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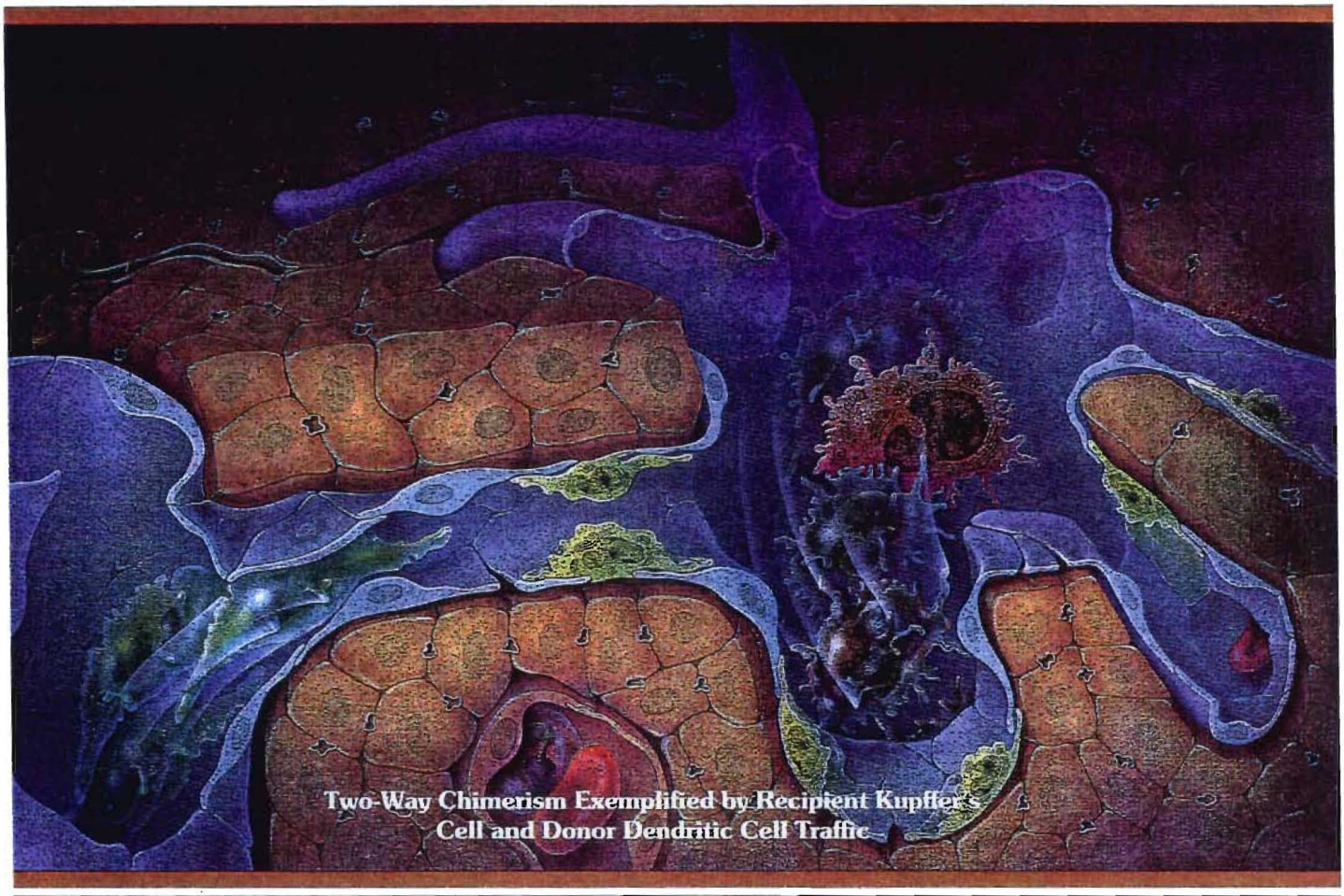

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Vol. 30 No. 10 October 15, 1995 **Hospital Practice**

The Changing Immunology of Organ Transplantation

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The engrafted organ becomes a chimera as the recipient's leukocytes station themselves in the transplant. Remarkably, the recipient becomes chimeric as well, in a reverse migration involving immune cells from the graft. Interactions between donor and recipient cells are tolerogenic—a process with implications for the goal of graft acceptance with minimal immunosuppression.

More than three decades have passed since clinical organ transplantation first emerged from investigations that identified graft rejection as an immune reaction reversible by immunosuppressive drugs. Until recently, however, the very successes of transplantation hid an odd truth: The successes are immunologically enigmatic and have become more so even as new drugs have broadened the therapeutic possibilities. Among current immunosuppressants, deoxyspergualin appears to block early stages of lymphocyte activation by impeding antigen presentation to resting helper T cells. Cyclosporine and FK 506 (tacrolimus) affect later stages, disrupting T-cell internal signals and thus suppressing secretion of cytokines—notably, interleukin-2. Rapamycin permits IL-2 secretion but blocks IL-2's actions. Antimetabolites, including azathioprine, cyclophosphamide, and methotrexate, act even more distally, inhibiting immune-cell clonal proliferation. Despite these diverse and nonspecific mechanisms, the drugs all promote a donor/recipient immunologic balance. It is as if they encourage an unknown tolerogenic process.

The nature of that process is beginning to be defined. Almost from the outset of clinical organ transplantation, it was apparent that a successful graft becomes chimeric, adopting immune cells from the recipient. It is now clear that the recipient becomes chimeric too (Figure 1). Evidently, the donor and recipient immune-cell populations interact to foster graft acceptance. The crucial immunologically active cells migrating from donor tissue to recipient target sites appear to be dendritic cells—a type of immune cell that is difficult to isolate and was until recently impossible to maintain in culture, and yet is the most potent of all cells that present antigens to T lymphocytes. Study of dendritic cells in animal allograft recipients suggests the existence of tolerogenic mechanisms in which immature donor dendritic cells may act as "veto cells" to reprogram the recipient's immune surveillance. The findings raise the possibility of increasing the success of organ transplantation by various means, including perioperative donor-cell infusions.

