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Terasaki's Seminal Contributions in HLA and Organ Transplantation

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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.[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[2] and panel reactive antibody tests[3]

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Table 3-1. Paul Terasaki Landmarks

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

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] 4) efficient techniques of organ preservation (beginning with the Collins/Terasaki solution) that allowed time for HLA typing,[5] 5) epidemiologic investigation of the effect of biologic variables and different therapies on transplantation outcome,[6,7] 6) discovery of the beneficial effect of blood transfusions on kidney allograft survival,[8] 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.[9,10] These were the natural killer (NK) cells more completely delineated and popularized 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 complication[2] 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."[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[21,22] and subsequently in cases of cadaver kidney transplantation.[23] In both studies, the degree of HLA match had little influence on clinical outcome unless the match was perfect or near perfect (ie, 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 (eg, spouses) and kidneys from one haplotype matched (eg, parental) related donors. In both related and unrelated donor cases, there was no demonstrable survival advantage unless there was a zero-antigen mismatch.[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.[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).[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-

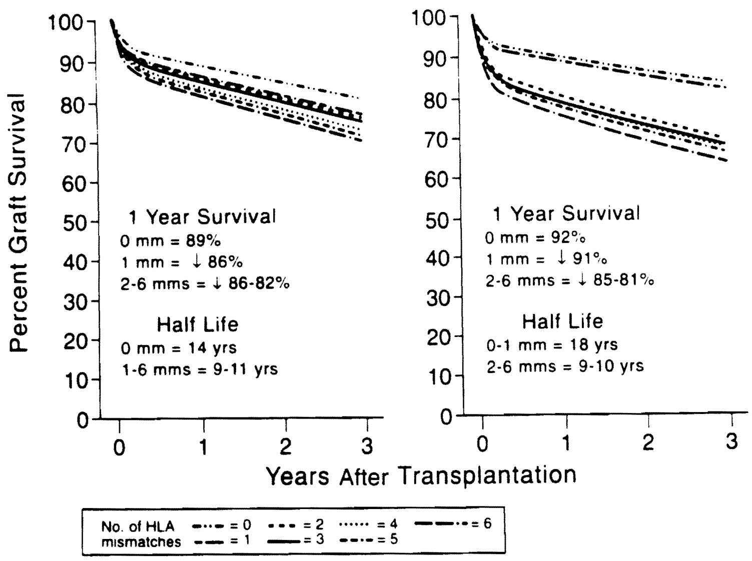

Figure 3-1. The influence of zero-antigen to six-antigen HLA mismatches on the 1- and 3-year survival and the "half-life" of first cadaver kidney allografts. Left: UNOS experience 1991-95 (n = 31,291) exclusive of Pittsburgh cases. Right: Pittsburgh experience 1981-95 (n = 1780). Data from Starzl et al.[25]

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(p156),27] 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

