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HISTORY OF ORGAN TRANSPLANTATION:

VIA THE TWO-WAY PARADIGM\*

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How whole-organ transplantation came to be a clinical discipline has been told elsewhere by many of the persons directly involved (1). The events through 1959 was dominated by the kidney (2). However, the extrarenal vacuum rapidly filled in the late 1950s with the development in several laboratories of canine transplant models with which to study all of the intra-abdominal and thoracic organs. Pig and rodent models came later.

Each organ-defined specialty has had its historians, but in all such accounts the preoccupation has been with a succession of events rather than with the poorly understood biologic principles by which all organs can escape rejection. This conventional approach can be capsulized by noting the first successful allotransplantation of the kidney (3), liver (4), heart (5), lung (6), pancreas (7), intestine (8), multiple abdominal viscera (9), and bone marrow (10-12). Such milestones are important. However, our concern here will be with the steps by which organ transplantation was developed empirically without knowing how this had been accomplished, and then the understanding that came later. Such generic information may be of use to anesthesiologists who care for all kinds of transplant recipients.

#### **THE IMMUNOLOGIC BARRIER**

By avoiding problems with rejection, the potential benefit of human whole organ replacement was unequivocally demonstrated with the identical twin transplantation performed in December 1954, by Joseph E. Murray (Nobel Laureate, 1990). However, this achievement was symbolic only, showing with an identical twin organ what was already known to be possible with skin grafts. Seven years later, the Nobel Laureate (1960), Macfarland Burnet, wrote in the New England Journal of Medicine that " . . . much thought has been given to ways by which tissues or organs not genetically and antigenetically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success . . . "

" (13)

## **THE ONE-WAY PARADIGM**

### **Rejection**

What was the genetically determined barrier? Although details are obscure, there was little mystery after 1944 about the general meaning of transplant rejection, following its elucidation by Medawar (co-Nobel Laureate with Burnet, 1960) as an immunologic event (14). This great contribution created the indelible image that a tissue (or organ) allograft was an island in a hostile recipient sea (Figure 1A).

## Tolerance

In contrast, why allografts or xenografts can escape from rejection with or without the aid of immunosuppression has been one of the most arcane subjects in biology ever since the description of acquired tolerance by Billingham, Brent, and Medawar (15,16) more than 4 decades ago. A simple explanation for the tolerance in their special model was at first beguiling. Immunocompetent adult spleen cells were injected in utero or perinatally into mice that had not yet evolved the immunologic equipment to reject them. The engrafted cells flourished, perpetuated themselves, and in effect endowed the recipient with the donor immune system. Thereafter, the chimeric mice failed to recognize donor strain skin or other tissues as alien.

Tolerance in this second landmark contribution from Medawar's laboratory was explained as a switch in immunologic apparatus and was consistent with the definition of transplantation immunology in terms of a unidirectional immune reaction (a "one-way paradigm"). This view was strengthened by the studies of Main and Prehn (17) who demonstrated the same tolerance outcome as Billingham, Brent, and Medawar in irradiated adult mice, whose cytoablated hematolymphopoietic cells were reconstituted with bone marrow. Hundreds of subsequent tolerance induction experiments in animals, and eventually clinical bone

marrow transplantation seemingly depended upon a similar natural, or iatrogenically imposed, defenseless recipient state (Figure 1B).

### **Graft Vs Host Disease (GVHD)**

The anticipated clinical application of this kind of tolerance induction was temporarily derailed in 1957 when it was realized that an immunologically active graft could turn the tables and reject the recipient (graft versus host disease [GVHD]). Billingham and Brent showed in their mouse model (18) and Simonsen in chickens (19) that this risk (also called runt disease) was roughly proportional to the extent of the major histocompatibility complex (MHC) barrier. Such disparities became measurable in humans after identification of the HLA antigens by Dausset (20) (Nobel Laureate, 1980), Terasaki, and others (21). The complication of GVHD in rodent (22) and large animal irradiation chimera models (23-26) forestalled for many years the clinical use of HLA mismatched bone marrow cells or other mature immunocytes, either for immunologic reconstitution for purely hematologic purposes or as a means of facilitating whole organ graft acceptance.