One-Way Paradigm

Perhaps nothing has so impeded discovery of the donor/recipient immune interactions that follow organ transplantation as the divergences between the therapeutic traditions of bone marrow and solid organ grafting. Each has laid down its own concepts of the immunologic requirements for clinical success. A discussion of this misleading dichotomy is a good starting point for a survey of recent developments and their clinical implications.

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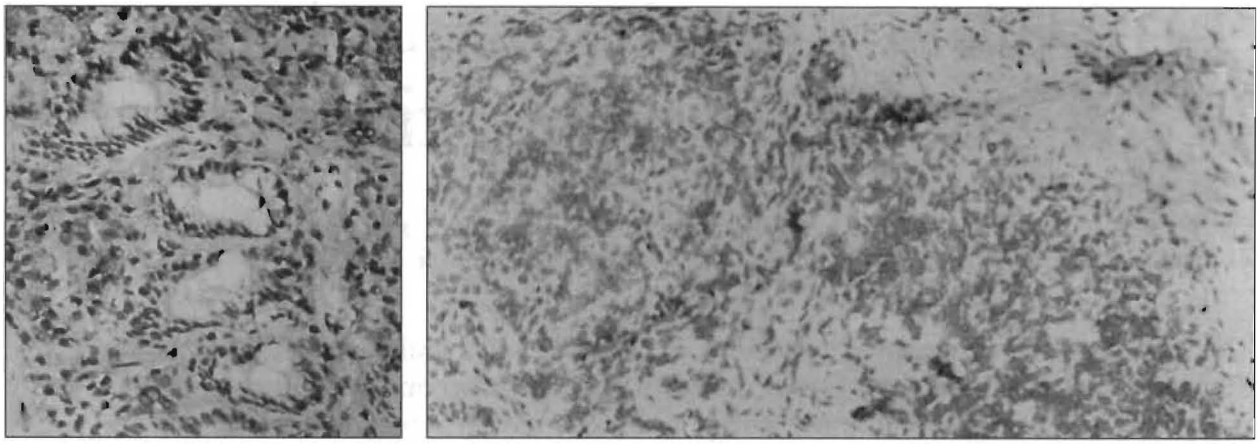

Figure 1. **Two-way chimerism following organ transplantation is evidenced by immunostaining for specific HLA alleles in patients with a graft from a donor mismatched at that locus. Graft chimerism is shown in a biopsy specimen from a small-intestinal graft (left), obtained 54 days after the surgery. Red-colored staining for the recipient's HLA-Bw4 shows that recipient cells have populated the graft's lamina propria. The blue-staining epithelium and endothelium are still of donor origin. Host chimerism is displayed in tissue from an inguinal lymph node of a kidney recipient (right). Red-colored staining marks an even scattering of cells positive for the kidney donor's HLA-B7,40. The transplantation had been performed 29 years earlier. Two-way chimerism appears to characterize all successful allografts.**

Therapeutic bone marrow transplantation derived in the 1960s from laboratory investigations of Peter Medawar and colleagues in England, whose work provided a pioneering description of acquired immune tolerance. In initial experiments, spleen cells from adult mice were injected into immunoincompetent fetal or neonatal mice. The injected cells proliferated, essentially endowing each host with the donor's immune system. The host was thereby rendered incapable of recognizing subsequent donor grafts as nonself. Further studies established that irradiation of adult mice achieved the same end: Ablation of hematolymphopoietic cells rendered the animals "newborn," in the sense of being incapable of rejecting engrafted bone marrow.

It soon emerged, however, that an immunologically active graft could reject its recipient. The risk proved to be roughly proportional to the extent of mismatch between donor and recipient histocompatibility antigens. Hence, close matching would be needed. Eventually, a strategy for clinical bone marrow grafting emerged from the experimental findings. In receiving bone marrow after cytoablative irradiation, the patient got a new immune system from the donor. But HLA matching between donor and recipient was essential to prevent graft-versus-host disease. After successful engraftment, maintenance immunosuppression was often not needed—a circumstance reminiscent of the acquired tolerance identified in mice.

For solid organ transplantation, the situation seemed quite different. By 1968, when bone marrow grafting achieved its first clinical successes, thousands of solid organ transplantations, chiefly of kidneys, had been performed, using immunosuppression to prevent rejection and relying less on HLA matching. The number of renal transplantations had started to climb in mid-1962, when it became clear that rejection of renal allografts by patients receiving baseline azathioprine therapy could be reversed by the addition of, or intensification of therapy with, the highly dose-maneuverable corticosteroid prednisone (Figure 2). Agents that came into use later as baseline therapy, including cyclosporine and tacrolimus, were more potent and reliable. Allotransplantation was expanded to include transplantation of liver, heart, lungs, pancreas, and intestine. Meanwhile, it was becoming evident that despite lack of HLA matching, patients' need for maintenance immunosuppression often gradually declined. Indeed, in occasional patients such treatment could eventually be discontinued.

What precisely did immunosuppression achieve in recipients of a solid organ transplant? The graft-versus-host disease seen after bone marrow transplantation could be viewed as a unidirectional immune reaction in which engrafted immune cells attack a defenseless host. By analogy, rejection of an engrafted