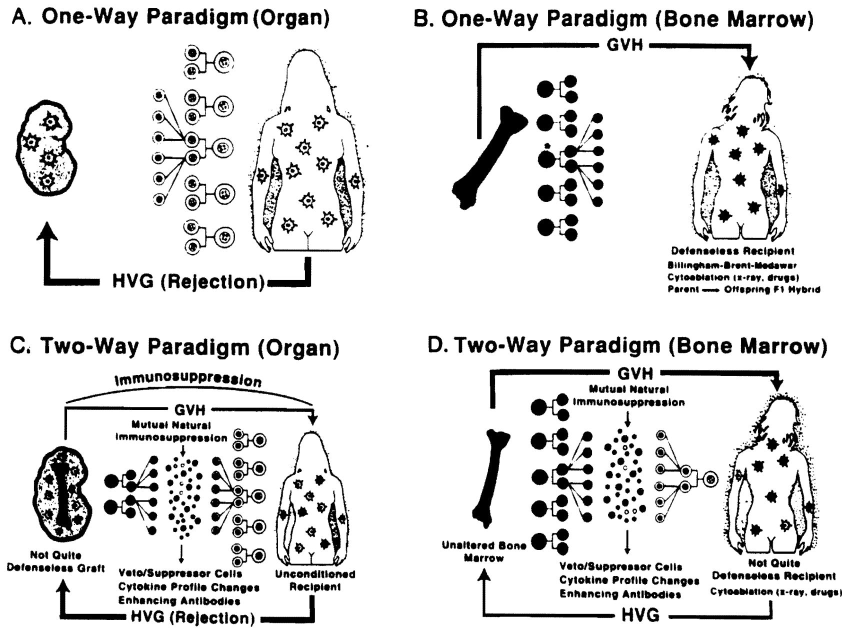

Figure 3-2. Top panels. Historical conception of transplantation immunology in terms of a unidirectional immune transaction: (left) host-vs-graft (HVG) reaction with whole organs and (right) graft-vs-host (GVH) reaction with marrow or other hematolymphopoietic transplants. Bottom panels. Correct view of transplantation as a bidirectional and mutually canceling immune reaction that is (left) predominantly HVG with whole organ grafts, and (right) predominantly GVH with marrow grafts. The bone silhouette in the kidney (bottom left) connotes the "passenger leukocytes" of marrow origin that are constituents of all organs.

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.[36-40]

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 transplanted under an umbrella of immunosuppression.[11] 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

Feature	Organ Transplantation	Marrow Transplantation
Host cytoablation	No	Yes*
HLA matching	Not critical	Critical
Principal complication	Rejection	Graft-vs-host disease
Immunosuppression-free	Uncommon	Common
Term for success	Acceptance	Tolerance

*This therapeutic step allows a relatively unopposed graft-vs-host reaction and accounts for the other differences.

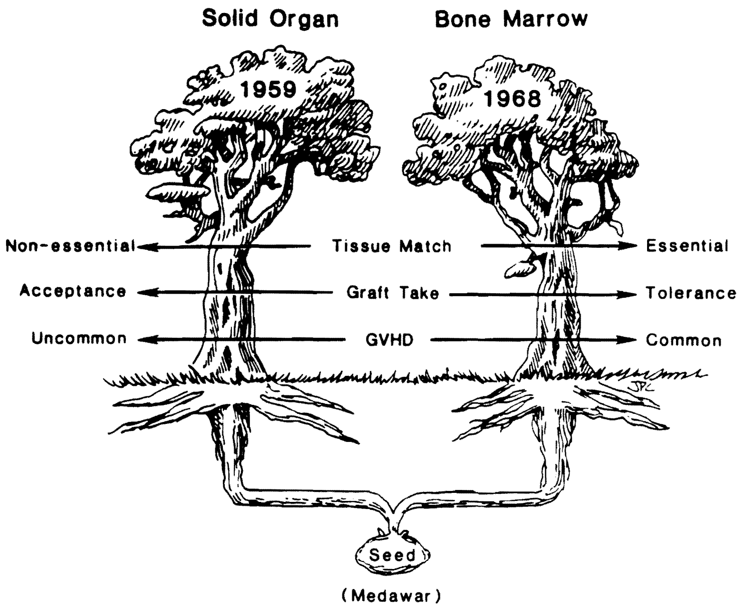

Figure 3-3. The division of transplantation into two separate disciplines, caused by different treatment policies.

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,[42] and then the French teams of Hamburger[43,44] and Kuss[45] 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

Patient	Reference	Surgery Date	Donor	Survival (months)*
1	42,46	1-24-59	Frat twin	>50
2	43,44	6-29-59	Frat twin	>45
3	45	6-22-60	Unrelated†	18 (Died)
4	43	12-19-60	Mother†	12 (Died)
5	45	3-12-61	Unrelated†	18 (Died)
6	44	2-12-62	Cousin†	>13
7	46,47	4-5-62	Unrelated	10

*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.
†Adjunct steroid therapy.

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.[47] 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-maneuverable prednisone. Eight of the first 10 recipients had prolonged kidney allograft survival[41] 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 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."[41] 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.[48] These same posttransplant events of an immunologic confrontation and resolution were ultimately demonstrated with liver,[49] 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.[49,50] Among the 42 longest surviving cadaveric liver recipients at the

