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Pediatric Surgery

SIXTH EDITION

VOLUME ONE

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2006

Chapter 42

Principles of Transplantation

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Histocompatibility matching, immunosuppression, tissue preservation, and techniques of implantation have been considered to be the generic struts of both organ and bone marrow cell transplantation. However, neither kind of transplantation could have emerged as a clinical service were it not for the induction by the graft itself of various degrees on donor-specific nonreactivity (tolerance). Without this fifth factor, no transplant recipient could survive for long if the amount of immunosuppression given to obtain initial engraftment had to be continued.

THE ENIGMA OF ACQUIRED TOLERANCE

The variable acquired tolerance on which transplantation depends has been one of the most enigmatic and controversial issues in all of biology. This was caused, in part, by the unexpected achievement of organ engraftment at an early time—a decade before successful bone marrow transplantation and in ostensible violation of the very principles that would shape the impending revolution in general immunology. As a consequence, clinical organ transplantation was developed empirically rather than as a branch of classic immunology. This occurred in four distinct phases, each lasting more than a decade. Only at the end was it possible to explain organ engraftment and thereby eliminate the mystique of transplantation.

Phase 1: 1953-1968

Phase 1 began between 1953-1956 with the demonstration that neonatal mice[8,9] and irradiated adult mice[36] develop donor-specific tolerance after successful engraftment of donor hematolymphopoietic cells. The key observation was that the mice bearing donor cells (donor leukocyte chimerism) could now accept skin grafts from the original donor strain but from no other strain (Fig. 42-1). The chimeric neonatal mice and the irradiated adult mice were analogues of today's bone marrow transplantation into immune deficient and cytoablated humans, respectively. But because a good histocompatibility match was required for avoidance of graft-versus-host disease (GVHD) and of rejection,[39] clinical application of bone marrow transplantation had to await discovery of the human leukocyte antigens (HLA). When this was accomplished,[3,21,99] the successfully treated human bone marrow recipients of 1968 were oversized versions of the tolerant chimeric mice.

By the time of the clinical bone marrow transplant breakthrough of 1968, kidney transplantation[22,23,29,42,48,49,64] already was an established clinical service, albeit a flawed one.[65] In addition, the first long survivals had been recorded after liver[72] and heart transplantation[5]; these were followed in 1968-1969 by the first prolonged survival of a lung[18] and a pancreas recipient[34] (Table 42-1). All of the organ transplant successes had been accomplished in the ostensible absence of leukocyte chimerism, without HLA matching and with no evidence of GVHD. By going

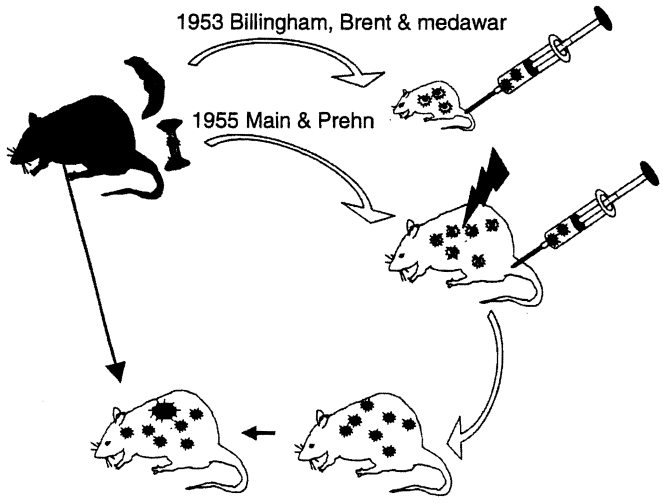


Figure 42-1 The mouse models of acquired tolerance described between 1953 and 1956. White cells (leukocytes) were isolated from the spleen or bone marrow of adult donor mice *(upper left)* and injected into the bloodstream of newborn mice *(upper right)* or of irradiated adult mice *(middle right)*. Under both circumstances, the recipient immune system was too weak to reject the foreign cells *(dark shaded)*. With engraftment of the injected cells (i.e., donor leukocyte chimerism), the recipient mice now could freely accept tissues and organs from the leukocyte donor but from no other donor *(bottom left)*.

TABLE 42-1 First Successful Transplantation of Human Allografts (Survival > 1 Year)

Organ	City	Date	Physician/ Surgeon	Reference
Kidney	Boston	Jan. 24, 1959	Merrill/ Murray	42, 48
Liver	Denver	July 23, 1967	Starzl	72
Heart	Cape Town	Jan. 2, 1968	Barnard	5
Lung	Ghent	Nov. 14, 1968	Derom	18
Pancreas	Minneapolis	June 3, 1969	Lillehei	34

beyond the leukocyte chimerism boundaries established by the mouse tolerance models, organ transplantation had entered unmapped territory.

"Pseudotolerant" Organ Recipients

Two unexplained features of the alloimmune response had made it feasible to forge ahead precociously with organ transplantation.[64] The first was that organ rejection is highly reversible. The second was that an organ allograft, if protected by nonspecific immunosuppression, could induce its own acceptance. "Self-induced engraftment" was observed for the first time in 1959 in two fraternal twin kidney recipients, first in Boston by Joseph Murray[48] and then in Paris by Jean Hamburger.[22] These were the first successful transplantations in the world of an organ allograft, in any species. Both patients had been conditioned with 450 R sublethal total-body irradiation before transplantation. The renal allografts functioned for more than 2 decades without a need for maintenance drug therapy, which was, in fact, not yet available.

A similar drug-free state was next occasionally observed after kidney transplantation (and more frequently after liver replacement) in mongrel dogs who were treated with a single immunosuppressive agent: 6-mercaptopurine (6-MP),[55,112] azathioprine,[50,66] prednisone,[113] or antilymphocyte globulin (ALG).[70] After treatment was stopped, rejection in some animals never developed (Fig. 42-2A). Such results were exceedingly rare; less than 1% of the canine kidney experiments done under 6-MP and azathioprine up to the summer of 1962. However, the possibility that an organ could be inherently tolerogenic was crystallized by the human experience summarized in the title of a report in 1963 of a series of live donor kidney recipients treated in Denver: "The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance."[64] The recipients had been given azathioprine *before* as well as after renal transplantation, adding large doses of prednisone to treat rejections that were monitored by serial testing of serum creatinine (Fig. 42-3A). Rejection occurred in almost every case, and 25% of the grafts were lost to uncontrolled acute rejection. However, the 1-year survival of 46 allografts obtained from familial donors over a 16-month period in 1962-1963 was an unprecedented 75%.

The development of partial tolerance in many of the survivors was inferred from the rapidly declining need for treatment after rejection reversal (see Fig. 42-3A). Nine (19%) of the 46 allografts functioned for the next 4 decades, each depicted in Figure 42-4 as a horizontal bar. Moreover, all immunosuppression eventually was stopped in seven of the nine patients without rejection for periods ranging from 6 to 40 years (the solid portion of the bars). Eight of the nine patients are still alive and bear the longest surviving organ allografts in the world.[92]

What was the connection between the tolerant mouse models, the irradiated fraternal twin kidney recipients in Boston and Paris, the ultimate drug-free canine organ recipients (see Fig. 42-2A), and the unique cluster of "pseudotolerant" human kidney recipients in Denver (Fig. 42-4)? The mystery deepened with the demonstration in 1966 in France,[16] England,[11,12,53] and the United States[74] that the liver can be transplanted in about 20% of outbred pigs without any treatment at all (see Fig. 42-2B). None of the animal or human organ recipients, whether off or on maintenance immunosuppression, was thought to have donor leukocyte chimerism.