### **Clinical Bone Marrow Transplantation**

Nevertheless, a strategy for clinical bone marrow transplantation eventually was assembled directly from the rodent experiments, but with similar histocompatibility-imposed restrictions (23). After recipient cytoablation with total body irradiation (TBI) or cytotoxic drugs, stable chimerism could be induced in humans by the infusion of donor bone marrow if there was a good HLA match. Otherwise there was an intolerable incidence of GVHD. After successful engraftment, maintenance immunosuppression frequently was not needed, mimicking the kind of acquired immunologic tolerance originally described by Billingham, Brent, and Medawar (15,16), and then Main and Prehn (17). The eventual success of clinical bone marrow transplantation (10-12) was a straight line extension from these rodent models as Nobel Laureate Thomas (1990) has summarized (23).

### **Clinical Organ Transplantation**

With Total Body Irradiation --- The achievement of clinical bone marrow transplantation effectively detached from a scientific base the surgeons who by this time already had recorded many successful human whole organ transplantations (mostly kidneys) under continuous immunosuppression --- without dependence on HLA matching or the complication of GVHD, and as it turned out, without host preconditioning. Preconditioning with

sublethal TBI was in fact used in the first successful renal allotransplantation described by Murray and Merrill et al in 1960 (3). However, the kidney recipient, whose donor was his fraternal (dizygotic) twin brother, was not given bone marrow, already a significant departure from the Billingham-Brent-Medawar framework. The recipients own bone marrow recovered, and the transplanted kidney and patient survived for 20 years. Six additional examples of protracted kidney graft survival (> 1 year) after recipient irradiation without marrow were recorded in Paris over the next 36 months (27,28). Five of the 6 donors were more distant than a fraternal twin and two were genetically unrelated (28). However, these were isolated successes in a sea of failures.

**Chemical Immunosuppression** --- The frustration continued after the introduction for human renal transplantation of 6-mercaptopurine (6-MP) and its analogue azathioprine by Murray et al (29) following extensive experimental studies, first with rodent skin transplantation (30,31) and then with canine kidney transplant models (29,32-34). The drugs originally had been developed as antileukemic agents by Elion and Hitchings (35) (Nobel Laureates, 1988) and were first demonstrated to be immunosuppressive by Schwartz and Dameshek (36). Although the sixth patient treated by Murray with one or the other of these myelotoxic drugs had function of a non-related renal allograft

for 17 months, the clinical results were poor at first (29,37), similar to those with TBI.

**The Double-Drug Breakthrough** --- The tidal wave of whole organ cases began in earnest in 1962 when azathioprine was combined with prednisone (38). Now, a characteristic cycle was identified in which rejection could be reversed surprisingly easily with prednisone. More importantly, the need later on for maintenance immunosuppression frequently declined, and in occasional cases treatment could be stopped. The same sequence has been seen since with all other organs transplanted and with all of the immunosuppressive regimens (Figure 2). Agents introduced later were more potent and reliable in chaperoning the desired chain of events: antilymphocyte globulin (ALG) (39), cyclosporine (40), and FK 506 (41). Notwithstanding their diversity, all of the drugs seemed in a fundamentally similar way to have allowed something to change in the host, the graft or both. But what?

Answers were not provided by the one-way paradigm of transplantation immunology that had gained ascendancy nearly a half century ago. The false conception of a unidirectional reaction was never seriously challenged after it was seemingly supported by studies with the one-way mixed lymphocyte reaction (MLR) introduced in 1963 by Bach and Hirschorn (42) and Bain et al (43). These in vitro techniques (so-called minitransplant



models) generated thousands of increasingly sophisticated cellular and ultimately molecular studies of unidirectional immunologic reactions. Ironically, the resulting plethora of new information resembled at times an exponentially expanding phone book filled with wrong numbers. Most seriously, the flawed context lured successive generations of investigators into the trap of believing that tolerance induction for whole organ recipients (the "holy grail") lay in variations on the HLA-limiting strategy used for bone marrow transplantation, that included host preconditioning in preparation for a variety of donor leukocyte preparations.

#### **THE TWO-WAY PARADIGM**

##### **Whole Organ Transplantation**

A plausible explanation did not emerge for the success of the empirically developed whole organ transplantation procedures until 1992. Then, it was discovered in a study of pioneer kidney and liver recipients who were still extant from the earliest clinical trials that donor leukocytes of bone marrow origin which are part of the structure of all complex grafts ("passenger leukocytes" [44,45]) had migrated from the organs and survived ubiquitously in these patients for up to 30 years (46,47). Thus, organ allograft acceptance was associated with the cryptic survival including stem cells of a small fragment of

extramedullary donor marrow (depicted as a bone silhouette in Figure 1 C), which was assimilated into the overwhelmingly larger immunologic network of the host. The cell movement was in both directions, with small numbers of residual donor leukocytes (microchimerism) in both the graft and host.