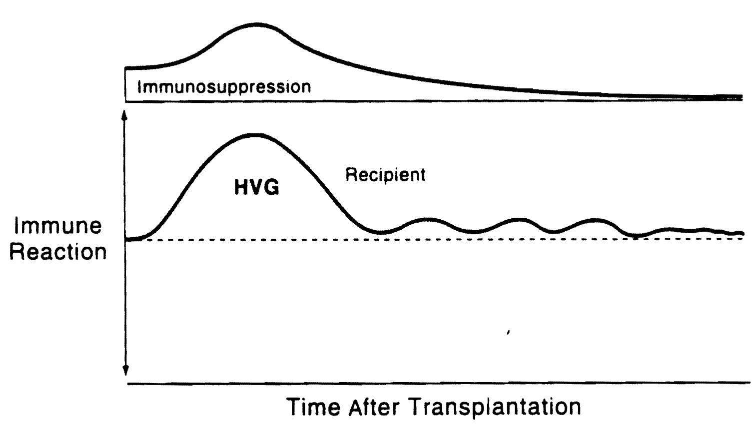

Figure 3-4. Historical view of events after successful organ transplantation: rejection, its reversal and the development of donor-specific nonreactivity.[41]

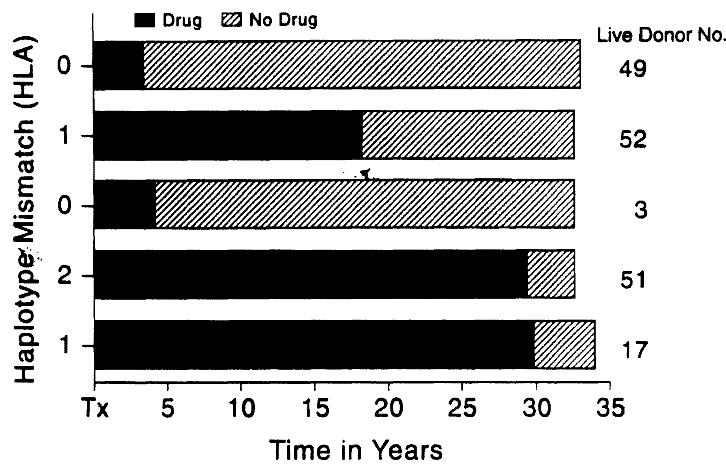

Figure 3-5. Time on immunosuppression and time off treatment as of October 1996, in five patients whose renal allografts had functioned continuously since their transplantation in 1962-63. After 3-1/2 more years, these patients remain drug-free. Data from Starzl et al.[48]

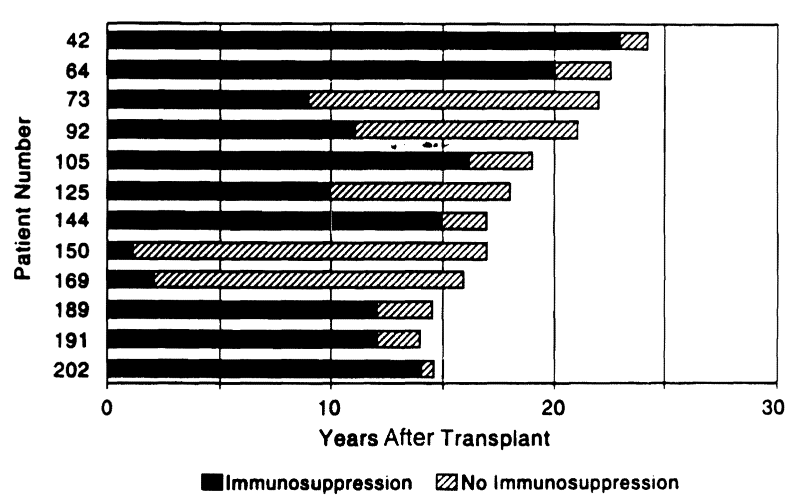

Figure 3-6. Time on and off immunosuppression of 12 long-term surviving liver recipients who were free of drug treatment in October 1995. Patients 150 and 169 stopped their medication less than 2 years after transplantation because of noncompliance. The others were weaned because of complications of chronic immunosuppression. After 3-1/2 more years, these 12 patients remain drug-free. Data from Starzl et al.[48]

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.[51-53] Ten years later, further improvements were made possible with the introduction of tacrolimus.[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.[57]

Table 3-4. Empirical Therapeutic Dogma of Immunosuppression

Ingredients of Strategy	Baseline Agents
Baseline therapy	Azathioprine*
Secondary adjustments of prednisone dose, or antilymphoid agents†	Cyclosporine
Case-to-case trial (and potential error) of weaning	Tacrolimus

*Alone or with prophylactic prednisone. Equivalent results were obtained with cyclophosphamide instead of azathioprine.
†Initially used for prophylactic "induction."

