The HLA System: Basic Biology and Clinical Applications

Editor

Scott Murphy, MD

American Association of Blood Banks
Bethesda, Maryland
1999
ALL OF US HAVE heroes. Paul Terasaki is one of mine, not only because of what he has achieved in life, but because of how he has done it. More than a half century ago, the Terasaki boy was peering out through the fence of a concentration camp where he and other loyal Americans of Japanese ancestry had been unjustly imprisoned during World War II. Yet, from this unfriendly soil grew the man who today is the recipient of the Emily Cooley Memorial Award of the American Association of Blood Banks.

The Terasaki Record

The list of Terasaki's innovative contributions is extensive (Table 3-1). It is noteworthy that these were all linked in one way or other to the microcytotoxicity test, with which antibody reactivity against human lymphocytes and other cells can be detected.\textsuperscript{1} The observations and clinical applications made possible with this technology elevated Terasaki to a leadership position in multiple areas that were essential for the orderly advance of organ and marrow transplantation.

His accomplishments include: 1) development of the cytotoxic crossmatch\textsuperscript{2} and panel reactive antibody tests\textsuperscript{3}
### Table 3-1. Paul Terasaki Landmarks

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microdroplet assay for human serum cytotoxins</td>
<td>1964</td>
</tr>
<tr>
<td>Cytotoxic crossmatch for transplantation</td>
<td>1965</td>
</tr>
<tr>
<td>Panel reactive antibody for detecting presensitization</td>
<td>1971</td>
</tr>
<tr>
<td>Discovery of new HLA antigens</td>
<td>1965-present</td>
</tr>
<tr>
<td>Discovery of HLA and disease associations</td>
<td>1972-present</td>
</tr>
<tr>
<td>First prospective trial in transplantation of HLA matching</td>
<td>1966</td>
</tr>
<tr>
<td>Collins/Terasaki solution for organ preservation</td>
<td>1969</td>
</tr>
<tr>
<td>Epidemiologic investigation of survival factors with transplantation</td>
<td>1968-present</td>
</tr>
<tr>
<td>Guidelines for organ sharing</td>
<td>1969-present</td>
</tr>
<tr>
<td>The blood transfusion effect on allograft survival</td>
<td>1973</td>
</tr>
<tr>
<td>Discovery of natural killer cells</td>
<td>1973</td>
</tr>
</tbody>
</table>

used universally today to detect recipient presensitization to donor tissues, 2) the detection of new HLA antigens and their disease associations, 3) the first use of tissue (HLA) matching as the basis of donor selection for tissue and organ transplantation, 4) efficient techniques of organ preservation (beginning with the Collins/Terasaki solution) that allowed time for HLA typing, 5) epidemiologic investigation of the effect of biologic variables and different therapies on transplantation outcome, 6) discovery of the beneficial effect of blood transfusions on kidney allograft survival, and 7) contributions to network development for organ sharing. The ripple effects of this work have, of course, extended into blood bank practices and clinical medicine far beyond the boundaries of transplantation, and have inspired numerous initiatives.

Some of Terasaki's discoveries have not received due credit, in part because of his disinterest in pursuing priority claims. For the record, however, it was he and his associates who discovered the presence of lymphocytes in normal nonimmunized persons that killed a wide range of cultured tumor cells, but were not tumor-specific. These were the natural killer (NK) cells more completely delineated and pop-
ularized by workers at the American National Cancer Institute,11-13 in Sweden,14,15 and elsewhere. In addition, Terasaki's recognition of hyperacute rejection by preformed host antigraft cytotoxins and his introduction of the crossmatch test to prevent this complication1 have often been attributed to Kissmeyer-Nielsen of Denmark.16

An American Parallel to the Lysenko Affair

In contrast to his indifference to personal credit, Terasaki's integrity in promptly and accurately presenting clinically relevant data is legendary. This scrupulousness led to events not unlike those of the Lysenko Affair. Many readers will recall Professor Trofim D. Lysenko, a geneticist who controlled research resources in the Soviet Union before and after World War II, aided by personal support from Josef Stalin.17

From this administrative power base, Lysenko was able to stifle opposition to his views on genetics which, as it turned out, were naive and wrong. Lysenko eventually was fired in 1964 after efforts to improve farm crops with his methods came to a disastrous end.18 However, his reign of scientific terror had eliminated reinforcement of the genetics talent pool in the Soviet Union for more than 20 years, with an aftermath that remains a national tragedy.19

The analogy to Terasaki's difficulties is readily apparent. Terasaki's "offense," like that of scientists who were crushed by Lysenko, was to make observations that did not conform to bureaucratic expectations. His peers (and Terasaki himself) had predicted that the development of clinical transplantation would hinge on identifying gradations of the HLA match between the donor and recipient.