A

B

Figure 42-2 *A*, Caine recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The dog was treated for only 120 days with azathioprine and died of old age after 13 years. *B*, A spontaneously tolerant pig recipient described by Caine.[12]

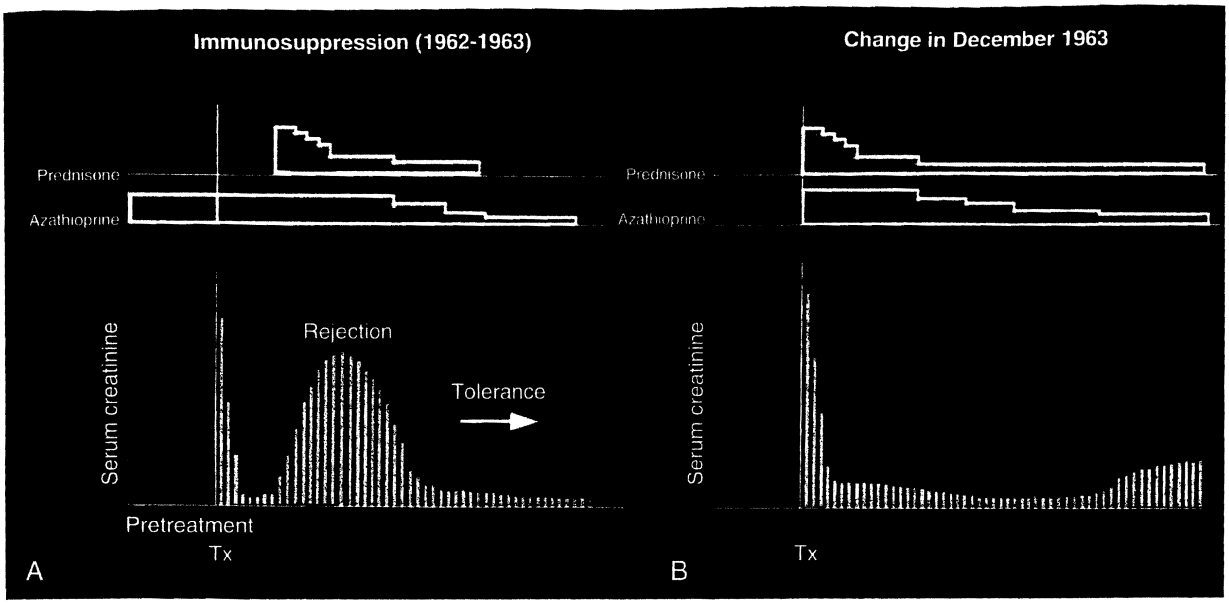


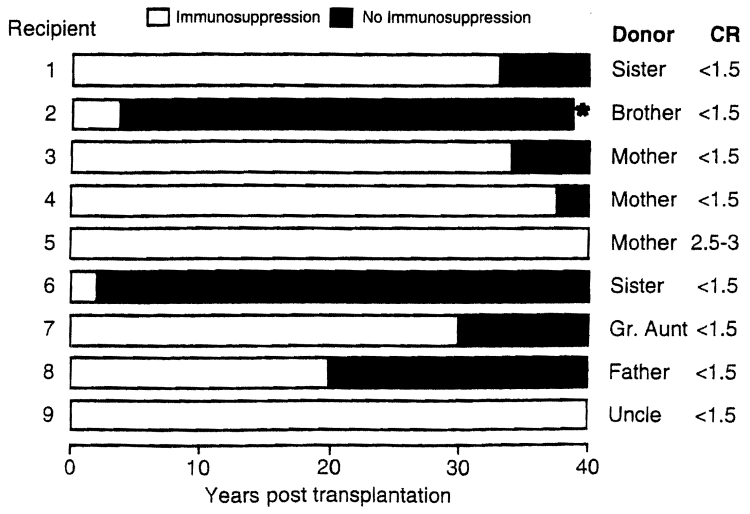
Figure 42-3 *A,* Empirically developed immunosuppression used for kidney transplant recipients in 1962-1963. Note the reversal of rejection with the addition of prednisone to azathioprine. More than a third of a century later it was realized that the timing of drug administration had been in accord with the tolerogenic principles of immunosuppression (see text). *B,* Treatment revisions in immunosuppression made at the University of Colorado in December, 1963, that unwittingly violated principles of tolerogenic immunosuppression. Pretreatment was de-emphasized or eliminated, and high doses of prednisone were given prophylactically instead of as needed. Although the frequency of acute rejection was reduced, the drug-free tolerance shown in Figure 42-4 was no longer seen.

False Premises of Phase 1

Thus, organ transplantation became disconnected at a very early time from the scientific anchor of leukocyte chimerism that had been established by the mouse models and was soon to be exemplified by human bone marrow transplantation. The resulting intellectual separation of the two kinds of transplantation (Fig. 42-5) was an unchallenged legacy of phase 1, passed on from generation to generation ever since.

There was another dark legacy of phase 1. This was a modified version of the treatment strategy that had been developed with azathioprine and prednisone (see Fig. 42-3B). The principal change was the use of large prophylactic doses of prednisone from the time of operation, instead of the administration of corticosteroids only when needed. In a second modification, the pretreatment was de-emphasized (see Fig. 42-3B). The incidence of acute rejection was greatly reduced after these changes. However, no cluster of drug-free kidney recipients like that shown in Figure 42-4 was ever seen again, anywhere in the world. More than 35 years passed before the long-term immunologic consequences of the modifications were realized.

Figure 42-4 Nine (19%) of the 46 live donor kidney recipients treated at the University of Colorado over an 18-month period beginning in the autumn of 1962. The solid portion of the horizontal bars depicts the time off immunosuppression. Note that the current serum creatinine concentration (CR) is normal in all but one patient.
*Murdered: kidney allograft normal at autopsy.