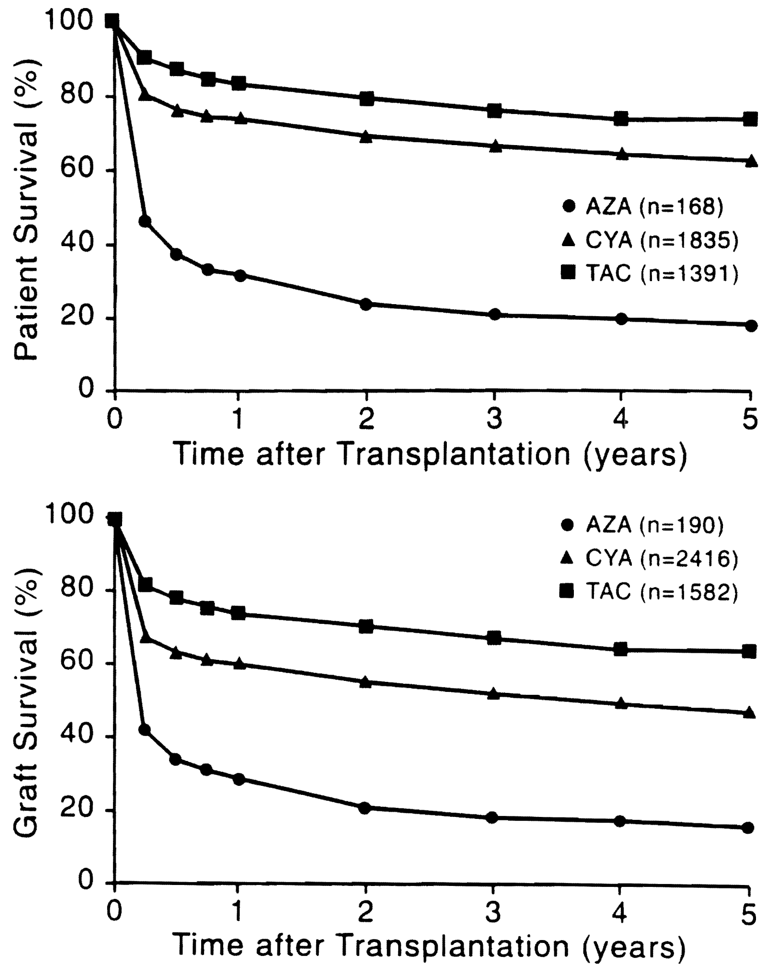

Figure 3-7. The three eras of orthotopic liver transplantation at the Universities of Colorado (1963-80) and Pittsburgh (1981-1993), defined by azathioprine-, cyclosporine-, and tacrolimus-based immune suppression. Similar but less dramatic stepwise improvement has been seen with all organs. Patient 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).

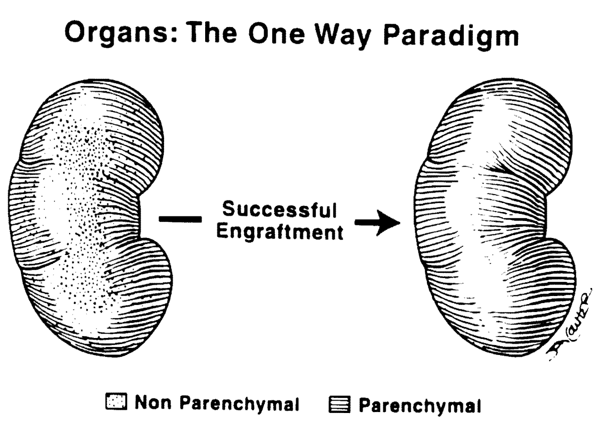

Figure 3-8. Conventional view of a successfully transplanted allograft in which the nonparenchymal white cells (passenger leukocytes) are depicted on left as a bone silhouette. These donor cells were assumed to have been destroyed by the host immune system (silhouette absent on right).