The critical need for HLA matching in marrow transplantation was promptly and unequivocally verified. Infusion of anything less than perfectly or near perfectly matched donor marrow resulted in a high rate of graft-vs-host disease (GVHD) or else rejection of the graft. This was the explicit message in the report of the first successful human marrow transplantation by Meuwissen, Gatti, Terasaki, Hong, and Good entitled "Treatment of lymphopenic hypogammaglobulinemia and bone-marrow aplasia by transplantation of
allogeneic marrow: Crucial role of histocompatibility matching.\textsuperscript{20}

Paradoxically, tissue matching proved not to be critical for successful transplantation of the kidney or any other organ. Terasaki documented this, first in cases of live donor kidney transplantation\textsuperscript{21,22} and subsequently in cases of cadaver kidney transplantation.\textsuperscript{23} In both studies, the degree of HLA match had little influence on clinical outcome unless the match was perfect or near perfect (i.e., a zero-antigen mismatch). This was ultimately verified with other kinds of organ transplantation.

The seemingly opposite conclusions about the crucial role of HLA matching for marrow but not for organ transplantation were both correct. Very little has been added to Terasaki's controversial kidney transplant observations of three decades ago, as illustrated by two more recent publications. One report describes a multicenter study of kidney transplantation in which equivalent results were obtained with transplantation of kidneys from randomly matched live unrelated donors (e.g., spouses) and kidneys from one haplotype matched (e.g., parental) related donors. In both related and unrelated donor cases, there was no demonstrable survival advantage unless there was a zero-antigen mismatch.\textsuperscript{24}

The other report describes a study of more than 31,000 first-time recipients of cadaver kidneys entered into the United Network for Organ Sharing (UNOS) registry between 1991 and 1995.\textsuperscript{25} Although optimal matches had been sought prospectively, zero-antigen mismatched kidneys had been found for only about 7% of the patients; this small cohort had a significant survival advantage. It was noteworthy that the survival curves of the HLA-incompatible cadaver kidneys were surprisingly close to the zero-antigen mismatched organs. Approximately 85% of the patients received kidneys mismatched for two to five antigens. In this mismatch range, the 1- and 3-year graft survival was bracketed within less than a 5% spectrum. Half-life projections of kidneys surviving 1 year were in the narrow spread of 9-11 years (Fig 3-1, left).\textsuperscript{25} An independent analysis of 1780 cadaver cases showed the same lack of a stepwise matching effect, although there was an equal survival advantage for zero-antigen mis-
matched kidneys and for kidneys mismatched for a single HLA antigen (Fig 3-1, right).25

The foregoing results were remarkably similar to those published by Terasaki between 1969 and 1971. Yet, his early reports were treated as a scientific scandal.26-28 The response of the medical establishment was swift and severe. Within a few weeks after he presented his results to the International Transplantation Society at The Hague in September of 1970,22,23 an emergency site visit was made to Terasaki’s laboratory by National Institutes of Health (NIH) authorities and their scientific advisors. In an unprecedented exercise of bureaucratic power, his research contract was canceled, leaving him without financial support.

When he later was proved to have been correct, Terasaki emerged as the father of clinical HLA matching and as an enduring symbol of integrity. Extrapolation of his impeccably documented conclusions about HLA matching for organ transplantation breathed life into the still struggling fields of liver, heart, and lung transplantation where most candidates
could not wait for a well-matched donor. It was a relief to know that the use of randomly matched donors was not going to result in an intolerable penalty.27

**The One-Way Paradigm**

Why was it that tissue typing was not essential for the evolution of clinical organ transplantation, but was a prerequisite for successful marrow transplantation? The answer can be fully understood only by peeling back the layers of history. The dawn of modern transplantation immunology usually is set during World War II, with the demonstration by Peter Medawar (a zoologist) and Thomas Gibson (a plastic surgeon) that rejection is an immune response.28,29

Their research had been stimulated by the proposed use of skin allografts from cadaver donors for the treatment of fire bomb victims during the Battle of Britain. Because allografts were invariably rejected, they were perceived from the beginning as defenseless islands in a hostile recipient sea: ie, the targets of a one-way host-vs-graft (HVG) immune reaction (Fig 3-2, upper left, shown with a kidney). This was the unchallenged paradigm of transplantation immunology for the next half century. It probably remains the mental image of most people today.