From this information, a revision of transplantation immunology was possible in which the immunologic confrontation following whole organ transplantation could be seen as bidirectional (GVH as well as HVG) and mutually cancelling (Figure 3), providing the 2 participants in the David/Goliath mismatch could survive the initial onslaught. In a clinical context, but not in several animal models, this survival requires an umbrella of immunosuppression that protects both cell populations equally (Figure 1 C). Current research is targeted to understanding the amplification device by which a small number of cells can so profoundly affect the immunologic vision of the vast army against which it is arrayed. Although the chimeric leukocytes are multilineage (46-49), the antigen presenting dendritic cells of Steinman and Cohn (50,51) are thought to be critical because they can modify the expression of cell interaction, MHC, and adhesion molecules --- all of which determine how antigen signals are heeded by T cells (51).

**Historical Enigmas** --- With the two-way paradigm, virtually every previously unexplained experimental or clinical observation

after whole organ transplantation became either transparent, or at least susceptible to experimental inquiry (46,47). It could be understood why organ grafts are inherently tolerogenic, why HLA matching is so poorly predictive of outcome, and why GVHD does not develop after the transplantation of immunologically active grafts such as the liver and intestine.

With the two-way mutual cancellation implicit in this concept, the loss or blunting of an HLA matching effect is easy to understand. With each further level of histoincompatibility, the reciprocal effect is postulated to escalate both ways providing the process is chaperoned with an effective immunosuppressive umbrella (Figure 4). The consequent dwindling of the matching effect as donor-specific and recipient-specific nonreactivity evolves accounts for blind folding of the expected HLA effect. In addition to explaining why the HLA matching effect is "blind folded", this bidirectional cancelling effect of the 2 cell populations explains why GVHD does not develop after liver, intestinal, multivisceral, and heart-lung transplantation despite the heavy lymphoid content of those organs.

**Augmentation of Spontaneous Chimerism** --- Historical efforts to give extra donor antigen in the form of bone marrow (52,53) or donor blood transfusions (54-56) had been hampered in design or execution by the assumption that the infused cells would be destroyed without recipient preconditioning, justifiable anxiety

about GVHD if host preconditioning was provided, and a lack of information about the appropriate timing of the infusions. The new information that chimerism is a naturally occurring event after whole organ transplantation (46,47) exposed a perioperative window of opportunity during which unaltered HLA incompatible bone marrow or donor specific blood transfusion was predicted to be safe without recipient preparation or deviation from the generic practices of immunosuppression for whole organ transplantation that had evolved over the years from the original azathioprine-prednisone formula (38).

The validity of this strategy was verified recently in non-preconditioned recipients of cadaveric kidneys, livers, hearts, and lungs who were given  $3-5 \times 10^8$ /kg adjuvant bone marrow at the same time as organ transplantation under standard FK 506-prednisone treatment (Figure 5) (57). Chimerism estimated to be  $> 1000 \times$  that occurring in conventional whole organ recipients was reliably and safely produced and sustained. The persistent blood chimerism (usually  $>1\%$ ), trend toward donor specific nonreactivity, and high rate of patient and graft survival has marked these bone marrow augmented recipients as an advantaged cohort. They are the first patients to undergo HLA-mismatched cadaveric organ transplantation with the reasonable prospect of eventually becoming drug free. The process of tolerance induction and drug weaning is expected to take 5 to 10 years in

most patients who are given mismatched organs and in some the drug free state may never be attainable.

#### **With Bone Marrow**

With the discovery that whole organ transplantation caused spontaneous chimerism, it was realized that seemingly vast gap between the bone marrow and whole organ transplantation fields merely reflected entrenched differences of treatment strategy (Figure 6). The mutually censoring immunologic limbs were being left intact with organ transplantation, whereas the recipient limb was deliberately removed (cytoablation) in preparation for bone marrow grafting procedures. It is doubtful that it is ever possible (much less desirable) with the cytoablation techniques of bone marrow transplantation to completely eliminate the entire recipient immune system. Although this was long assumed to have occurred in successful cases (Figure 1 B), a trace population of recipient leukocytes has been almost invariably detected with sensitive techniques in patients previously thought to have complete bone marrow replacement (58,59). These bone marrow recipients were in fact mirror images of successfully treated whole organ recipients, the difference being that their own rather than donor leukocytes constituted the trace population. In either kind of recipient (whole organ or bone marrow), the appearance of MHC restricted veto and suppressor cells, enhancing antibodies, and changes in cytokine profile could be construed as

by-products of and accessory to the seminal event of mixed chimerism (Figure 1 C and D).

