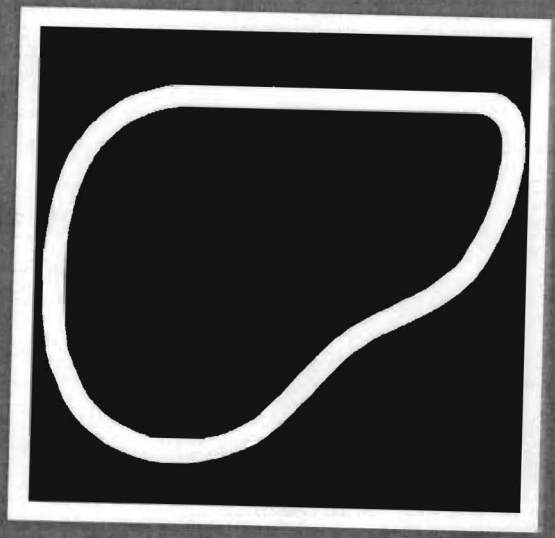
FALK SYMPOSIUM 137

Liver Diseases: Advances in Treatment and Prevention

In honour of Hans Popper's 100th birthday



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The connected past and future of transplantation, with particular emphasis on the liver

T. E. STARZL

INTRODUCTION

Every major advance in liver and other kinds of organ transplantation of the last half century has required the overthrow of some scientific dogma or the revision of a social, ethical, or legal doctrine. Consequently, the growth of transplantation was more a 50-year war against the *status quo* than an orderly evolution. The war can be divided into five distinct phases. Although my main focus will be on phase 4, it is essential to understand what happened from the beginning.

PHASE 1

The spark that ignited the war was the demonstration in 1953 by Billingham, Brent, and Medawar that immunologically immature neonatal mice or irradiated adult mice whose bone marrow had been 'replaced' by the haematolymphopoietic cells of an adult donor (donor leucocyte chimerism) could accept skin from the cell donor strain but from no other strain[1,2]. This was the first example of acquired transplantation tolerance. The next step appeared to be obvious; i.e. bone marrow transplantation from the donor before or at the same time as the organ transplantation. The hazard of this strategy was recognized by Medawar's associates, Billingham and Brent[3,4] and by Simonsen[5], who discovered that the engrafted donor immune cells could turn the tables and reject the mouse recipients (graft-versus-host disease). This complication was avoidable only with a good donor–recipient tissue match.

This work established the association of alloengraftment of tissues (and subsequently organs) with donor leucocyte chimerism. Shortly afterwards, and to the surprise of most immunologists, successful kidney transplantation without

infusion of donor leucocytes (i.e. in the ostensible absence of leucocyte chimerism) was accomplished six times between January 1959 and February 1962[6–10] (Table 1). All six patients had been conditioned before transplantation with sublethal total-body irradiation. Such trials would not be possible today. Until well into 1960, prolonged survival had never been achieved in an animal after kidney transplantation with any kind of treatment. Nevertheless, surgeons had forged ahead with clinical kidney transplantation, and with the development of experimental models of transplantation of all other major organs. My own interest had turned to the liver. By 1960 the operation of liver replacement in dogs had been perfected in our laboratory[11,12] and in Boston[13,14].

Without the availability of immunosuppression such efforts were made, at first, in a vacuum. However, a sea change began in 1960 with the demonstration that the survival of rabbit skin allografts[15,16] and of canine kidney allografts[17–19] was prolonged by treatment with the drug 6-mercaptopurine and its imidizole derivative, azathioprine (better known as Imuran®). The drugs also were tested in canine liver recipients[20]. Although survival of the canine kidney recipients for as long as 100 days was limited to 5% or less, this did little to dampen the initial burst of enthusiasm. The enthusiasm evaporated when all but one of the first 13 kidney recipients treated with the new drugs in the Boston[10] and London clinical trials[21] died in less than 6 months. The only ray of hope lay with Murray's single surviving patient – the recipient of a kidney from a non-related donor on 5 April 1962[10].