This concept was reinforced in 1953 when it was demonstrated in mice by Billingham, Brent, and Medawar that tolerance to allogeneic leukocytes could be acquired. In the original experimental model,30,31 the engraftment of adult spleen or marrow cells depended on the inability of the immature immune system of neonatal mouse recipients to reject the allogeneic cells. Subsequently, an analogous immunologically defenseless state was produced in adult mouse recipients by destroying their immune system with supralethal total body irradiation.32,33 If the donor immune cells engrafted (Fig 3-2, upper right) the recipients in later life could accept skin or other tissues and organs from the original donor strain, but not from other strains.

However, it was soon learned in the mouse experiments,34,35 and later confirmed in large animals and humans, that the hematolymphopoietic graft would turn the tables on the recipient unless there was a perfect or near perfect
histocompatibility match. The clinical result was the dreaded graft-vs-host (GVH) reaction. These observations were interpreted in the same “defenseless island in a hostile sea” context as organ transplantation, but in mirror image (ie. now the graft rejected the host). As with the simplistic view of organ transplantation (Fig 3-2. upper right), this was a conceptual error. Nevertheless, the demonstration that tolerance could be acquired and was associated with donor leukocyte chimerism was a seminal turning point. It ultimately led in a straight line to the clinical field of marrow transplantation.

The second turning point in transplantation immunology occurred in the early 1960s. This was the demonstration that organ allografts could “self-induce” tolerance. If they were trans-
planted under an umbrella of immunosuppression. This discovery galvanized a revolution in clinical organ transplantation. The downside, however, was the erroneous conclusion that engraftment of organs (turning point 2) occurred by different mechanisms than the leukocyte chimerism dependent engraftment of spleen or marrow cells (turning point 1).

The striking disparities between marrow and organ transplantation (Table 3-2) seemed too great to permit any other conclusion. The clinical differences were: 1) dependence on or independence from HLA matching for successful transplantation, 2) risk vs freedom of risk from GVHD, and 3) frequent vs infrequent achievement of drug-free status after transplantation. The semantic distinction between the “tolerance” of marrow transplantation and the “acceptance” of organ grafts reflected the assumption that engraftment involved different mechanisms.

Thus, although the original seed of transplantation was universally conceded to be Medawar’s demonstration that rejection was an immune event, it was thought for many years that the seed had given root to fundamentally unrelated clinical trees (Fig 3-3). As it turned out, all of the differences were explained by cytoablation of the marrow recipient but not of the organ recipient. How this came to be recognized, along with an explanation of Terasaki’s heretical observations about the role of HLA matching for both kinds of transplantation, is the focus of the following sections.

Table 3-2. Differences between Organ and Marrow Transplantation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Organ Transplantation</th>
<th>Marrow Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host cytoablation</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>HLA matching</td>
<td>Not critical</td>
<td>Critical</td>
</tr>
<tr>
<td>Principal complication</td>
<td>Rejection</td>
<td>Graft-vs-host disease</td>
</tr>
<tr>
<td>Immunosuppression-free</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Term for success</td>
<td>Acceptance</td>
<td>Tolerance</td>
</tr>
</tbody>
</table>

*This therapeutic step allows a relatively unopposed graft-vs-host reaction and accounts for the other differences.
The Empirical Development of Organ Transplantation

While clinical marrow transplantation was a logical extension of the neonatal tolerance model, organ transplantation appeared to be disconnected from a rational scientific base. The intellectual handicap notwithstanding, whole organ transplantation was successfully performed in humans nearly 10 years before this was first achieved unequivocally with marrow. Between January 1959 and March 1963, Merrill and Murray in Boston, and then the French teams of Hamburger and Kuss produced six clinical examples of kidney allograft survival exceeding 6 months after pretreating their uremic patients with sublethal total body irradiation, but without infusion of donor marrow (Table 3-3). The first two recipients, whose donors were fraternal twins, survived with good renal function for more than 20 years.
Table 3-3. Kidney Transplant Recipients Surviving ≥ 6 Months as of March 1963