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.[50,58,59] 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.[50,60]

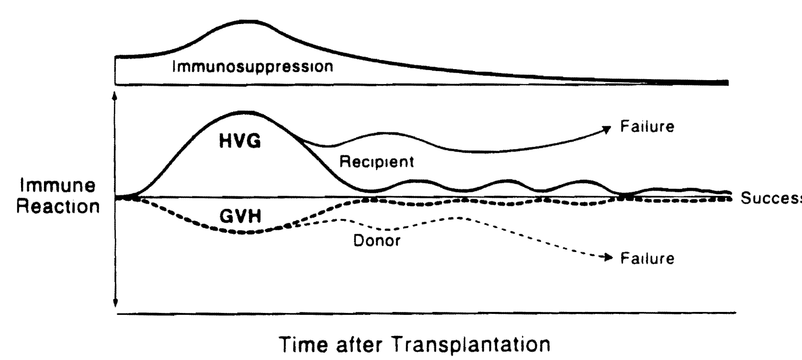

Figure 3-9. Contemporaneous HVG and GVH reactions that occur after transplantation. Treatment failure is defined as the inability to control one of the reactions, or sometimes both. Acute reciprocal clonal exhaustion after successful transplantation is maintained subsequently by chimerism-dependent low-grade stimulation of both leukocyte populations that may wax and wane. (Used with permission from Ramsey et al.[illegible])

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."[50,58] 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.[61] 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[62-64] but made more complex by the presence of the double immune reaction and by the additional factor of immunosuppression.[61] The four interrelated events shown in Fig 3-10 must occur in close temporal prox-

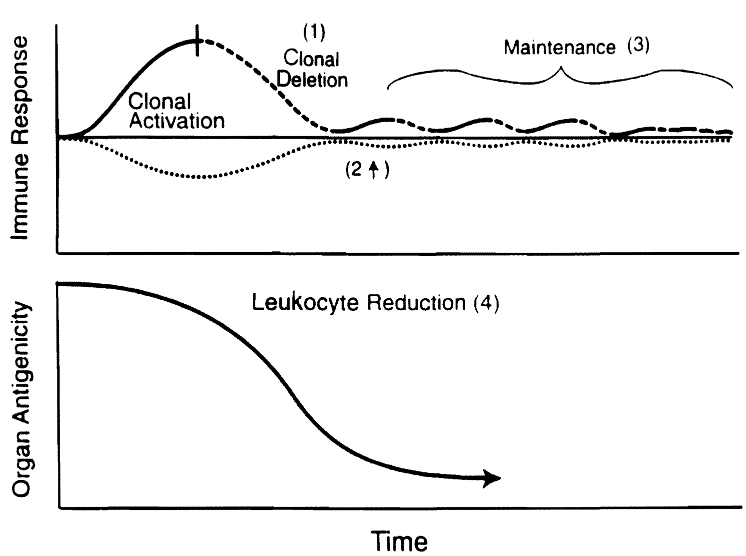

Figure 3-10. The four events that occur in close temporal proximation when there is successful organ engraftment: above, double acute clonal exhaustion (numbered 1 and 2) and subsequent maintenance clonal exhaustion (3) plus, below, loss of organ immunogenicity due to reduction of the graft's passenger leukocytes (4). (Used with permission from Starzl et al.[65])

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.[61]

With the double immune reaction, and induction of allospecific 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 histo*in*compatibility, 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.[20] 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, providing the patients are not immunologically weakened in advance by cytoablation or other means.[48]

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.[66] 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.