This kidney in Murray's patient functioned for 17 months, adding a seventh human to the 1-year kidney transplant survival list – and for the first time, without total body irradiation (Table 1, below the dashed line); it was a landmark case, but because of the otherwise dismal results, we concluded that we would have to develop kidney transplantation from the ground up before contemplating our primary goal of liver transplantation. During the summer of 1962 we made three reproducible new observations in canine kidney recipients. A few months later these were confirmed in human recipients[22]. First, kidney rejection in dogs that developed under Imuran could almost always be reversed by adding large doses of prednisone[23]. Second, mean survival was nearly doubled by pretreating the animals with Imuran for 1–4 weeks instead of beginning the drug at the time of transplantation[24]. The third and most important observation was the development of what we considered to be variable donor-specific tolerance. Tolerance

Table 1 Kidney transplantation ≥6 months survival as of March 1963

	City/ref.	*Date*	*Donor*	*Survival (months)*
1.	Boston[6]	24 January 1959	Fraternal twin	>50
2.	Paris[7]	29 June 1959	Fraternal twin	>45
3.	Paris[9]	22 June 1960	Unrelated*	18 (died)
4.	Paris[8]	19 December 1960	Mother*	>12 (died)
5.	Paris[9]	12 March 1961	Unrelated*	18 (died)
6.	Paris[8]	12 February 1962	Cousin*	>13
7.	Boston[10]	5 April 1962	Unrelated	11

* Adjunct steroid therapy.
Boston: J. E. Murray (1 and 7); Paris: J. Hamburger (2, 4 and 6); R. Kuss (3 and 5).

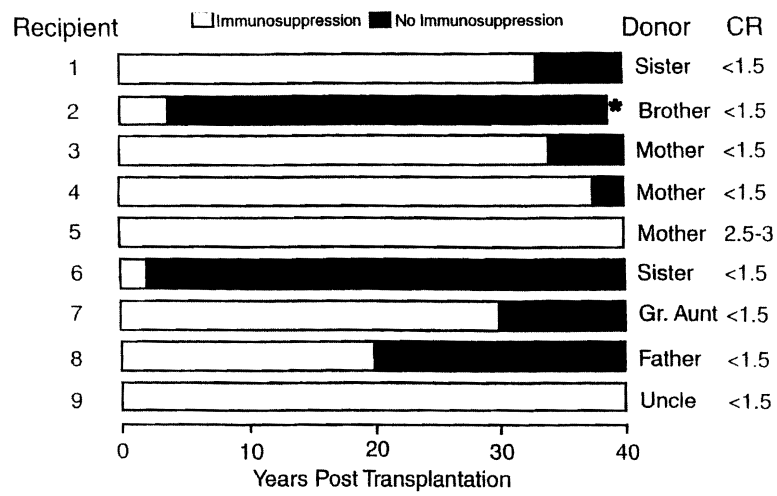

Figure 1 Nine (19%) of the 46 live-donor kidney recipients treated at the University of Colorado over an 18-month period beginning in the autumn of 1962. The solid portion of the horizontal bars depicts the time off immunosuppression. Note that the current serum creatinine concentration (CR) is normal in all but one patient. * Murdered: kidney allograft normal at autopsy

was inferred from the declining need for immunosuppression after the successful reversal of rejection.

These observations in humans, and our interpretation of the findings, were summarized in the title of a report in the October, 1963 issue of *Surgery, Gynecology & Obstetrics*[22]. Our use of the word 'tolerance', was severely criticized at the time; but it proved to be the correct term. The nine horizontal bars in Figure 1 represent nine patients (or 19%) of those given live-related kidneys in Denver from the autumn of 1962 to December 1963. The nine allografts functioned for the next four decades[25,26]. The important point is that seven of the nine recipients stopped all drugs without suffering rejection, for periods ranging from 3 to 39 years (the black portion of the horizontal bars). One of the nine patients was recently murdered, and had a normal kidney at autopsy. The eight who remain bear the longest surviving kidney allografts in the world today, 40 or more years post-transplantation.