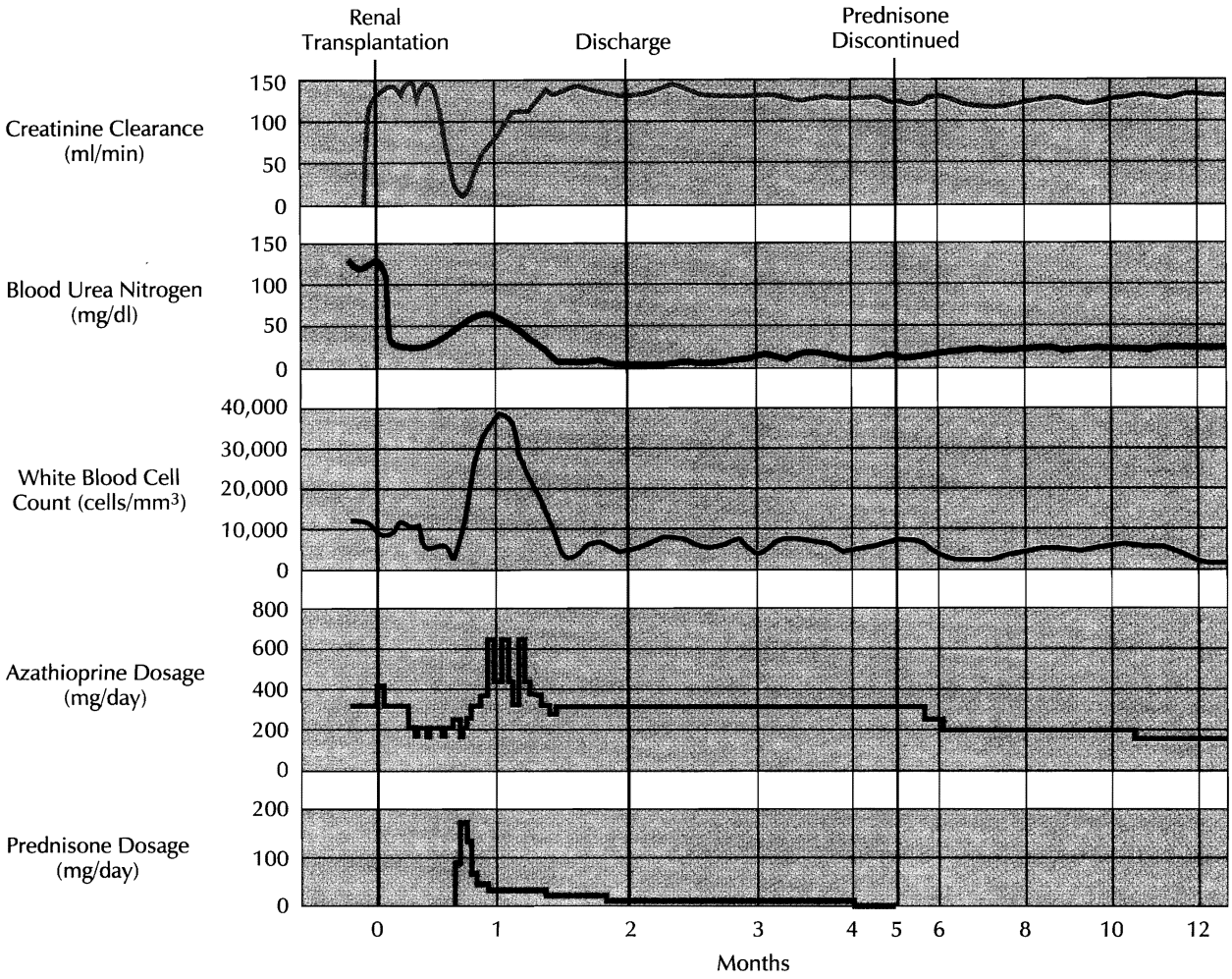

Figure 2. **Typical use of immunosuppressive drugs to circumvent transplant rejection is shown by the postoperative course of an early (1963) kidney allograft recipient. After more than two weeks of azathioprine therapy and good renal function, deterioration of creatinine clearance and blood urea nitrogen level revealed the onset of rejection, which was reversed by addition of prednisone. The patient was weaned from the corticosteroid, and the azathioprine dosage was decreased to levels less than those that had earlier failed to forestall rejection. Subsequent graft function remained stable, despite a lack of HLA matching between donor and recipient.**

solid organ could be viewed as a one-way process in which host immune cells destroy a defenseless allograft (Figure 3). Immunosuppression would thus serve simply to stifle the host immune system. However, there were hints of a more complex, accommodative process in organ recipients.

Two-Way Paradigm

An early clinical hint emerged in 1964 from studies of kidney donors and recipients by Charles Kirkpatrick and W. E. C. Wilson, immunology fellows on the service of David Talmage at the University of Colorado. The investigators looked at kidney transplantations from donors with positive skin tests for tuberculin or other antigens to recipients with negative skin tests. After surgery, 77% of the recipients (47 of 61) showed positive tests, indicating that skin-test conversion had been acquired along with the organ. In the remainder, who still had negative skin tests, the transplant had been rejected. The implication—that functioning immune cells had migrated from successful grafts into recipients' tissues—was generally deemed untenable, since the kidney was thought to be leukocyte-poor. Similar clues emerged in liver-transplant recipients, who were found to have acquired circulating donor-specific immunoglobulin types. This, too, was generally discounted.