Beyond an adjuvant role for whole organ transplantation, an important question is whether HLA mismatched bone marrow without an accompanying organ can be engrafted in patients whose disease can be corrected with a minimal or even microchimeric state, using the same immunosuppression as for marrow-augmented kidney, liver, and heart recipients. The potential list of indications in which complete marrow replacement is unnecessary is a long one, exemplified by the lysosomal enzyme deficiencies (60). Another look into the future has been provided by the demonstration that xenograft transplantation is followed by the same cell migration process as that seen with allografts (61).

#### **EPISTEMOLOGY VERSUS DRY HISTORY**

The legendary immunologist, Melvin Cohn (father of the 2-signal concept of self/non-self discrimination), wrote in 1994 that "In its recent history, immunology has advanced largely by volume [of publications], complete with waste." (62). In Cohn's opinion, the reason for the failure of more rapid conceptual advancement in his branch of science has been the preference of immunologists for small theories that explain one or only a few facts (articulated by Mitchison [63]) as opposed to the

development of generalized principles with which all facts could be explained (coherence of context). It would be hard to find a better way to illustrate the consequences of a small theory than those derivative from the durable one-way paradigm which was blindly accepted in spite of its failure to explain what was being seen daily in every transplantation clinic and laboratory. Virtually no hint of the two-way paradigm can be found in the literature before the description in June 1992 of microchimerism in organ recipients. If the spontaneous development of chimerism after organ transplantation had been known a third of a century ago, it would have been possible to correctly interpret observations in splenocyte and bone marrow transplant experiments reported by Simonsen (64,65) and Michie, Woodruff and Zeiss (66). The hypothesis of these earlier workers --- that acquired tolerance must result from a 2-way (donor/recipient) immune reaction --- resembled that later used to explain organ graft acceptance. Their great idea was abandoned because it could not be proved, delaying a true understanding of transplantation immunology for a third of a century.

#### CONCLUSION

Beacons of understanding shine forward as well as back. Comprehending the history of transplantation in terms of the two-way paradigm provides the intellectual means to devise better

treatment strategies, including the achievement of drug free tolerance, and ultimately the goal of xenotransplantation.



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## FIGURE LEGENDS

**Figure 1** --- **(Upper panels)** One-way paradigm in which transplantation is conceived as involving a unidirectional immune reaction: host-versus-graft (HVG) with whole organs (A) and graft-versus-host (GVH) with bone marrow or other lymphopoietic transplants (B). **(Lower panels)** Two-way paradigm with which transplantation is seen as a bidirectional and mutually cancelling immune reaction that is predominantly HVG with whole organ grafts (C), and predominantly GVH with bone marrow grafts and (D).

**Figure 2** --- Pattern of postoperative events with whole organ allograft acceptance, in the framework of the one-way paradigm.

**Figure 3** --- The pattern of convalescence after either organ or bone marrow transplantation in the framework of the two-way paradigm.

**Figure 4** --- Explanation for the loss of an HLA matching effect with whole organ transplantation. Rx: immunosuppression.

**Figure 5 ---** Iatrogenic augmentation of the GVH component of the 2-way paradigm by infusing  $3-6 \times 10^8$  unaltered donor bone marrow cells at the same time as heart or other whole organ transplantation. When the recipient is not cytoablated, there is essentially no risk of GVHD.

**Figure 6 ---** The growth as separate disciplines of bone marrow (right) and whole organ transplantation (left) from the seed planted by Peter Medawar during World War II. It was recognized in 1992 that these seemingly disparate disciplines were mirror images caused by different treatment strategies as explained in the text. **GVHD, Graft versus host disease.**