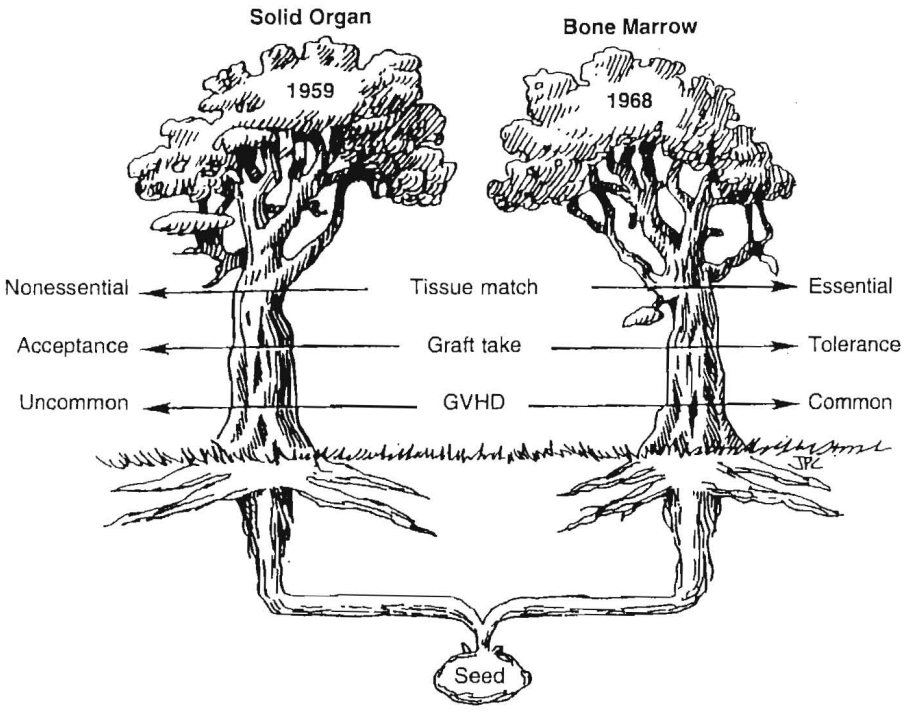


Figure 42-5 The developmental tree of bone marrow *(right)* and organ transplantation *(left)* after it was demonstrated that rejection is an immunologic response. GVHD, graft-versus-host disease.

Phase 2: 1969-1979

Throughout the succeeding phase 2 that began in 1969, immunosuppression for organ transplantation was based on azathioprine and prophylactic high-dose prednisone to which ALG was added after 1966[70,71] in about 15% of centers. Phase 2 was a bleak period. In the view of critics, the heavy mortality, and particularly the devastating morbidity caused by corticosteroid dependence, made organ transplantation (even of kidneys) as much a disease as a treatment. Most of the liver and heart transplant programs that had been established in an initial burst of optimism after the first successful cases closed down.

But in the few remaining centers, patients like the one shown in Figure 42-6 bore witness to what some day would be accomplished on a grand scale. Four years old at the time of her liver replacement for biliary atresia and a hepatoma in 1969, she is the longest surviving recipient of an extrarenal organ.

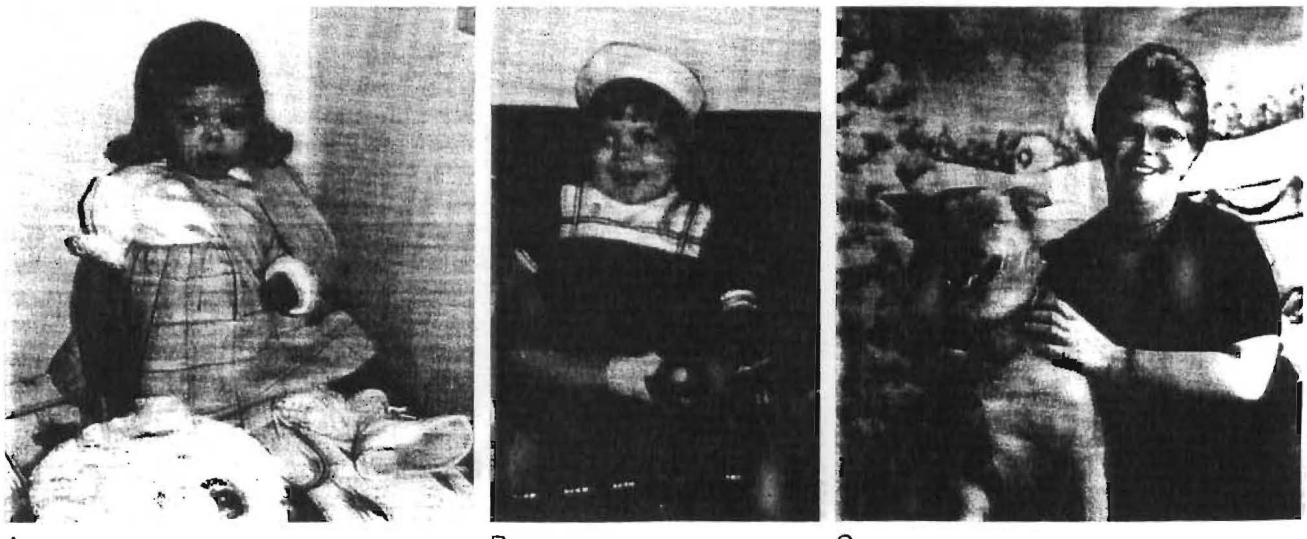


Figure 42-6 Four-year-old at the time of liver replacement for biliary atresia and a hepatoma but now in her 35th post-transplant year. She is the longest surviving recipient of an extrarenal organ.

Phase 3: 1980-1991

In fact, what had appeared to be the sunset of extrarenal organ transplantation was only the dawn of phase 3, which began with the clinical introduction of cyclosporine,[13,14,77,78] followed a decade later by that of tacrolimus.[20,81,82,102] The use of these drugs was associated with stepwise improvements with all organs, but their impact was most conclusively demonstrated with liver and heart transplantation. The results with liver transplantation shown in Figure 42-7 using azathioprine-, cyclosporine-, and tacrolimus-based immunosuppression were presented at the meeting of the American Surgical Association in April 1994.[103] By then, intestinal transplantation under tacrolimus-based immunosuppression had become a service.[104,105]

As the new agents became available, they were simply incorporated into the modified formula of heavy prophylactic immunosuppression that had been inherited from phases 1 and 2. Used in a variety of multiple-agent combinations from the time of surgery, the better drugs fueled the golden age of transplantation of the 1980s and early 1990s. Acute rejection had become almost a "non" problem. However, the unresolved issues now were chronic rejection, risks of long-term immunosuppression (e.g., infections and de novo malignancies), and drug toxicity (e.g., the nephrotoxicity of cyclosporine and tacrolimus).

Phase 4: 1992-Present

It was clear that relief from the burden of lifetime immunosuppression would require elucidation of the mechanisms of alloengraftment and of acquired tolerance. An intensified search for the engraftment mechanisms has dominated the current phase 4, which began in the early 1990s.

The Historical Dogma

Until this time, organ engraftment had been attributed to mechanisms that did not involve either the presence or a role of leukocyte chimerism. Although it was known that organs contain large numbers of passenger leukocytes, these donor cells were largely replaced in the successfully transplanted allograft by recipient leukocytes as shown in Figure 42-8A. The missing donor cells were thought to have undergone immune destruction with selective sparing of the specialized parenchymal cells. As for bone marrow transplantation (see Fig. 42-8B), the ideal result had been perceived as complete replacement of recipient immune cells (i.e., total hematolymphopoietic chimerism).

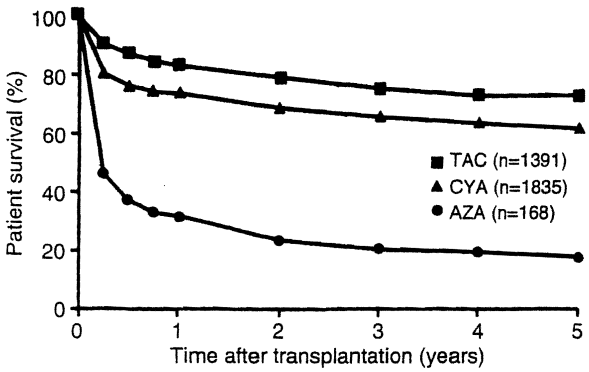


Figure 42-7 Patient survival: results with orthotopic liver transplantation at the Universities of Colorado (1963-1980) and Pittsburgh (1981-1993), in periods defined by azathioprine (AZA)-, cyclosporine (CYA)-, and tacrolimus (TAC)-based immune suppression. Stepwise improvements associated with the advent of these drugs also were made with other kinds of organs.