<table>
<thead>
<tr>
<th>Patient</th>
<th>Reference</th>
<th>Surgery Date</th>
<th>Donor</th>
<th>Survival (months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42,46</td>
<td>1-24-59</td>
<td>Frat twin</td>
<td>&gt;50</td>
</tr>
<tr>
<td>2</td>
<td>43,44</td>
<td>6-29-59</td>
<td>Frat twin</td>
<td>&gt;45</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>6-22-60</td>
<td>Unrelated*</td>
<td>18 (Died)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>12-19-60</td>
<td>Mother*</td>
<td>12 (Died)</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>3-12-61</td>
<td>Unrelated*</td>
<td>18 (Died)</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>2-12-62</td>
<td>Cousin*</td>
<td>&gt;13</td>
</tr>
<tr>
<td>7</td>
<td>46,47</td>
<td>4-5-62</td>
<td>Unrelated</td>
<td>10</td>
</tr>
</tbody>
</table>

* The kidneys in patients 1, 2, and 6 functioned for 20.5, 25, and 15 years, respectively. Patient 7 rejected his graft after 17 months and died after return to dialysis.

Pretreatment of the recipient with irradiation was too impractical and dangerous for general use. Consequently, these few successes were exceptions in a sea of failures. However, a seventh kidney recipient (Table 3-3) survived almost 1 year after transplantation: he had been treated from the time of surgery with the 6-mercaptopurine analogue, azathioprine. It had been learned by this time that for more than an occasional success in either dogs or humans, azathioprine needed a partner drug. This proved to be prednisone.

It was known from canine kidney and liver transplant studies at the University of Colorado that prednisone could reverse 90% of the rejections developing under azathioprine. With this information, the clinical kidney transplant program in Denver was begun in the autumn of 1962, combining azathioprine with dose-manageable prednisone. Eight of the first 10 recipients had prolonged kidney allograft survival including two who still bear the longest continuously functioning allografts in the world after more than 36 years.

As had been expected, rejection was regularly reversible. Far more important, the transplanted kidneys appeared to have self-induced variable donor-specific tolerance. Both ob-
Observations were capsulized in the title of the report of this experience: “The reversal of rejection in human renal homografts with subsequent development of homograft tolerance.” The best evidence of tolerance was the diminishing need for maintenance immunosuppression following successful reversal of rejection (Fig 3-4). The nonreactivity was donor-specific enough to allow many patients to go home to an unrestricted environment within a few weeks. Eventually, the tolerance was shown in some patients to be independent of immunosuppression. These same posttransplant events of an immunologic confrontation and resolution were ultimately demonstrated with liver, heart, lung, and pancreas transplantation.

Ten (22%) of the first 46 recipients of living related donor kidneys in the original Colorado series still have functioning original allografts. 35 to nearly 37 years later. Five of the 10 recipients have been drug-free for 6 to 33 years. By October 1995, the cumulative time of these patients off drugs already equaled the time on treatment (Fig 3-5). Four more years have now passed. Although two received HLA-identical allografts, two received one-haplotype mismatched kidneys (second and bottom bars), and one received a completely mismatched kidney from a great aunt (second bar from bottom).

The liver has been the most tolerogenic organ. Among the 42 longest surviving cadaveric liver recipients at the

![Figure 3-4. Historical view of events after successful organ transplantation: rejection, its reversal and the development of donor-specific nonreactivity.](image)
Figure 3-5. Time on immunosuppression and time off treatment as of October 1996, in five patients whose renal allografts had functioned continuously since their transplantation in 1962-63. After 3-1/2 more years, these patients remain drug-free. Data from Starzl et al.42

Figure 3-6. Time on and off immunosuppression of 12 long-term surviving liver recipients who were free of drug treatment in October 1995. Patients 150 and 169 stopped their medication less than 2 years after transplantation because of noncompliance. The others were weaned because of complications of chronic immunosuppression. After 3-1/2 more years, these 12 patients remain drug-free. Data from Starzl et al.44
Universities of Colorado and Pittsburgh, now 18 to 30 years after their transplantation, 20 (nearly half) have been drug-free for 1 to 20 years. For the first 12 recipients to come off drugs, the cumulative time off immunosuppression as of 1996 already had exceeded the time on treatment (Fig 3-6).

These observations showed the feasibility of organ transplantation and defined a formulaic management strategy (Table 3-4) that was applicable to all organs. However, the early loss of both grafts and patients remained so high for another 13 years that cadaver organ transplantation (even of the kidney) remained controversial until the advent of cyclosporine in 1979.\textsuperscript{51-53} Ten years later, further improvements were made possible with the introduction of tacrolimus.\textsuperscript{54-56} Thus, the improvement with transplantation of the kidney, liver, and all other organs has occurred in three distinct drug-defined rather than HLA-defined eras.