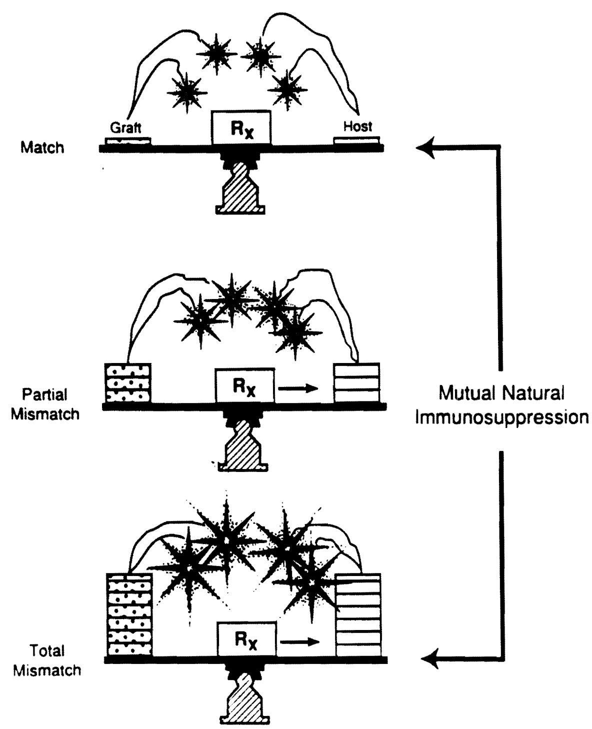

Figure 3-11. The reciprocal immune reaction that occurs with increasing intensity in proportion to HLA mismatch following organ transplantation to a noncytoablated recipient. The nullification effect of the donor and recipient cell population "blindfolds" the HLA mismatching effect.

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

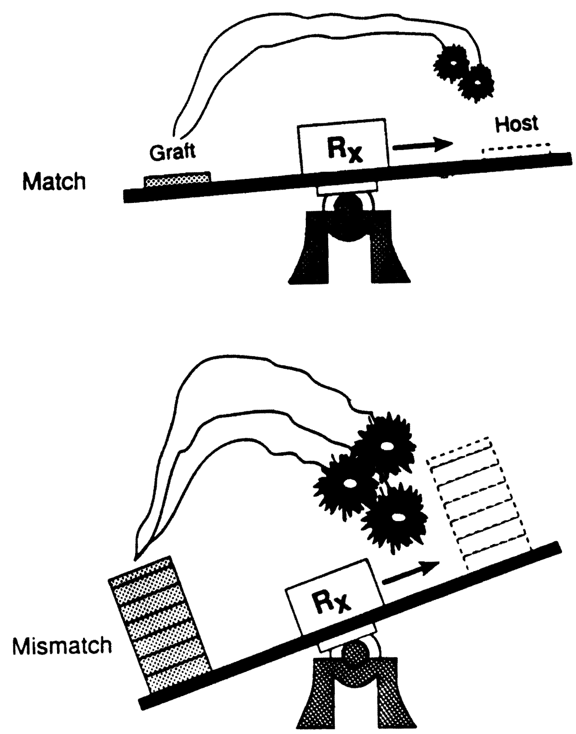

Figure 3-12. Explanation for uncontrollability of GVHD with MHC-mismatched donors when the mutual cell engagement shown in Fig 3-11 is prevented by host cytoablation (ie, in preparation for marrow transplantation).

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."[7]

References

1. Terasaki PI, McClelland JD. Microdroplet assay of human serum cytotoxins. Nature 1964;204:998.
2. Terasaki PI, Marchioro TL, Starzl TE. Sero-typing of human lymphocyte antigens: Preliminary trials on long-term kidney homograft survivors. In: Histocompatibility testing. Washington, DC: National Academy of Science/ National Research Council, 1965:83-96.
3. Terasaki PI, Mickey MR, Kreisler M. Presensitization and kidney transplant failures. Postgrad Med J 1971;47: 89-100.
4. Terasaki PI, Vredevoe DL, Mickey MR, et al. Serotyping for homotransplantation. VI. Selection of kidney donors for thirty-two recipients. Ann NY Acad Sci 1966;129: 500-20.
5. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportations. Initial perfusion and 30-hours' ice storage. Lancet 1969;ii:1219-22.
6. Opelz G, Mickey MR, Terasaki PI. Prolonged survival of second human kidney transplants. Science 1972;178: 617.
7. Opelz G, Mickey MR, Terasaki PI. Influence of race on kidney transplant survival. Transplant Proc 1977;9:137.
8. Opelz G, Sengar DPS, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplant. Transplant Proc 1973;4:253-9.
9. Takasugi M, Mickey MR, Terasaki PI. Reactivity of lymphocytes from normal persons on cultured tumor cells. Cancer Res 1973;33:2898-902.
10. Takasugi M, Mickey MR, Terasaki PI. Studies on specificity of cell-mediated immunity. J Natl Cancer Inst 1974; 53:1527-38.
11. Herberman RB, Oldham RK. Problems associated with study of cell-mediated immunity to human tumors by microcytotoxicity assays. J Natl Cancer Inst 1975;55: 749-53.
12. Herberman RB, Nunn ME, Lavrin DH. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors: Distribution of reactivity and specificity. Int Cancer 1975;16:216-29.