The Discovery of Microchimerism

A flaw in this historical dogma began to be exposed in the early 1990s. The first puzzling observation in Seattle[56] and Helsinki[107] was the invariable presence of a small residual population of recipient hematolymphopoietic cells in patients previously thought to have complete bone marrow replacement (see Fig. 42-8D). This was followed in 1992 by the discovery of donor leukocyte microchimerism in long-surviving human organ recipients. Now it was evident that organ engraftment (see Fig. 42-8C) and bone marrow cell engraftment (see Fig. 42-8D) were mirror-image versions of leukocyte chimerism, differing in the reversed proportion of donor and recipient cells.

The discovery of microchimerism in organ recipients was made with a very simple clinical study.[83-87] With the use of sensitive detection techniques, donor hematolymphopoietic cells of different lineages (including dendritic cells) were found in the blood, lymph nodes, skin, or other tissues of 30 of 30 liver or kidney recipients who had borne functioning allografts for up to 30 years. The donor leukocytes obviously were progeny of donor precursor or pluripotent hematolymphopoietic stem cells that had migrated from the graft into the recipient after surviving a double immune reaction that presumably had occurred just after transplantation, years or decades earlier.[35,45,57,94]

It was concluded that organ engraftment had been the result of "responses of co-existing donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion."[83,85] The host response (the upright curve in Fig. 42-9) was the dominant one in most cases of organ transplantation but with the occasional exception of GVHD. In the conventionally treated bone marrow recipient, host cytoablation simply transferred immune dominance from the host to the graft (the inverted curve in Fig. 42-9), explaining the high risk of GVHD. All of the major differences between the two kinds of transplantation were caused by the recipient cytoablation. After an estrangement of more than a third of a century, the intellectual separation of bone marrow and organ transplantation was ended (Fig. 42-10).

Immune Regulation by Antigen Migration and Localization

But how was the exhaustion-deletion of the double immune reaction shown in Figure 42-9 maintained after its

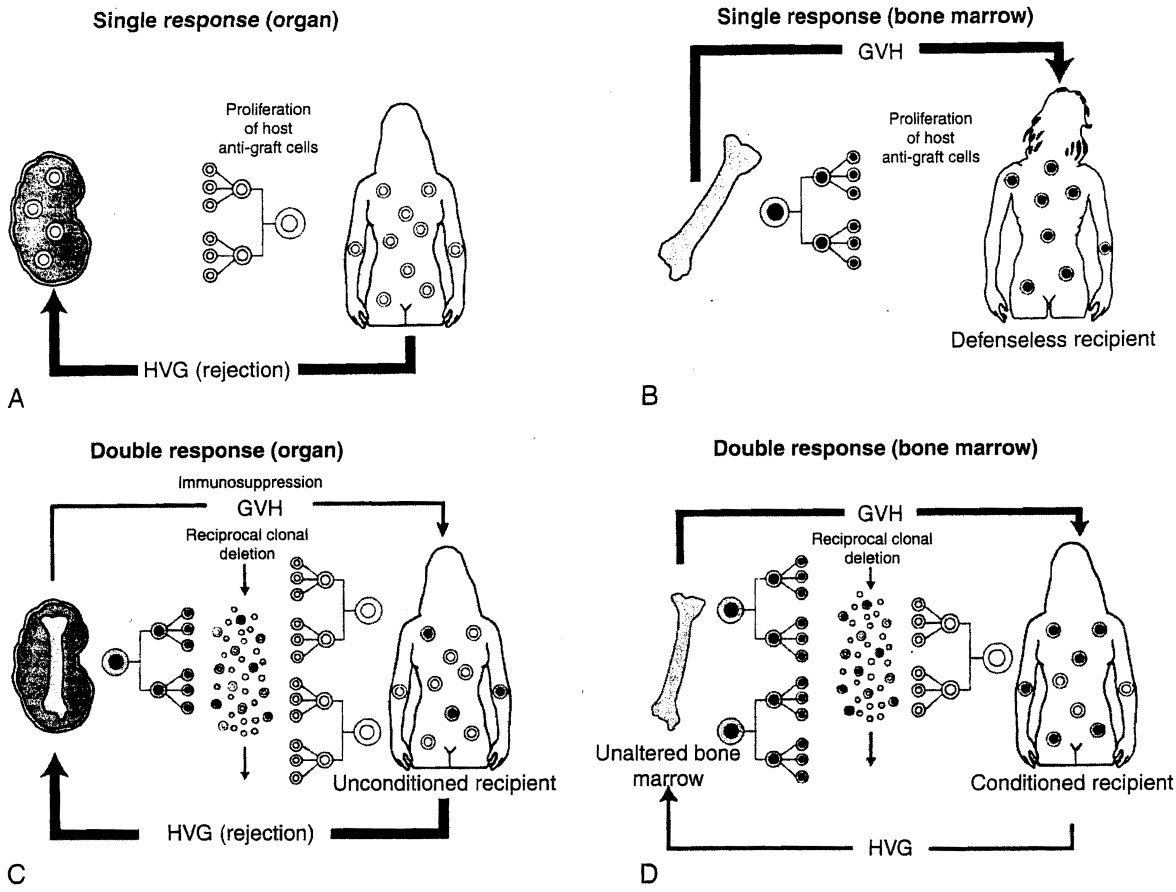


Figure 42-8 Old (*A* and *B*) and new views (*C* and *D*) of transplantation recipients. *A*, The early conceptualization of immune mechanisms in organ transplantation in terms of a unidirectional host-versus-graft (HVG) response. Although this readily explained organ rejection, it limited possible explanations of organ engraftment. *B*, Mirror image of *A* depicting the early understanding of successful bone marrow transplantation as a complete replacement of the recipient immune system by that of the donor, with the potential complication of an unopposed lethal unidirectional graft-versus-host (GVH) response, that is, rejection of the recipient by the graft. *C*, Our current view of bidirectional and reciprocally modulating immune responses of coexisting immune competent cell populations. Because of variable reciprocal induction of deletional tolerance, organ engraftment was feasible despite a usually dominant HVG reaction. The bone silhouette in the graft represents passenger leukocytes of bone marrow origin. *D*, Our currently conceived mirror image of *C* after successful bone marrow transplantation. Recipient's cytoablation has caused a reversal of the size proportions of the donor and recipient populations of immune cells.