# One-Way Paradigm (Organ)

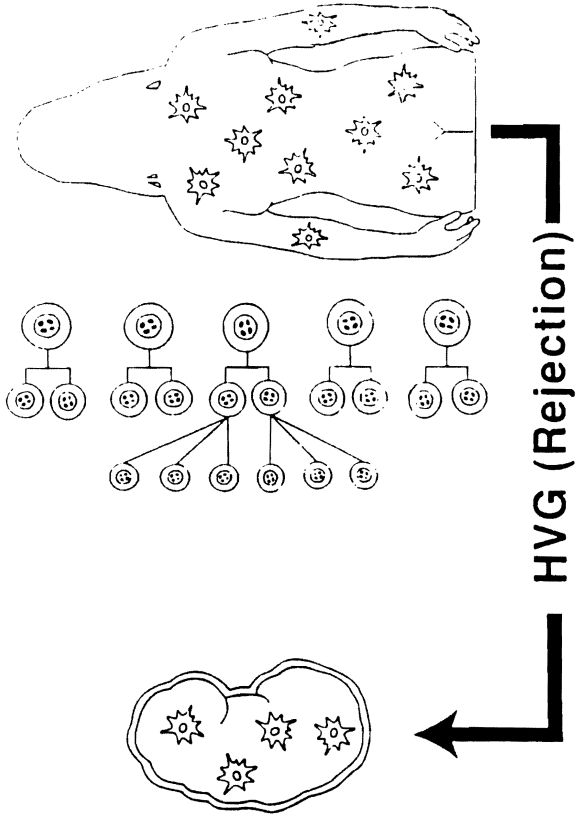


FIGURE 1A

# One-Way Paradigm (Bone Marrow)

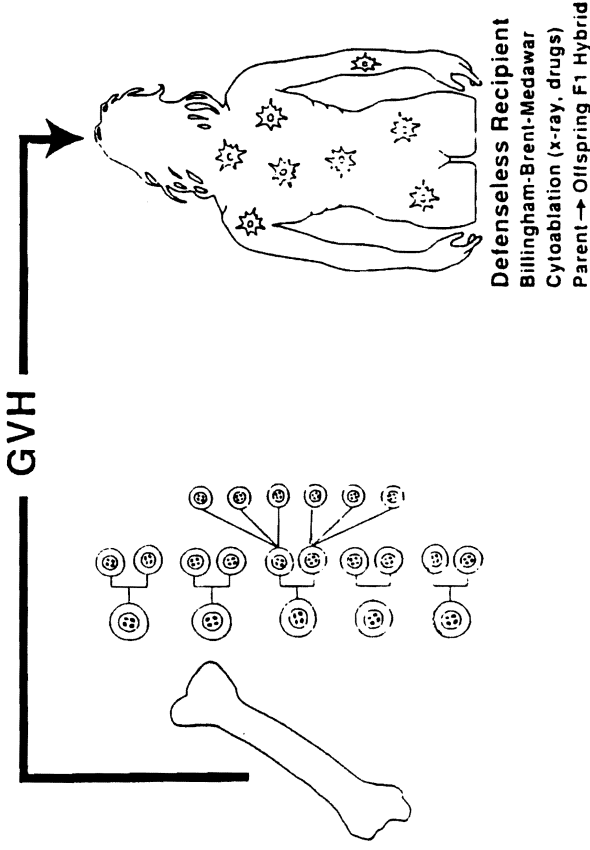


