁷

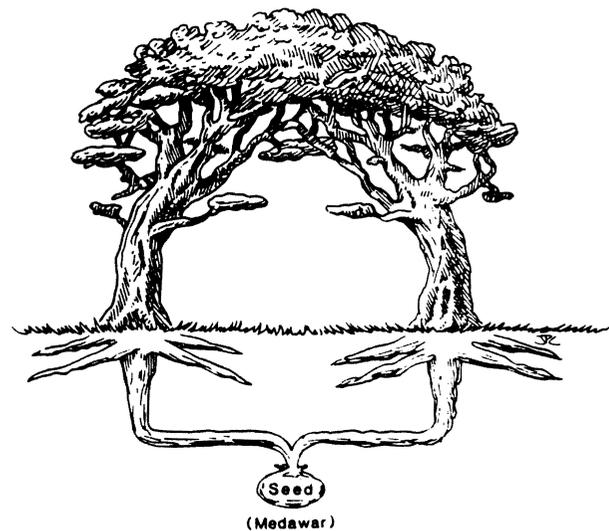


Fig 10. Reconciliation of whole-organ and cell transplanters.

CONCLUSIONS

With the cell migration concept, the framework given to us by Billingham, Brent, and Medawar is considerably expanded and provides immediate clinical applications, such as a better understanding of why HLA matching is not more discriminating for whole organ allocation, and how to induce tolerance. This means a reunification is inevitable of the long-separated interests and ideologies of bone marrow and solid organ transplantation (Fig 10). These are the directions that our Society will be taking. Medawar would smile if he could come back for just one day to hear this. At least we still can report these things directly to our friends, Billingham and Brent.

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