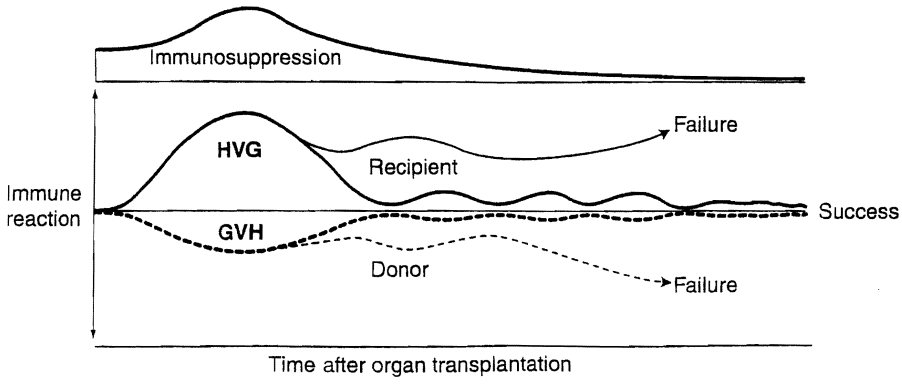


Figure 42-9 Contemporaneous HVG *(upright curves)* and GVH *(inverted curves)* responses after transplantation. In contrast to the usually dominant HVG reaction of organ transplantation, the GVH reaction usually is dominant after bone marrow cell transplantation to the irradiated or otherwise immunodepressed recipient. Therapeutic failure with either type of transplantation implies the inability to control one, the other, or both of the contemporaneous responses with a protective umbrella of immunosuppression. (Starzl TE, Zinkernagel R: Antigen localization and migration in immunity and tolerance. N Engl J Med 1998;339:1905-1913.)

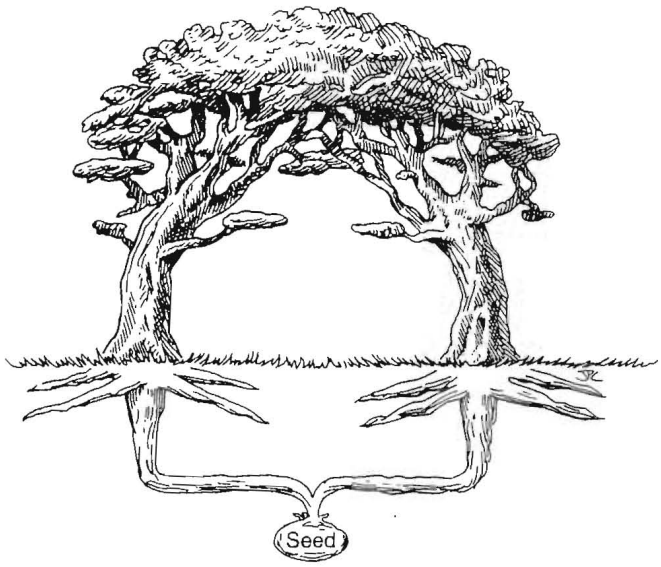


Figure 42–10 Unification of organ and bone marrow transplantation (See text).

acute induction by the first wave of migratory leukocytes? Rolf Zinkernagel, in Zurich (Fig. 42-11), had addressed this question during the 1990s in experimental studies of the nonresponsiveness that may develop to intracellular microorganisms such as tubercle bacillus and noncytopathic viruses.[43,109-111] The analogies between the syndromes caused by such infectious agents and the events following transplantation were described in 1998 in a joint review with Zinkernagel in the *New England Journal of Medicine*.[89]

Figure 42–11 Rolf Zinkernagel (1944-). Swiss physician-immunologist whose discovery (with Peter Doherty) of the mechanisms of the adaptive immune response to noncytopathic microorganisms earned the Nobel prize in 1996.

The analogies between transplantation and infection had been obscured by the characteristic double immune reaction of transplantation and by the complicating factor of immunosuppression. Now, these analogies were obvious. The antidonor response induced by the initially selective migration of the graft's leukocytes to host lymphoid organs (Fig. 42-12, left)[17,32,44,51] is comparable to the response induced by a spreading intracellular pathogen. The migration patterns of the donor leukocytes were the same whether these cells emigrated from an organ or were delivered as a bone marrow cell infusion. Cells that survived the antidonor response that they had induced begin within a few days to move on (see Fig. 42-12, right) to protected nonlymphoid niches where their presence may be detected no longer by the immune system (immune ignorance[4,27,30,31,89]). This was a survival tactic of noncytopathic microorganisms.

The migration of donor leukocytes is shown schematically in Figure 42-13, left by centrifugal arrows: first by hematogenous routes to lymphoid organs and, after a few weeks, on to nonlymphoid sites (outer circle). A subsequent reverse migration of donor cells from protected nonlymphoid niches back to host lymphoid organs is depicted by the inwardly directed dashed arrows in Figure 42-13, right. The retrograde migration is a two-edged sword. On one hand, these cells may sustain the clonal exhaustion-deletion induced at the outset, usually requiring an umbrella of maintenance immunosuppression. But on the other hand, these cells can perpetuate alloimmunity in the same way as surviving residual microorganisms perpetuate protective immunity. Not surprisingly, therefore, an alternative consequence of microchimerism may be the high panel reactive antibody (connoting sensitization to HLA antigens) that commonly develops after unsuccessful transplantation.[25,61]

Therapeutic Implications

How could the new insight be exploited clinically? The window of opportunity for the donor leukocyte-induced clonal deletion that corresponds with collapse of the antigraft response (Fig. 42-14, left) is open only for the first few post-transplant weeks.[46,47,57,95] It was apparent that the window could be closed by excessive postoperative immunosuppression (see Fig. 42-14, middle). With later reduction of the initial overimmunosuppression, recovery of the inefficiently deleted clone would be expected, leading to the delayed acute rejection, or the chronic rejection, that was being seen in the transplant clinics. Even in the best-case scenario, the patients would be predestined to lifetime dependence on immunosuppression. However, too little immunosuppression would result in uncontrolled rejection (see Fig. 42-14, right).

The problem faced by clinicians was how to find just the right amount of post-transplant immunosuppression. In 2001, it was suggested that this dilemma could be addressed by successively applying two historically rooted therapeutic principles: recipient pretreatment, followed by minimalistic post-transplant immunosuppression.[90] With pretreatment, the recipients, immune responsiveness would be reduced