FIGURE 1B

# Two-Way Paradigm (Organ)

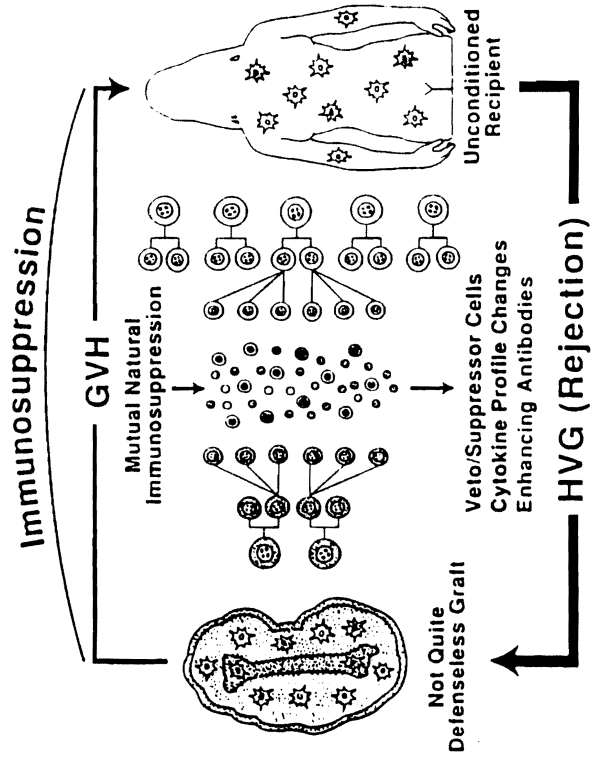


FIGURE 1C

# Two-Way Paradigm (Bone Marrow)