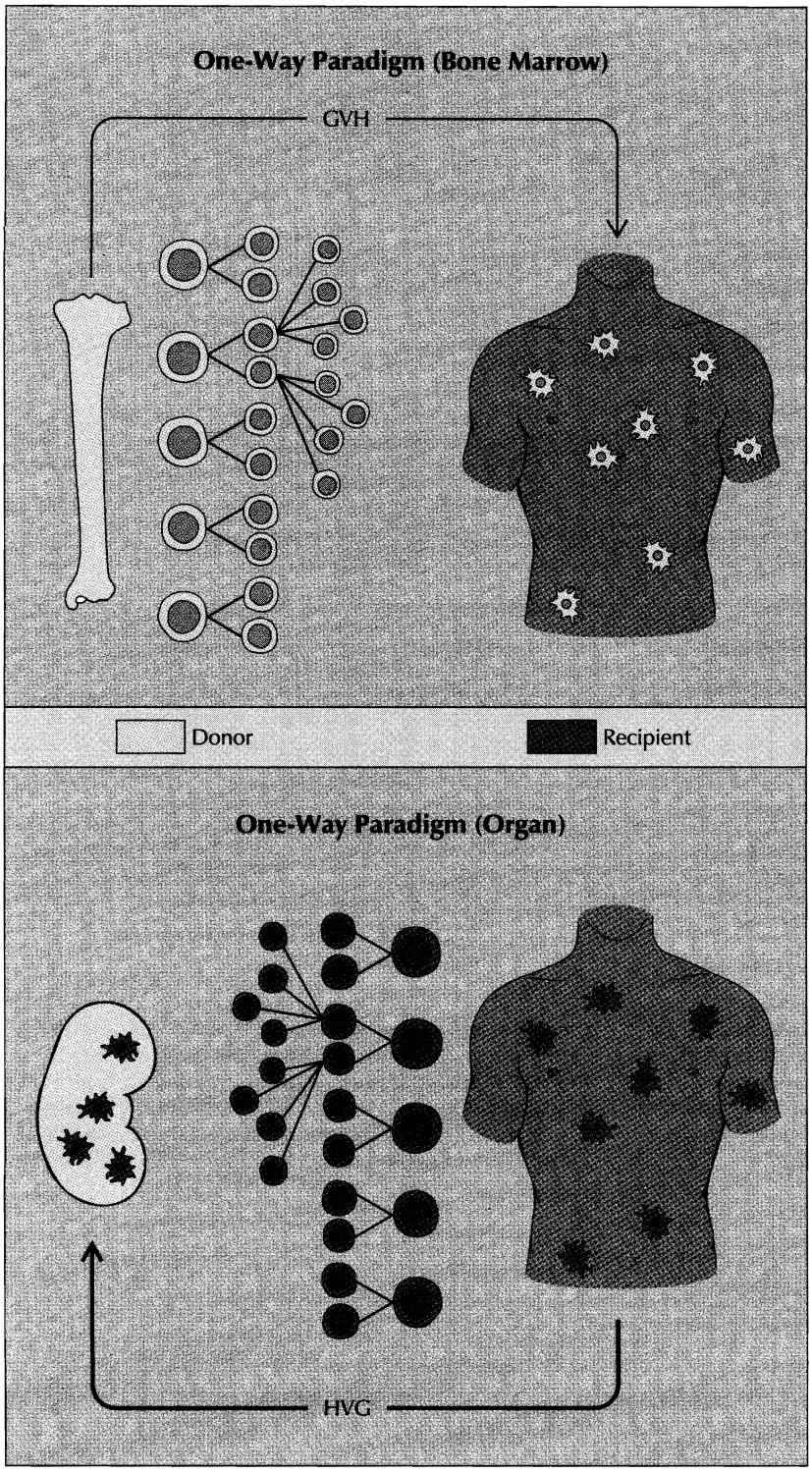

Figure 3. **One-way paradigms of immunologic events in transplantation reflect early concepts of poor outcomes as the result of one-sided wars. In bone marrow transplantation (top), the host, pretreated with cytoablative irradiation, was thought to have no residual immune system. Thus, in the absence of HLA matching, graft immune cells would proliferate and mount an unanswered attack (graft-versus-host [GVH] disease). In organ transplantation (bottom), the graft (e.g., kidney) was thought to have no inherent immune system. In the absence of pharmacologic immunosuppression, host cells would proliferate and attack (host-versus-graft [HVG] disease).**

Meanwhile, it was becoming clear that immune cells could migrate from host to graft. The first hint came in 1969 from karyotyping studies in female recipients of livers from male cadavers. In the engrafted organ, hepatocytes and the endothelium of the major blood vessels retained the donor male sex karyotype. But within 100 days of transplantation, the entire macrophage system, including Kupffer cells, had been replaced by female macrophages, as evidenced by the cells' Barr bodies.

In 1991, it was found, first in rats and then in humans, that transplanted intestine becomes chimeric in much the same way. The bowel epithelium remains that of the donor, but lymphoreticular cells become those of the recipient. For the first time, it was proposed that graft chimerism might be common to all accepted grafts—a speculation soon confirmed in studies of kidney, heart, and lung grafts.

Until then, the assumption had been that an engrafted organ's lymphocytes were simply destroyed by the host. Animal experiments began to suggest otherwise when work at the University of Pittsburgh showed that donor lymphocytes from small-bowel allografts in rats receiving tacrolimus used vascular routes to home in on widely distributed host lymphoid tissues. Although a graft-versus-host reaction was identified, it was suspected to be a peculiarity of the rat-strain combination being utilized.

Thus, in 1992, Pittsburgh investigators undertook to find systemic chimerism (donor leukocytes inhabiting host tissues) in human kidney and liver transplant recipients. Those studied included some of the same patients whose skin tests

had been investigated three decades earlier, who were now among the world's longest survivors of kidney grafts.

The search for donor cells in such hosts was facilitated by new techniques of immunostaining or polymerase chain reaction (PCR) analysis for identification of a Y chromosome—unequivocal evidence of systemic chimerization when found in cells of female recipients of organs from male donors—or of HLA alleles characteristic of chromosome 6 of the donor but not the recipient. Five kidney recipients were studied 27 to 29 years after transplantation. In one, all immunosuppressive treatment had been stopped 12 years earlier; the others were still receiving azathioprine with or without prednisone. For four recipients, the kidney donor was still available for immunologic studies, including HLA retyping. In each case, lymphocytes that resembled dendritic cells and had HLA types matching the donor but not the recipient were identified in the recipient's skin and lymph nodes. In the fifth patient, a woman who had received one of her father's kidneys 29 years earlier, cells with a Y chromosome were identified in the skin. In all five, kidney biopsy showed that donor immune cells had been replaced by recipient cells.

Liver recipients had the same patterns. Of 210 patients treated at either the University of Colorado or the University of Pittsburgh from 1963 to 1981, 44 were still living in January 1992. Six had not taken baseline immunosuppressive drugs for five to 13 years, and five had successfully stopped taking prednisone. For most of the others, drug weaning had been started. The five drug-free patients, and an additional group randomly selected from those still taking immunosuppressants, consented to biopsy studies. In every one of 22 recipients examined, donor cells could be identified in skin and lymph nodes by Y-chromosome testing, HLA typing, or both.