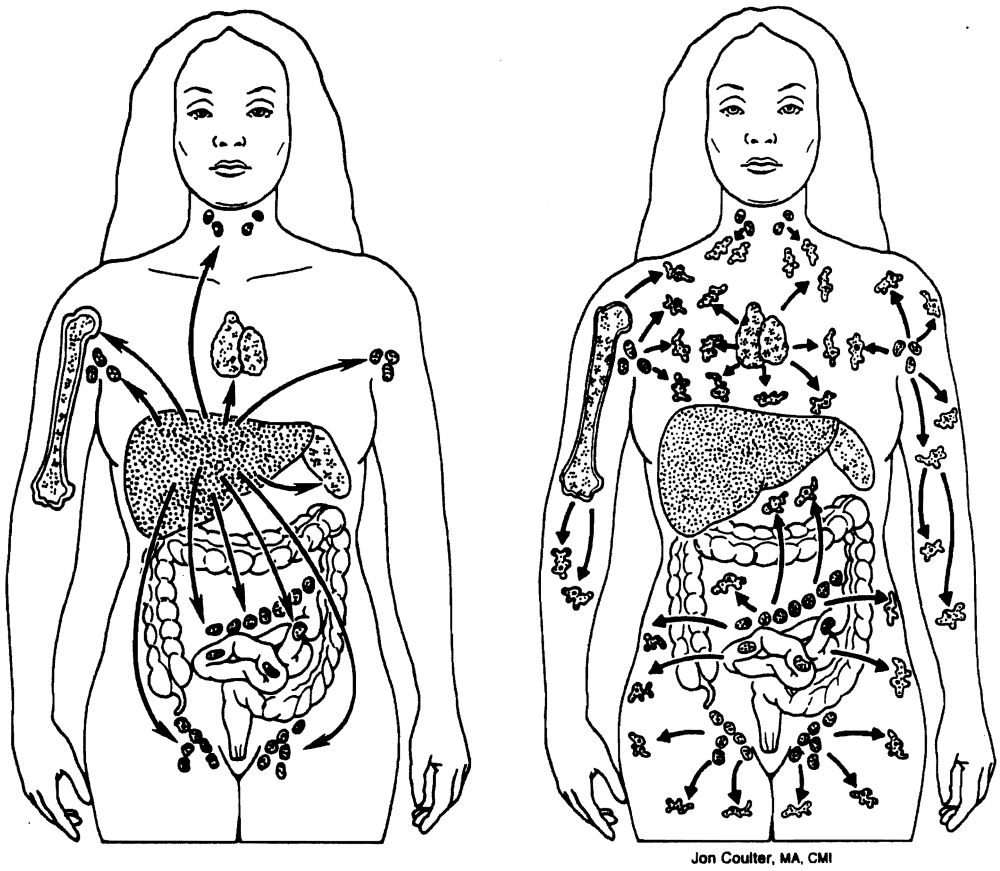


Figure 42–12 Initial preferential migration of passenger leukocytes from organ allografts (here a liver) to host lymphoid organs *(left)*, where they induce a donor-specific immune response. After about 30 days, many of the surviving cells move on to nonlymphoid sites *(right)*.

before exposure to donor antigen, thereby lowering the anticipated donor-specific response into a more readily deletable range (Fig. 42-15). Clonal deletion by the kidneys' passenger leukocytes undoubtedly is what had been accomplished after sublethal irradiation alone in the ground-breaking fraternal twin (i.e., sublethal total body irradiation or myelotoxic drugs) cases of 1959.[22,48] In fact, radical pretreatment by recipient cytoablation ultimately became the essential therapeutic step for conventional bone marrow transplantation. Because of the high risk of GVHD, this approach was too dangerous and too restrictive to be practical for organ transplantation.

However, less drastic lymphoid depletion by ALG or other measures (so-called nonmyeloablative conditioning) had been repeatedly shown since the 1960s to be effective without causing GVHD[71] (see Fig. 42-15).

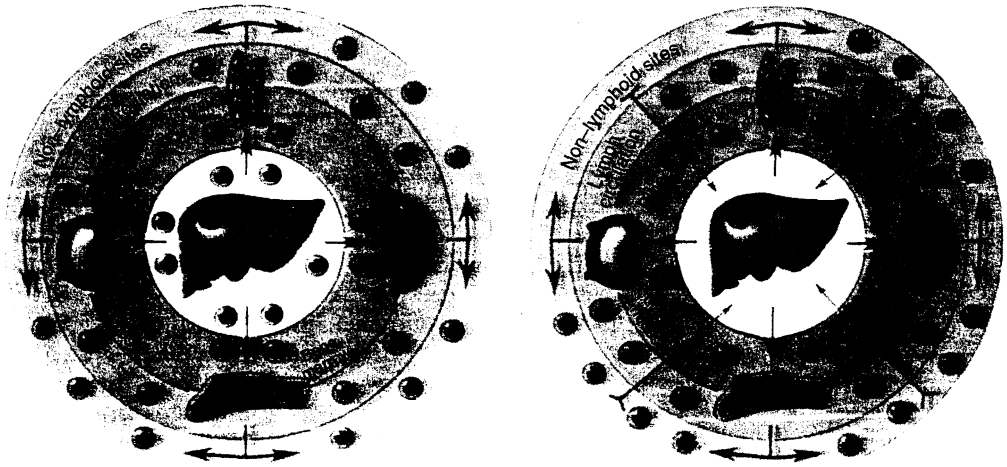


Figure 42–13 The migration routes of passenger leukocytes of transplanted organs are similar to those of infused bone marrow cells. *Left*, Selective migration at first to host lymphoid organs. After 15 to 30 days, surviving leukocytes begin to secondarily move to nonlymphoid sites. *Right*, Establishment of reverse traffic by which the exhaustion-deletion induced at the outset can be maintained.

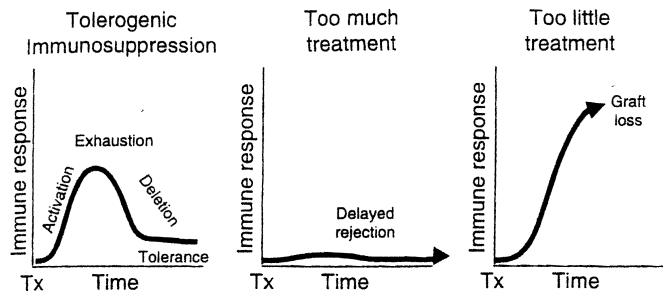


Figure 42-14 The effect of post-transplant immunosuppression on the seminal mechanism of clonal exhaustion deletion. *Left,* Just the right amount. *Middle,* Too much. *Right,* Too little. See text.

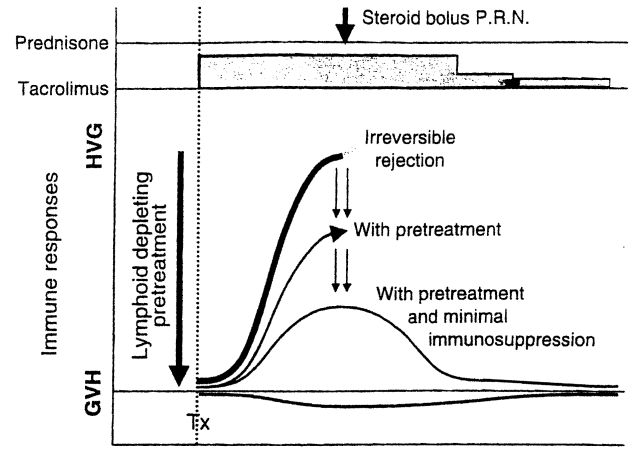


Figure 42-16 Conversion of rejection *(thick dark arrow)* to an immune response that can be exhausted and deleted by combination of pretreatment and minimalistic post-transplant immunosuppression.

After pretreatment with one of today's potent antilymphoid antibody preparations, the preemptively weakened clonal activation could proceed efficiently to clonal deletion under minimalistic short- and long-term maintenance therapy (Fig. 42-16). In July 2001, we instituted the double-principle strategy in adult organ recipients. The pretreatment was with a single infusion of 5 mg/kg of thymoglobulin. Beginning in 2002, a single Campath dose of 30 mg was substituted for thymoglobulin in most adult cases. After either kind of lymphoid depletion, treatment after transplantation was given with a conservative daily dose of a single drug (usually tacrolimus), adding other agents only in the event of breakthrough rejection and for as brief a period as possible. The strategy was extended to infants and children for intestinal transplantation in 2002 and for all kidney transplantations after April 2003.

After 4 to 8 months, weaning from monotherapy to less than daily doses was begun in adults whose graft function was stable: every other day, then three times per week, twice a week, and in many cases to once a week by 1 year (Fig. 42-17). The strategy has been used for the treatment of more than 1000 adult kidney, liver, intestine, pancreas, and lung recipients.[40,59,91] This experience has demonstrated that the quality of life of transplant recipients can be improved. For the first time, children are being considered for spaced weaning.