The liver graft and patient survival curves shown in Fig 3-7 illustrate the azathioprine-, cyclosporine-, and tacrolimus-based treatment eras. Because retransplantation became increasingly more reliable with the more potent agents, patient survival was better than graft survival. With the advent of tacrolimus, which was the first immunosuppressant to be evaluated primarily with liver transplantation, intestinal transplantation finally became a viable clinical option in the 1990s.\textsuperscript{57}

Table 3-4. Empirical Therapeutic Dogma of Immunosuppression

<table>
<thead>
<tr>
<th>Ingredients of Strategy</th>
<th>Baseline Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline therapy</td>
<td>Azathioprine*</td>
</tr>
<tr>
<td>Secondary adjustments of prednisone dose, or antilymphoid agents\textsuperscript{2}</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Case-to-case trial (and potential error) of weaning</td>
<td>Tacrolimus</td>
</tr>
</tbody>
</table>

* Alone or with prophylactic prednisone. Equivalent results were obtained with cyclophosphamide instead of azathioprine.
1 Initially used for prophylactic "induction."
Figure 3-7. The three eras of orthotopic liver transplantation at the Universities of Colorado (1963-80) and Pittsburgh (1981-1993), defined by azathioprine-, cyclosporine-, and tacrolimus-based immune suppression. Similar but less dramatic stepwise improvement has been seen with all organs. Patient survival was about 10% higher than graft survival in both the cyclosporine (1980-89) and tacrolimus eras (1989-93) because of effective retransplantation, an option that, for all practical purposes, did not exist with azathioprine-based therapy.
The Discovery of Occult Chimerism in Organ Recipients

Despite the diversity of the immunosuppressants, the basic pattern of convalescence shown in Fig 3-4 remained the same with all the drugs and for all transplanted organs. Organ graft acceptance could be achieved with individualized dose adjustments of the increasingly potent drugs, guided by evidence or lack of evidence of rejection (Table 3-4). But what was being accomplished with this strategy?

When the answer came in 1992, it provided an explanation for the enigmatic lack of effect of HLA matching in organ transplantation first documented by Terasaki. Until then, it had been thought that the highly antigenic tissue leukocytes of marrow origin, which are a component of all tissue and organ allografts (Fig 3-2, bottom left and Fig 3-8, left, shown as a bone silhouette), were "the enemy" of engraftment. The assumption was that these "passenger leukocytes" had to be destroyed by the host immune system as a prerequisite for successful organ transplantation with selective sparing of the specialized parenchymal cells (Fig 3-8, right).

![Organs: The One Way Paradigm](image)

Figure 3-8. Conventional view of a successfully transplanted allograft in which the nonparenchymal white cells (passenger leukocytes) are depicted on left as a bone silhouette. These donor cells were assumed to have been destroyed by the host immune system (silhouette absent on right).
In 1992, we asked an obvious question, surprisingly for the first time: had these donor leukocytes really been destroyed, or had they merely migrated into the recipient with survival of their progeny? To obtain the answer, 30 long-term surviving liver and kidney recipients with functioning allografts were restudied 10-30 years after transplantation. In addition to blood samples, open biopsies were obtained of the transplanted organs, the recipient lymph nodes and skin, and when indicated, other host organs (eg, the heart, intestine, and marrow).

Small numbers of donor leukocytes were found in the host peripheral tissues or blood of all 30 patients. The donor leukocyte chimerism, including donor dendritic cells, was demonstrated with immunocytochemical methods, and confirmed with polymerase chain reaction studies. With this information, it was deduced that organ transplantation involved a double immune reaction, which had both an HVG response (rejection) and a covert GVH response (Fig 3-9). Following organ transplantation, the dominant host system usually rejects the graft. However, serious or lethal GVHD is not rare after transplantation of leukocyte-rich organs such as the liver.

Figure 3-9. Contemporaneous HVG and GVH reactions that occur after transplantation. Treatment failure is defined as the inability to control one of the reactions, or sometimes both. Acute reciprocal clonal exhaustion after successful transplantation is maintained subsequently by chimerism-dependent low-grade stimulation of both leukocyte populations that may wax and wane. (Used with permission from Ramsey et al.)
The critical events of allograft acceptance (and tolerance) were postulated to be the early ones, involving the seminal mechanism of "... [widespread] responses of co-existing donor and recipient immune cells, each to the other, causing reciprocal clonal expansion, followed by peripheral clonal deletion." The unusual tolerogenicity of the liver was explained by its large content of leukocytes, but the same mechanisms apply in varying degrees with transplantation of all organized tissues and organs.