These findings are paralleled by observations in children who have undergone liver transplantation for type IV glycogen storage disease, a congenital enzyme deficiency leading to systemic accumulation of an insoluble amylopectin-like polysaccharide. Patients who do not die from cirrhosis, which usually develops within a year or two after birth, remain at risk for lethal cardiomyopathy or neuromuscular syndromes. Remarkably, transplant recipients have shown amylopectin absorption in extrahepatic tissues, including the heart, as long as six years after liver replacement. In two such patients, donor lymphocytes were found in the heart, apparently serving as enzyme carriers, as long as 91 months after surgery.

Similar chimerization and metabolic benefit have followed liver transplantation in a child with the glucocerebrosidase deficiency of type I Gaucher's disease. Such disorders had been thought to be correctable only by bone marrow transplantation. Evidently, any successful transplantation procedure may restore metabolic function. Moreover, the number of allogeneic cells required appears to be surprisingly small.

Role of Dendritic Cells

In essence, every organ transplantation results in bidirectional traffic of immune cells. On the one hand, host cells migrate to the donated organ. On the other hand, immunologically active donor cells are assimilated into the host's vastly greater immune network (Figure 4). The traffic apparently leads to a mutual accommodation, provided that the graft and host can survive the initial confrontation.

A crucial issue is how small numbers of donor cells entering foreign territory can profoundly alter the activities of the host's immunologic army. Although donor cells have multiple lineages, the most important type appears to be the antigen-presenting dendritic leukocyte, described in the 1970s by Ralph M. Steinman and Zanvil A. Cohn at Rockefeller University. First isolated from mouse lymphoid tissue during studies of accessory cells in immune responses, dendritic leukocytes have long fascinated researchers. Among bone marrow–derived leukocytes, they are numerically small, yet they are distributed throughout the body, including the interstitium of organs such as the kidneys and heart, where immunologically active cells were once thought to be virtually absent. Unlike macrophages, they constitutively express high levels of major histocompatibility complex (MHC) class II molecules—which suggests specialization for antigen presentation. In fact, they are the most potent known cellular stimulators of T-cell responses, both in vitro and in vivo. Dendritic cells had been impossible to culture until the recent discovery that granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes propagation of dendritic-cell precursors.

A series of experiments conducted in Pittsburgh by Lina Lu and colleagues has probed the role of dendritic cells in inducing tolerance to an engrafted organ. The investigators studied the transplanted liver, which ap-

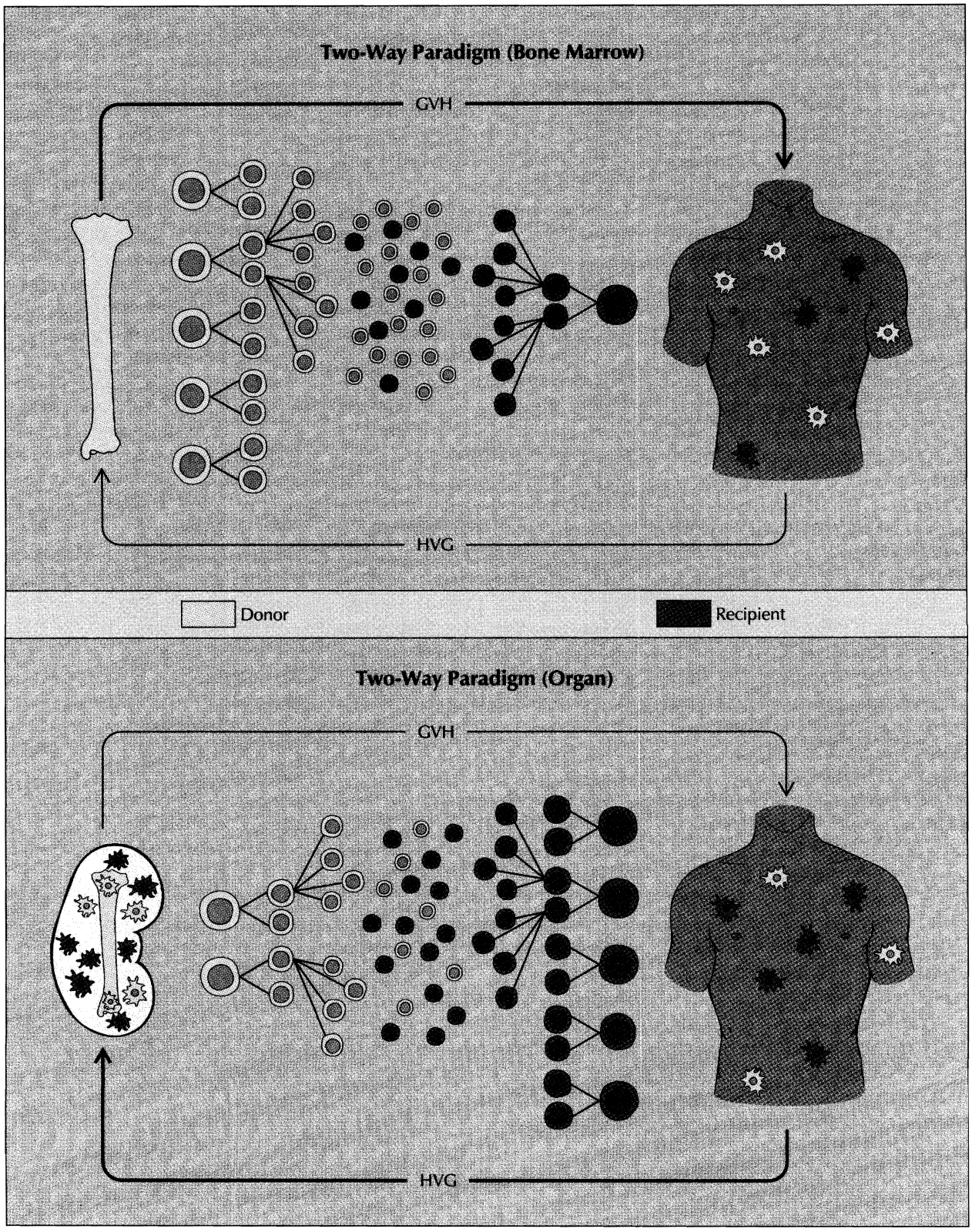

Figure 4. **Two-way paradigms of bone marrow and solid organ grafting reflect the recognition that both a graft and its recipient become chimeric. In marrow transplantation (top), cytoablative pretreatment never completely destroys the host's immune system; in organ transplantation (bottom), the donated organ always has "passenger leukocytes" (giving the host what amounts to a covert bone marrow graft). For the marrow recipient, the immune-cell traffic is predominantly graft-versus-host (GVH), whereas for the organ recipient, it is chiefly host-versus-graft (HVG).**