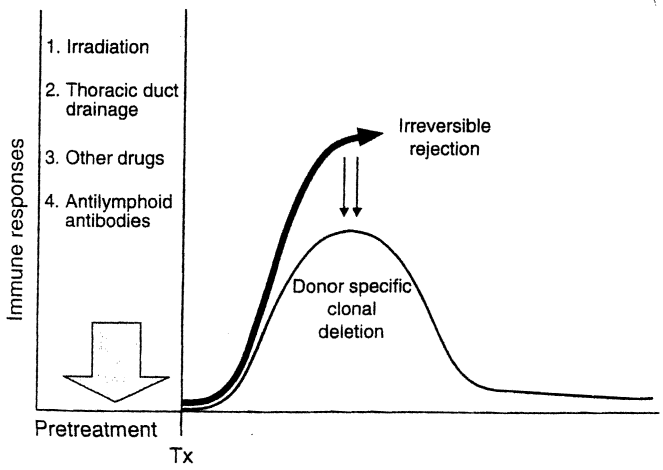


Figure 42-15 Rather than producing rejection *(thick dark arrow),* the donor-specific immune response to allografts may be exhausted and deleted, *as depicted by the fall of the initially ascending continuous thin line,* when recipient immune responsiveness is weakened in advance of transplantation (the pretreatment principle).

ORGAN PRESERVATION

Procurement

The breakthroughs of the early 1960s that made transplantation clinically practical were so unexpected that almost no formal preparation had been made to preserve the transplanted organs. Cardiac surgeons had used hypothermia for open-heart operations from 1950 onward and knew that ischemic damage below the level of aortic cross-clamping could be reduced by cooling the subdiaphragmatic organs.[58] In an early report, Lillehei and colleagues[33] immersed intestines in iced saline before autotransplantation. In Boston, Sicular and Moore[60] reported greatly slowed enzyme degradation in cold slices of liver.

Despite this awareness, kidneys were routinely transplanted until 1963 with no protection from warm ischemia during organ transfer. The only attempt to cool kidney allografts until then was by the potentially dangerous practice

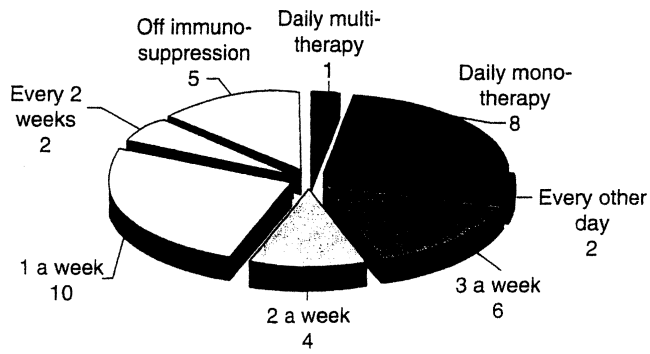


Figure 42-17 Diagram of 2½-year follow-up.

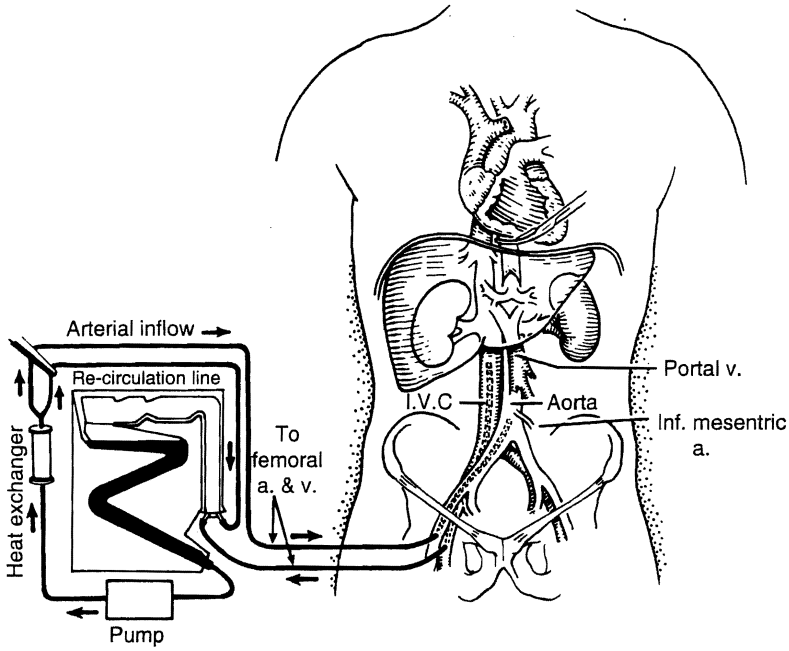


Figure 42-18 First technique of in situ cooling by extracorporeal hypothermic perfusion. The catheters were inserted into the aorta and vena cava by way of the femoral vessels as soon as possible after death. Temperature control was provided with a heat exchanger. Cross-clamping of the thoracic aorta limited perfusion to the lower part of the body. This method of cadaveric organ procurement was used from 1962 to 1969, before the acceptance of brain death criteria. The preliminary stages of this approach provided the basis for subsequent in situ infusion techniques.

(used by thoracic surgeons for open-heart surgery) of immersing the live donor in a bathtub of ice water (total-body hypothermia).[63] This cumbersome method of cooling was quickly replaced by infusion of chilled solutions into the renal artery after donor nephrectomy,[67] exploiting a principle of core (transvascular) cooling that had been standardized several years earlier for experimental liver transplantation.[62]

Core cooling in situ, the first critical step in the preservation of all cadaveric whole organs, is done today with variations of the technique described in 1963 by Marchioro and coworkers,[37] which permits in situ cooling to be undertaken[68] (Fig. 42-18). Ackerman and Snell[1] and Merkel and associates[41] popularized in situ cooling of cadaveric kidneys with simple infusion of cold electrolyte solutions into the donor femoral artery or distal aorta. Procurement techniques were eventually perfected that allowed removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs (Fig. 42-19).[79] Modifications of this flexible procedure have been made for unstable donors and even for donors whose hearts have stopped beating.[80] During the 5 years between 1980 and 1985, such techniques had become interchangeable in all parts of the world, setting the stage for reliable organ sharing. After the chilled organs are removed, subsequent preservation is possible with prototype strategies: simple refrigeration or continuous perfusion (see later).