By 1998, compelling evidence confirming this concept had accumulated from controlled animal experiments. Organ as well as marrow "acceptance" were related forms of chimerism-dependent acquired tolerance—not fundamentally different from the major histocompatibility complex (MHC)-restricted antigen-specific tolerance induced by noncytopathic microorganisms but made more complex by the presence of the double immune reaction and by the additional factor of immunosuppression. The four interrelated events shown in Fig 3-10 must occur in close temporal prox-

![Diagram](image-url)

**Figure 3-10.** The four events that occur in close temporal proximation when there is successful organ engraftment: above, double acute clonal exhaustion (numbered 1 and 2) and subsequent maintenance clonal exhaustion (3) plus, below, loss of organ immunogenicity due to reduction of the graft's passenger leukocytes (4). (Used with permission from Starzl et al.)
imity for successful organ engraftment: double acute clonal expansion and deletion, maintenance of the waxing and waning clonal exhaustion, and loss of organ immunogenicity as the passenger leukocytes depart from the graft. The only mechanisms required were clonal activation and deletion, and an ancillary mechanism of "immune indifference," both regulated by the migration and localization of the donor leukocytes.51

With the double immune reaction, and induction of allo-specific nonreactivity (each cell population to the other), it was easy to understand how the expected HLA-matching influence was "blindfolded" as Terasaki’s early studies had suggested. With each further level of histoincompatibility, the resulting nullification effect escalates both ways, providing the process occurs under an umbrella of immunosuppression that affects both cell populations equally (Fig 3-11). A serious tilt in one direction defines GVHD. With an uncontrolled imbalance in the other direction, the consequence is rejection.

With host cytoablation, as is carried out in preparation for conventional marrow transplantation, the tilt favoring the immunocompetent graft leukocytes is so extreme that GVHD is the most common complication (Fig 3-12. bottom). This can be controlled or avoided only with the use of HLA-matched donors (Fig 3-12. top) as was recognized in Terasaki’s earliest collaboration with Good.60 The nullification effect also explains why GVHD is so uncommon after organ transplantation, even of leukocyte-rich organs such as the liver and intestine, and why it is safe to infuse adjunct donor marrow in organ recipients, provided the patients are not immunologically weakened in advance by cytoablation or other means.60

In fact, conventional marrow transplantation is in principle a mirror image of organ transplantation, and also governed by antigen migration and localization (Fig 3-2. bottom right). The host leukocytes are not all eliminated by pretransplant cytoablation as has been proved by Przepiorka and Thomas et al.65 The weak HVG reaction mounted by those remaining recipient cells, and the parallel GVH reaction of the dominant population of donor cells can eventually result in reciprocal tolerance.
Figure 3-11. The reciprocal immune reaction that occurs with increasing intensity in proportion to HLA mismatch following organ transplantation to a noncytotoxicated recipient. The nullification effect of the donor and recipient cell population "blindfolds" the HLA mismatching effect.

The Terasaki Legacy

The Terasaki record summarized in Table 3-1 falls short of characterizing the Terasaki legacy. Looking back through defogged lenses, we are able to see the significance of what Terasaki accurately recorded decades ago from his studies of kidney transplant recipients. Far from a scandal, it was a key discovery that eventually was critical in uncovering the true meaning of allograft acceptance, acquired tolerance, and, in fact, the essence of self/nonself discrimination.

At a critical time, Terasaki separated himself from colleagues who were seduced by the power of anticipation. As a consequence, he was pilloried at first, then vindicated, and
ultimately honored. In between times, so many years had passed that it no longer really mattered. When the smoke cleared, we were left in the end with Paul Terasaki, the prototypical scientist described in the 19th century by Claude Bernard, the father of experimental medicine:

"There are, indeed, two sides to science in evolution: on the one hand, what is known already, and on the other hand, what remains to be acquired. In the already acquired, all men are more or less equal, and the great cannot be distinguished from the rest. Mediocre men often have the most acquired knowledge. It is in the darker regions of science that great men are recognized: they are marked by ideas which light up phenomena hitherto obscure and carry science forward."
References


63. Zinkernagel RM, Ehrl S, Aichele P, et al. Antigen localization regulates immune responses in a dose- and time-