pears to be the graft for which tolerance is achieved most easily. Indeed, experimental liver allotransplantation in mice—a technical tour de force achieved by Shiguang Qien and colleagues—usually requires no recipient immunosuppression. Additionally, a liver transplant gives the recipient mouse increased receptivity to concurrent or subsequent transplants from the donor strain. In such ways, the liver demonstrates an inherent capacity to render the recipient more accepting of all donor tissues; this may reflect the organ's richness in immunologically active cells, which in turn may reflect the liver's role as a fetal center of hematopoiesis.

In initial experiments, nonparenchymal cells from mouse liver were cultured in medium enriched with GM-CSF. About 10^7 such cells were obtainable from each organ. After seven days, a subpopulation of some two million cells floating free in the medium expressed cell-surface markers characteristic of dendritic cells. Macrophages and fibroblasts also proliferated but remained attached to the culture plate. Microscopic examination of the free-floating cells showed them to have the morphology of dendritic cells, including veil-like cytoplasmic extensions (Figure 5). The cells were avidly phagocytic but were poor stimulators of allogeneic T cells. In short, they resembled immunologically immature dendritic cells. They could not be induced to mature.

The impasse was broken by simulation of a hepatic microenvironment, created by transferring the cells to culture plates coated with type I collagen. This induced a hallmark of dendritic-cell maturity, strong expression of class II antigen. The cells exhibited a concomitant decrease in phagocytic activity and an increase in their ability to stimulate T-cell proliferation. Injected into the footpad of mice, purified dendritic-cell precursors homed in on T-cell areas of lymph nodes and the spleen, where they too could be shown to augment expression of class II antigen.

Next, liver transplantations were performed for a fully allogeneic (MHC class I–disparate and class II–disparate), but nonrejecting, mouse-strain combination. Samples of the recipient's bone marrow and spleen showed nidi of donor as well as recipient dendritic cells at varying stages of maturation, as identified by the techniques used in culture experiments. The proportions of immature and mature cells 150 days after transplantation were much the same as at two weeks.

The possible significance of these immunologic oases for the induction of tolerance to a graft is suggested by recent experiments of J. W. Streilein and colleagues at the University of Miami, and now at Harvard University, in which the anterior chamber of the eye, with its constituent iris, ciliary body, and other tissues, has proved to be an immunologically privileged site, lined by immature dendritic cells. An antigenic peptide (bovine serum albumin) injected into the eye of a laboratory animal is taken up by these cells, which within a few hours present the antigen to T cells in regional lymph nodes and the spleen. When the animal is systemically challenged with the same antigen 30 days later, the surprising consequence is an anergic response instead of the expected hypersensitivity.

Evidently, immature dendritic cells present antigen in an "abnormal" manner, which leads not to sensitization but to tolerogenesis—a phenomenon that Streilein's group calls the anterior-chamber–associated immune-deviation complex. The implication is that immature dendritic cells migrating from an engrafted organ and immature, antigen-bearing dendritic cells migrating from the anterior chamber of the eye are fundamentally the same.

Successful immunosuppressive treatment of an organ-transplant recipient thus appears to promote an immunologic balance. The nonspecific effects of immunosuppressive drugs, inimical to cell proliferation, indeed suppress clonal expansion—notably, that of host cytotoxic T lymphocytes, which would otherwise mount a rejection response. At the same time, however, such drugs permit a process dependent on the movement of donor cells from the graft to its recipient. The massive cytokine release representing the host's naive response to the insult of transplantation seems conducive to such traffic, in that mediators such as cytokines or conventional growth factors may promote cell passage from and into the graft. Immunosuppression enables graft and recipient immune cells to meet, mingle, and react, without leading to graft failure. The drugs thus chaperone a process of immunologic reeducation (Figure 6) that alters the host's immune surveillance as well as the migrating cells' reactivity.

The precise nature of that reeducation remains uncertain. In a suppressor mechanism, donor cells would be bystanders disrupting intercellular signaling among recipient cells such as CD4 helper T cells and CD8 cytotoxic T cells. The effect might be reversible, with resumption of clonal cytotoxic T-cell proliferation if the suppressor cells fail