13. Herberman RB, Nunn ME, Holden HT, Lavrin DH. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. II. Characterization of effector cells. Int J Cancer 1975;16:230-9.
14. Kressling R, Klein F, Wigzell H. "Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol 1975;5:112-7.
15. Kressling R, Klein F, Pross H, Wigzell H. "Natural" killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. Eur J Immunol 1975;5:117-21.
16. Kissmeyer-Nielsen F, Olsen S, Peterson VP, Fieldborg O. Hyperacute rejection of kidney allografts associated with preexisting humoral antibodies against donor cells. Lancet 1966;ii:662-5.
17. Huxley J. Soviet genetics: The real issue. Nature 1949; 163:935-40.
18. Soyfer VN. New light on the Lysenko era. Nature 1989; 339:415-20.
19. Joravsky D. Genetics besieged, review of *Lysenko and the Tragedy of Soviet Science* by Valery N. Soyfer (book review). Nature 1994;372:284-5.
20. Meuwissen HJ, Gatti RA, Terasaki PI, et al. Treatment of lymphopenic hypogammaglobulinemia and bone-marrow aplasia by transplantation of allogeneic marrow: Crucial role of histocompatibility matching. N Engl J Med 1969;281:691-7.
21. Starzl TE, Porter KA, Andres G, et al. Long-term survival after renal transplantation in humans: With special reference to histocompatibility matching, thymectomy, homograft glomerulonephritis, heterologous ALG, and recipient malignancy. Ann Surg 1970:172:437-72.
22. Terasaki PI, Mickey MR. Histocompatibility-transplant correlation, reproducibility, and new matching methods. Transplant Proc 1971:3:1057-71.
23. Mickey MR, Kreisler M, Albert ED, et al. Analysis of HLA incompatibility in human renal transplants. Tissue Antigens 1971:1:57-67.
24. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995:333:333-6.

25. Starzl TE, Eliasziw M, Gjertson M, et al. HLA and cross reactive antigen group (CREG) matching for cadaver kidney allocation. Transplantation 1997;64:983-91.
26. Brent L. Immunogenetics: Histocompatibility antigens—Genetics, structure and function. In: Brent L, ed. A history of transplantation immunology. San Diego: Academic Press, 1997:131-76.
27. Starzl TE. Tissue matching. In: Starzl TE, ed. The puzzle people: Memoirs of a transplant surgeon. Pittsburgh: University of Pittsburgh Press, 1992:118-24.
28. Gibson T, Medawar PB. The fate of skin homografts in man. J Anat 1943;77:299-310.
29. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 1944;78:176-99.
30. Billingham RE, Brent L, Medawar PB. "Actively acquired tolerance" of foreign cells. Nature 1953;172:603-6.
31. Billingham R, Brent L, Medawar P. Quantitative studies on tissue transplantation immunity. III. Actively acquired tolerance. Philos Trans R Soc Lond B Biol Sci 1956;239:357-412.
32. Main JM, Prehn RT. Successful skin homografts after the administration of high dosage X radiation and homologous bone marrow. J Natl Cancer Inst 1955;15:1023-9.
33. Trentin JJ. Mortality and skin transplantibility in X-irradiated mice receiving isologous or heterologous bone marrow. Proc Soc Exp Biol Med 1956;92:688-93.
34. Billingham R, Brent L. Quantitative studies on transplantation immunity. IV. Induction of tolerance in newborn mice and studies on the phenomenon of runt disease. Philos Trans R Soc Lond B Biol Sci 1959;242:439-77.
35. Simonsen M. The impact on the developing embryo and newborn animal of adult homologous cells. Acta Pathol Microbiol Scand 1957;40:480-500.
36. Mathe G, Amiel JL, Schwarzenberg L, et al. Haematopoietic chimera in man after allogeneic (homologous) bone-marrow transplantation. Br Med J 1963:2:1633-5.
37. Gatti RA, Meuwissen HJ, Allen HD, et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968:ii:1366-9.