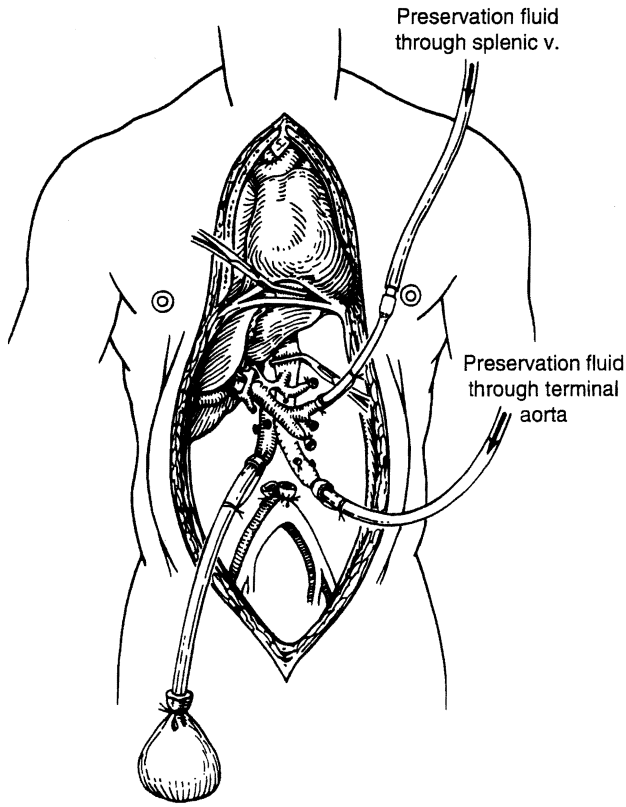


Figure 42-19 Principle of in situ cooling used for multiple organ procurement. With limited preliminary dissection of the aorta and of the great splanchnic veins (in this case the splenic vein), cold infusates can be used to chill organs in situ. In this case, the kidneys and liver were being removed. Note the aortic cross-clamp above the celiac axis.

Extended Preservation

Continuous Vascular Perfusion

Efforts to continuously perfuse isolated organs have proved to be difficult. For renal allografts, Ackerman and Barnard[2] used a normothermic perfusate primed with

blood that was oxygenated within a hyperbaric chamber. Brettschneider and colleagues[10] modified the apparatus and were able to preserve canine livers for 2 days, an unprecedented feat at the time. When Belzer and associates[6] eliminated the hemoglobin and hyperbaric chamber components, their asanguinous hypothermic perfusion technique was immediately accepted for clinical renal transplantation but then slowly abandoned in most centers when it was learned that the quality of 2-day preservation was not markedly better than that of simpler and less expensive infusion and slush methods (see later). However, refinement of perfusion techniques may someday permit true organ banking.

Static Preservation

With these "slush techniques," special solutions, such as those described by Collins and coworkers,[15] were instilled into the renal vascular system of kidneys or the vascular system of other organs after their preliminary chilling and separation. The original Collins solution or modifications of it were used for nearly 2 decades before they were replaced with the University of Wisconsin (UW) solution that was developed by the team of Folkert Belzer. Although it was first used for the liver,[7,26,101] the UW solution provides superior preservation of kidneys and other organs.[24,106] The UW preservation permitted longer and safer preservation of kidneys (2 days) and livers (18 hours), a higher rate of graft survival, and a lower rate of primary nonfunction. With the UW solution, national organ sharing was made economical and practical.

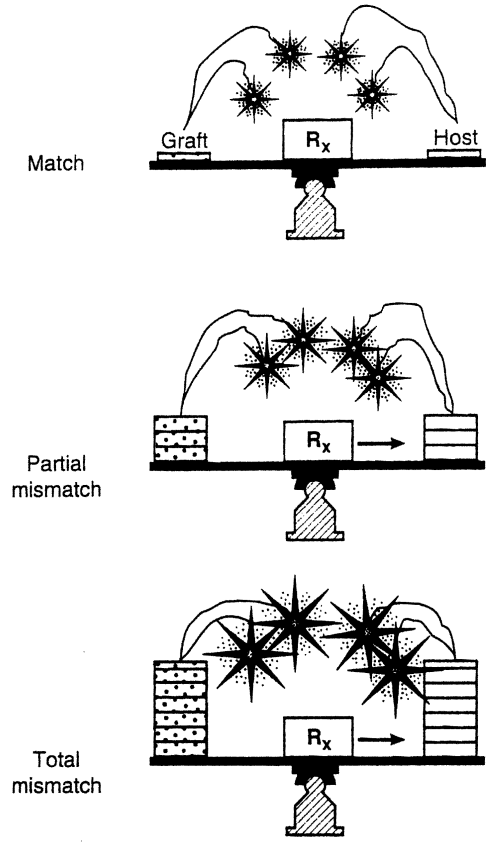


Figure 42-20 The nullification effect of simultaneous host-versus-graft (HVG) and graft-versus-host (GVH) reactions when organs are transplanted to recipients whose immune system has not been cytoablated. The reciprocal induction of tolerance, each to the other, of the coexisting cell populations is the explanation for the poor correlation of HLA matching with outcome after organ transplantation.

TISSUE TYPING

Antigen Matching

The first prospective antigen matching trials were begun in 1964 by Terasaki and associates[97] in collaboration with the University of Colorado kidney transplantation team. Although the value of this serologic technology was demonstrable when the kidney donor was a highly compatible family member (the "perfect match"),[75] lesser degrees of matching correlated poorly with renal transplantation outcome.[88] The reasons for this paradox were inexplicable until the discovery of recipient chimerism (Fig. 42-20). However, the belief that matching should be a prime determinant of success resulted in its use as an overriding factor for the allocation of cadaver kidneys in the United States.

The propriety of this kidney allocation policy has been repeatedly challenged on ethical as well as scientific grounds for nearly a third of a century. Those in favor of perpetuating the role of graded HLA matches cite multicenter case compilations in the United States and Europe showing a small gain in allograft survival with histocompatible kidneys, whereas many of the individual contributing centers see no such trend in their own experience.[19,38,58,93] In a compelling study, Terasaki and associates[98] reported that early survival and the subsequent half-life of kidneys from randomly matched, living unrelated donors was identical to that of parent-offspring (one haplotype matched) grafts. The inescapable conclusion is that more effective timing and dosage of immunosuppressive therapy rather than refinements in tissue matching and organ sharing will be the primary method of improving the results of whole-organ transplantation.

Crossmatching

None of the immunosuppressive measures available today can prevent immediate destruction of kidneys and other kinds of organ grafts in what has been called hyperacute rejection. This complication was first seen with the transplantation of kidneys from ABO-incompatible donors when they were placed in recipients with antidonor isoagglutinins.[69] After the description by Terasaki and associates[96] of hyperacute kidney rejection by a recipient with antidonor lymphocytotoxic antibodies, Kissmeyer-Nielsen and colleagues[28] and others[73,76,100,108] confirmed the association of hyperacute rejection with these antigraft antibodies. Although hyperacute rejection can usually be avoided with the lymphocytotoxic crossmatch originally recommended by Terasaki and associates, the precise pathogenesis of such rejection remains poorly

understood more than 30 years after its recognition as a complement activation syndrome.[73,76]

FUTURE PROSPECTS

The revisions in timing and dose control that encourage the seminal mechanisms of clonal exhaustion-deletion and immune ignorance should make it possible to systematically reduce exposure to the risks of chronic immunosuppression. Our prediction is that completely drug free tolerance will be largely, but not exclusively, limited to recipients of HLA-matched organs. But variable partial tolerance will be more regularly attainable in most of the others, not so much by developing better drugs as by the mechanism-based use of drugs we already have in hand. Xenotransplantation will have to be developed within the same immunologic framework. Here, the problem in principle is to create a better interspecies tissue match by transgenic modification. Although the α-1,3GT gene responsible for hyperacute rejection of pig organs by higher primates has been knocked out in pigs,[54] it is not yet known what further changes have to be made before porcine organs can be used clinically. Where stem cell biology will fit remains unknown. But it also will have to conform to the same immunologic rules.

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