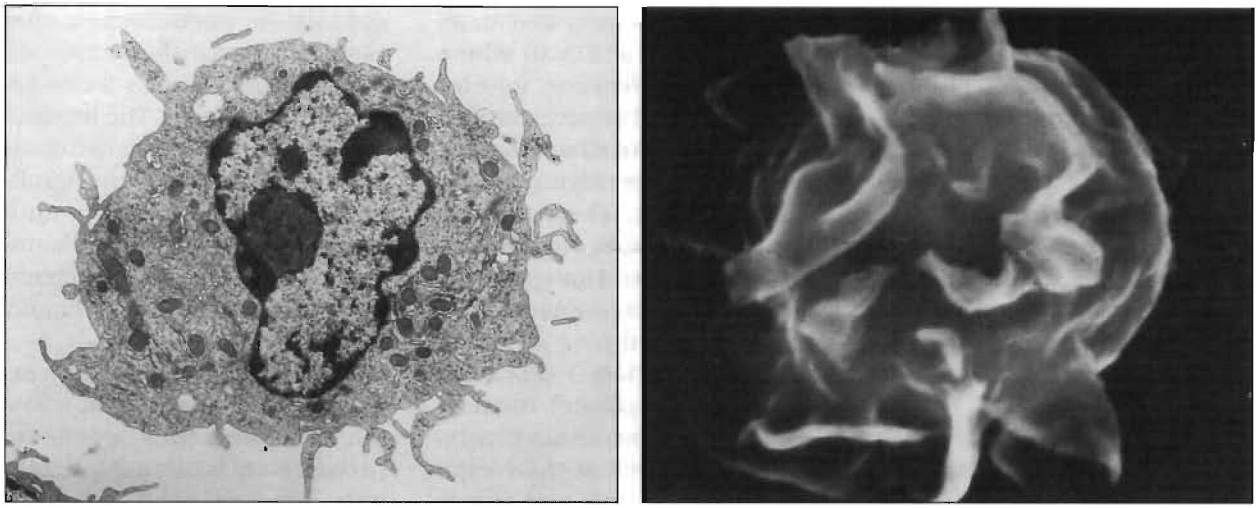

Figure 5. **The donor cell type crucial for induction of host tolerance to a graft appears to be the dendritic leukocyte, now known to be culturable in medium enriched in *granulo*cyte-macrophage colony-stimulating factor. The dendritic leukocytes shown were isolated after nine days of culture of nonparenchymal cells extracted from murine liver. Transmission (left) and scanning (right) electron micrographs demonstrate dendritic-cell morphology, including an irregular nucleus, prominent nucleoli, and veil-like extensions of the cell surface. In further studies, the cells have shown functional attributes of dendritic cells, including phagocytic activity, an ability to home in on a host's lymph nodes and spleen, and a strong influence on host T cells by antigen presentation.**

to block activation signals. In a veto mechanism, the antigen-presenting donor cell would itself be a "veto cell," irreversibly inactivating certain class I reactive cytotoxic T cells—namely, those host cells capable of recognizing and destroying donor cells. The work of Judith Thomas and colleagues at East Carolina University and now the University of Alabama implicates CD8 dendritic cells as candidate veto cells subserving tolerogenesis in a monkey model of combined kidney and bone marrow transplantation. Considering the present state of knowledge, however, it might be best not to ascribe tolerogenesis to any single mechanism. In immune reactions, nature appears to favor redundancy, with its opportunities for multiple levels of control.

Somewhat less uncertain is how the chimerism following organ transplantation might perpetuate itself for months in mouse models, and for decades in human transplant recipients, when the lifespan of the dendritic cell is thought to be only days or weeks. The identification of donor dendritic-cell precursors in the bone marrow of mouse liver allograft recipients up to a half-year after the surgery (equivalent to many years of human life) implies that the host bone marrow and the engrafted organ may both become repositories of dendritic-cell precursors. The precursors might include both pluripotent stem cells and their progeny of immature but committed cells. Donor cells could not be found in the bone marrow of mice that had acutely rejected a cardiac allograft.

Therapeutic Implications

Awareness that chimerism is a prerequisite for graft acceptance suggests strategies for moving toward the goal of drug-free graft acceptance. For one, there may be a perioperative window for adjuvant infusion of unaltered HLA-incompatible bone marrow or donor-specific blood cells (or perhaps eventually dendritic-cell precursors cultured from the donor). A clinical trial under way in Pittsburgh includes more than 100 recipients of cadaveric organs (kidney, liver, heart, lung, or small bowel) who also received, without alteration of their standard immunosuppressive regimen of tacrolimus and prednisone, an infusion of 3 to 5×10^8 cells/kg from the bone marrow of the cadaver's thoracicolumbar vertebrae, a rich source of leukocytes that tends to show a relatively low proportion of mature T cells.

At four to 16 months, the first 18 patients have had a good clinical outcome, and all but one (who could not be studied owing to perfect HLA matching with a donor of the same sex) have shown blood chimerism exceeding by more than a thousandfold the chimerism typical after organ