38. Bach FH, Albertini RJ, Joo P, et al. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. Lancet 1968;ii:1364-6.
39. DeKoning J, Dooren LJ, Van Bekkum DW, et al. Transplantation of bone marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency. Lancet 1969;i:1223-7.
40. Thomas ED. Allogeneic marrow grafting: A story of man and dog. In: Terasaki PI, ed. History of transplantation: Thirty-five recollections. Los Angeles: UCLA Tissue Typing Laboratory, 1991:379-93.
41. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 1963;117:385-95.
42. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the kidney between non-identical twins. N Engl J Med 1960;262:1251-60.
43. Hamburger J, Vaysse J, Crosnier J, et al. Renal homotransplantation in man after radiation of the recipient. Am J Med 1962;32:854-71.
44. Hamburger J, Vaysse J, Crosnier J, et al. Transplantation of a kidney between nonmonozygotic twins after irradiation of the receiver. Good function at the fourth month. Presse Med 1959;67:1771-5.
45. Kuss R, Legrain M, Mathe G, et al. Homologous human kidney transplantation. Experience with six patients. Postgrad Med J 1962;38:528-31.
46. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 1962;156:337-55.
47. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 1963;268:1315-23.
48. Starzl TE, Demetris AJ, Murase N, et al. The lost chord: Microchimerism. Immunol Today 1996;17:577-84.
49. Starzl TE, Marchioro TL, Porter KA, et al. Factors determining short- and long-term survival after orthotopic liver homotransplantation in the dog. Surgery 1965;58:131-55.

50. Starzl TE, Demetris AJ, Trucco M, et al. Cell migration and chimerism after whole-organ transplantation: The basis of graft acceptance. Hepatology 1993;17:1127-52.
51. Calne RY, White DJG, Thiru S, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978;ii:1323-7.
52. Calne RY, Rolles K, White DJG, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs; 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979;ii:1033-6.
53. Starzl TE, Weil R III, Iwatsuki S, et al. The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 1980;151:17-26.
54. Starzl TE, Todo S, Fung J, et al. FK 506 for human liver, kidney and pancreas transplantation. Lancet 1989;ii: 1000-4.
55. Todo S, Fung JJ, Starzl TE, et al. Liver, kidney, and thoracic organ transplantation under FK 506. Ann Surg 1990;212:295-305.
56. Starzl TE, Donner A, Eliasziw M, et al. Randomized trialomania? The multicenter liver transplant trials. Lancet 1995;346:1346-50.
57. Todo S, Tzakis AG, Abu-Elmagd K, et al. Cadaveric small bowel and small bowel-liver transplantation in humans. Transplantation 1992;53:369-76.
58. Starzl TE, Demetris AJ, Murase N, et al. Cell migration, chimerism, and graft acceptance. Lancet 1992;339: 1579-82.
59. Starzl TE, Demetris AJ, Trucco M, et al. Systemic chimerism in human female recipients of male livers. Lancet 1992;340:876-7.
60. Ramsey G, Nusbacher J, Starzl TE, Lindsay GD. Isohemagglutinins of graft origin after ABO-unmatched liver transplantation. N Engl J Med 1984;311:1167-70.
61. Starzl TE, Zinkernagel R. Antigen localization and migration in immunity and tolerance. N Engl J Med 1998; 339:1905-13.
62. Zinkernagel RM. Immunology taught by viruses. Science 1996;271:173-8.
63. Zinkernagel RM, Ehl S, Aichele P, et al. Antigen localization regulates immune responses in a dose- and time-

dependent fashion: A geographical view of immune reactivity. Immunol Rev 1997;156:199-209.
64. Zinkernagel RM, Bachmann MF, Kundig TM, et al. On immunologic memory. Annu Rev Immunol 1996;14: 333-67.
65. Starzl TE, Murase N, Thomson A, Demetris AJ. Stowaway stem cells in liver contribute to immunological tolerance in patients receiving liver transplants. Nat Med 1996;2:163-5.
66. Przepiorka D, Thomas ED, Durham DM, Fisher L. Use of a probe to repeat sequence of the Y chromosome for detection of host cells in peripheral blood of bone marrow transplant recipients. Am J Clin Pathol 1991;95:201-6.
67. Bernard C. An introduction to the study of experimental medicine. London: Macmillan, 1927. (Originally published in French 1865; English translation by H.C. Greene.)