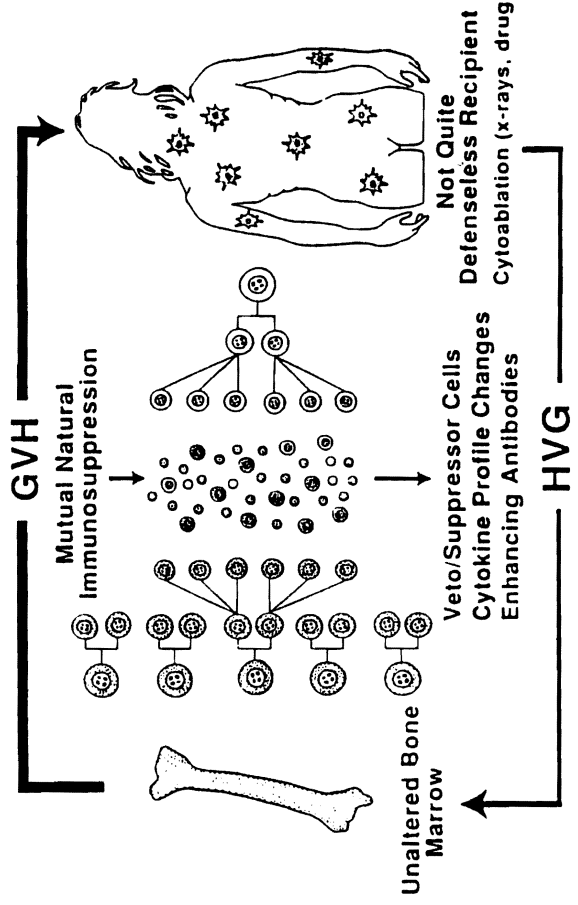


FIGURE 1D

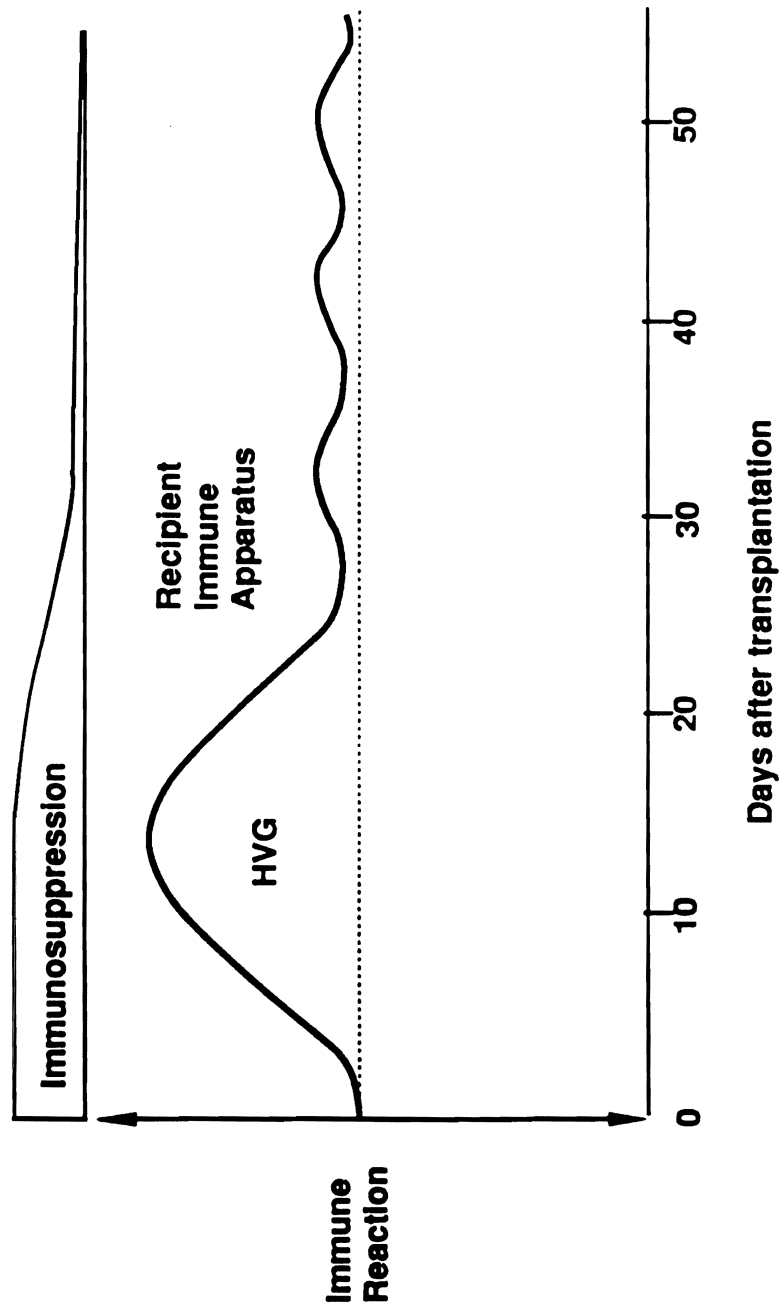


FIGURE 2

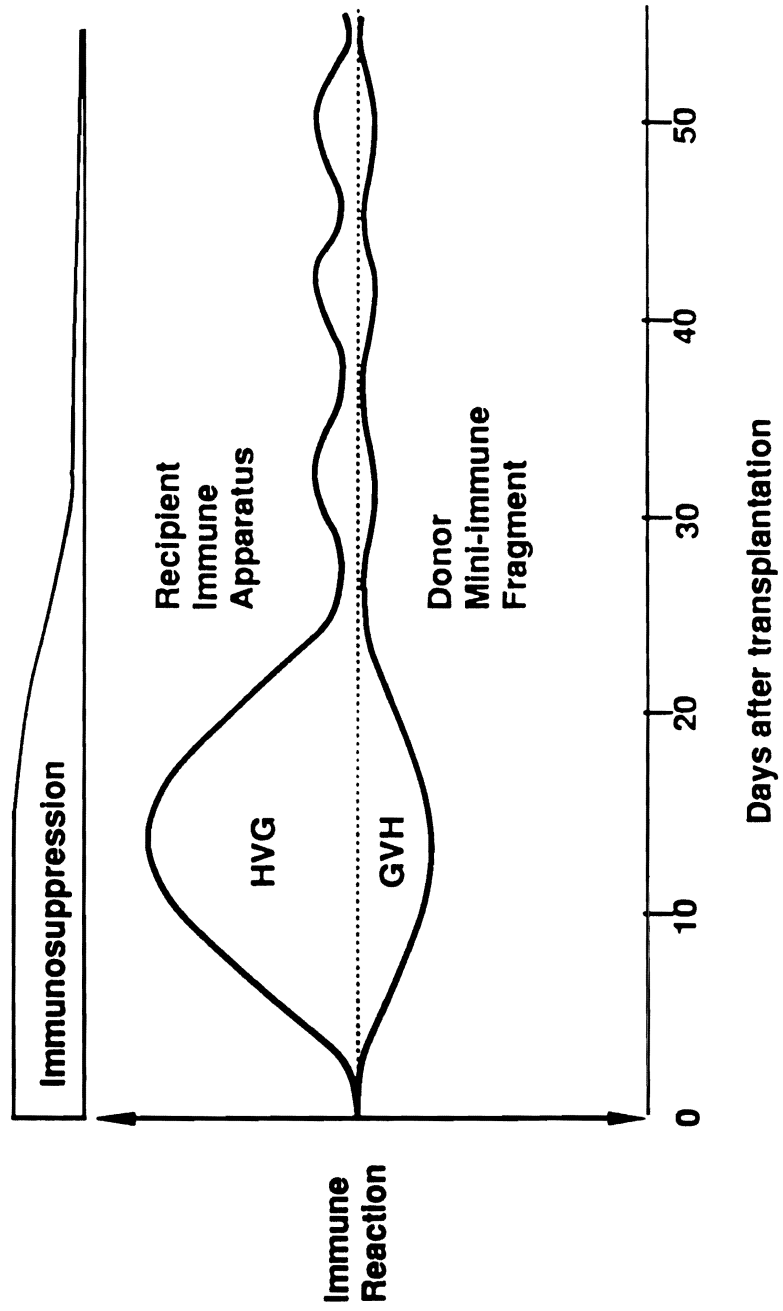


FIGURE 3