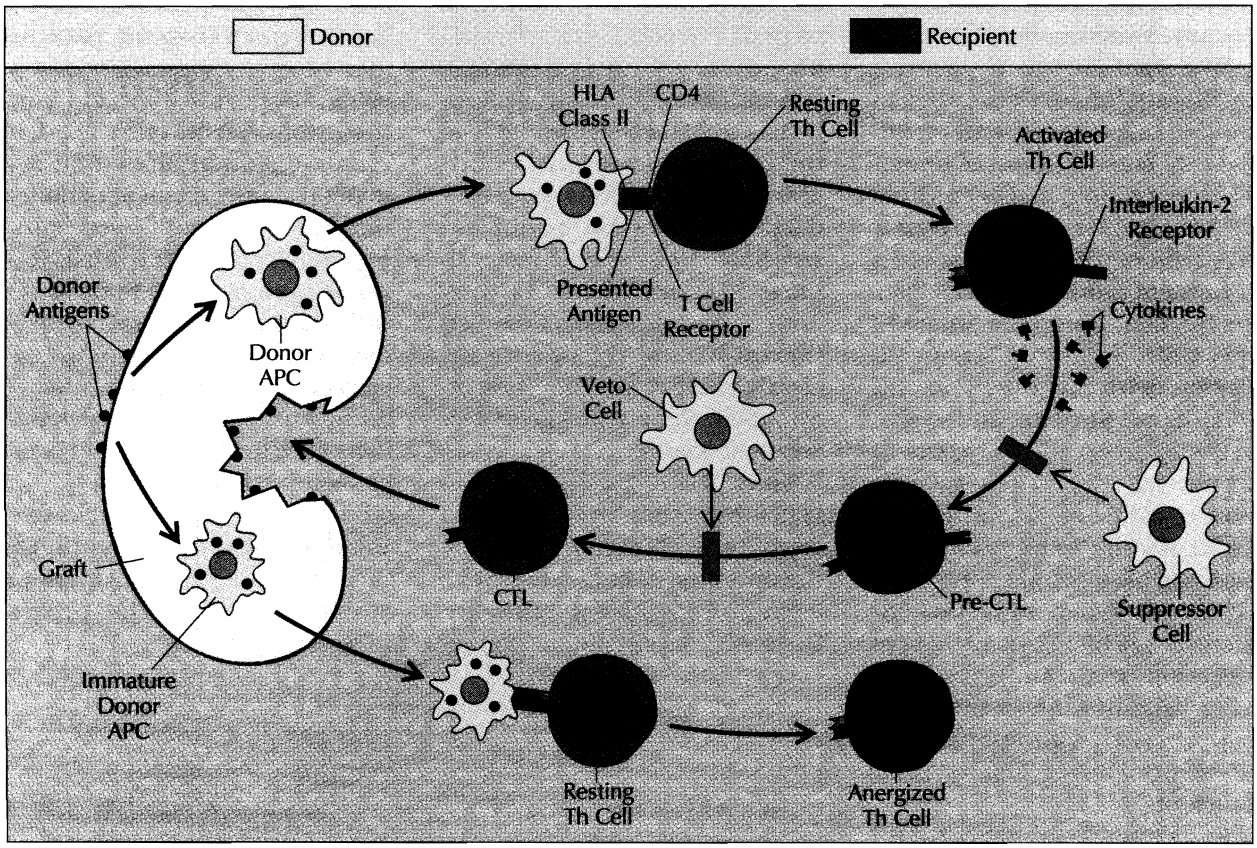

Figure 6. **Ability of donor antigen-presenting cells (APCs) to "reeducate" the immune system of a transplant recipient may take multiple forms. After transplantation, donor APCs (notably, dendritic cells) migrate from the graft into the recipient (top left), activating resting helper T cells (Th). These in turn participate in the generation of cytotoxic T lymphocytes (CTLs) specific for the graft. This cascade, however, can be altered, presumably by donor dendritic cells at various stages of activation. Donor cells acting by a suppressor mechanism would reversibly block a host-cell interaction (exemplified here by blockade of cytokine activation signals from a Th cell to a resting pre-CTL). In a veto mechanism, donor cells would specifically and irreversibly disable host CTLs capable of recognizing the donor phenotype. There is also evidence that emigrating donor dendritic cells (bottom left), because of their immature phenotype, may anergize rather than activate resting Th cells. All these interactions could induce donor-specific hyporesponsiveness, leading to allograft acceptance.**

transplantation alone. Rejection has been controlled with no unusual difficulty. The group's high rate of survival marks them as the first to undergo HLA-mismatched cadaveric organ transplantation with reasonable expectation that some may become drug-free after five to 10 years.

Perioperative infusions of donor lymphoreticular cells may be most notably useful in improving outcomes for transplantation of organs other than the liver. If the inherent capacity of an engrafted organ to promote its own acceptance depends on its content of immunologically active cells, the liver stands uppermost in tolerogenicity, with lung less inherently tolerogenic, and the heart and kidney least so. A microchimeric state induced by engraftment of HLA-mismatched bone marrow (and institution of immunosuppression) in the absence of any organ transplantation may also prove valuable for its own sake. The intriguing findings of metabolic correction following liver transplantation for type IV glycogen storage disease or type I Gaucher's disease indicate that amelioration of these and other pancellular enzyme deficiencies may not require total marrow replacement.

Eventually, adjuvant infusion of donor immune cells may benefit whole-organ xenotransplantation. In laboratory models of such efforts involving engraftments from hamster to rat, the first immunologic hurdle is raised by pre-formed xenospecific antibodies, which rapidly damage the graft's blood vessels. If that crisis can be averted, bidirectional cell migrations have already been found to establish

the same mutual chimerism that occurs in allotransplantation.

The chief causes of late death in current long-term studies of human organ-transplant recipients are complications of immunosuppression. Between June 1992 and June 1995, a prospective trial of weaning from such treatment has enrolled 73 liver recipients. Complete weaning has been accomplished in 20 (27%), with as much as 35 months of follow-up, and is progressing in 31 (42%), many of whom have been taking only homeopathic doses for as long as 33 months. Immunosuppression has been resumed in 22 patients (30%). In only two instances has histologically severe rejection occurred. It resolved after reinstitution of immunosuppression, without graft loss or demonstrable loss of graft function.

For kidney recipients, weaning appears to be more perilous. Even so, it seems feasible in isolated cases. Of 10 survivors of kidney transplantations performed in 1962 and 1963, five have been drug-free for one to 30 years. Long-term monitoring of a transplant recipient's evolving donor-specific nonreactivity may eventually assist in decision making regarding continued immunosuppression.

Conclusion

The mutual chimerism arising after successful organ transplantation can be viewed as cancelling the immunologic effects of donor and recipient. Throughout the process, however, the abundance of donor immune cells remains small compared with the numbers of host leukocytes. As managed by current immunosuppressive regimens, the process proceeds slowly in even the most successful cases. Failure manifests itself as graft rejection, graft-versus-host disease ("host rejection"), or sometimes both. Iatrogenically disabling the recipient side at the outset, as is done in bone marrow transplantation, renders the host prone to graft-versus-host disease and necessitates HLA matching. Leaving both sides intact, as in organ transplantation, removes the necessity for HLA matching and diminishes the risk of graft-versus-host disease.

Thus the apparent gap between bone marrow and solid organ transplantation is simply the outcome of entrenched differences in treatment strategies. On closer inspection, the gap essentially disappears. In receiving an organ transplant, patients also receive "passenger leukocytes"—a covert bone marrow transplant. On the other hand, it seems highly unlikely that cytoablative pretreatment of bone-marrow recipients ever completely destroys the host immune system. Even in patients with the best outcomes, sensitive techniques have now revealed trace populations of surviving host leukocytes. Such patients are in fact mirror images of solid-organ recipients (in whom donor immune cells are the numerical minority). In either group, the seminal event in successful engraftment appears to be chimerization. □

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