Although the follow-ups of the kidney recipients were still short, this promising experience with renal transplantation triggered the decision to begin a liver trial on 1 March 1963. The first patient was an unconscious and ventilator-bound child with biliary atresia. The child bled to death during the operation[27]. Four more attempts were made in Denver later in 1963[20,27] – as well as one each in Boston[28] and Paris[29]. Although five of the last six patients survived operation, they all died after 6–22 days (Table 2). With these successive failures by the end of 1963 all liver transplant activity ceased worldwide for the next $3\frac{1}{2}$ years.

The decision to stop was voluntary; it was reinforced, however, by widespread criticism of replacement of an unpaired vital organ with an operation that had come to be perceived as too difficult ever to be tried again by a responsible surgeon. In contrast, kidney transplantation, whose development in Denver was only a

Table 2 First seven recipients of livers

Age (years)	*Date*	*City/ref.*	*Liver disease*	*Survival (days)*	*Main cause of death*
3	1 March 1963	Denver[27]	Biliary atresia	0	Intra-operative bleeding
48	5 May 1963	Denver[27]	Hepatoma, cirrhosis	22	Pulmonary emboli, sepsis
68	3 June 1963	Denver[27]	Duct cell carcinoma	7.5	Pulmonary emboli
52	10 July 1963	Denver[20]	Hepatoma, cirrhosis	6.5	Gastrointestinal bleed, pulmonary emboli
58*	16 September 1963	Boston[28]	Colon metastases	11	Sepsis, liver failure
29	4 October 1963	Denver[20]	Hepatoma	23	Sepsis, pulmonary emboli
75†	? January 1964	Paris[29]	Colon metastases	0	Haemorrhage

* Boston; † Paris.

preliminary step to the main goal of liver transplantation, seized centre stage. This first textbook on renal transplantation, published in 1964, was based on our first 70 cases[30]. In contrast, liver transplantation had become a ticket to academic suicide.

During the $3\frac{1}{2}$-year liver moratorium three advances were made that were applicable to all organs. First, we showed, in a collaboration with Paul Terasaki of UCLA, that HLA matching had little association with kidney transplant outcome unless the match was perfect[31–33]. By inference, desperately ill liver, heart and other transplant candidates who could not wait for a well-matched organ would not suffer a major penalty by receiving a mismatched one. For those committed to HLA matching, however, these conclusions were not welcome. The guerilla war that followed was not resolved until the 1990s, when it could finally be understood why HLA matching was a prerequisite for bone-marrow transplantation, but was not essential for organ transplantation (see later).

The second objective was to improve immunosuppression. Antilymphocyte globulin (ALG) was prepared from the serum of horses immunized against lymphoid tissues. The ALG was tested in dogs and introduced clinically in 1966 in combination with Imuran and prednisone[34]. ALG, and the following generations of monoclonal antibody analogues, remain an important part of our treatment today. The studies in dogs during the moratorium resulted in many long-surviving recipients. The liver was the hardest organ to transplant, but it appeared to induce drug-free tolerance more readily than the kidney or any other organ. Most of these animals, including one that lived for 13 years, were treated only with a short course of Imuran[35], or a few doses of perioperative ALG[34]; but no-one was willing to consider these animals to be tolerant. Like our tolerant human kidney recipients the dogs ostensibly did not have the donor leucocyte chimerism of Medawar's acquired tolerance.

As our third objective we developed a sophisticated perfusion system in 1966 and 1967 that permitted the reliable preservation of canine livers for as long as

a day after their removal[36]. Now it was time to try again. After the clinical liver programme was reopened, in July 1967, several examples of prolonged human liver recipient survival were produced under triple-drug immunosuppression with Imuran, prednisone, and ALG[37]. Although less than half of the liver transplantations of 1967 resulted in prolonged survival, the successes had a domino effect. Between January 1968 and November 1969 the first long-surviving human heart[38], pancreas[39], and lung[40] recipients were produced in Capetown, Minneapolis, and Louvain all under the triple-drug immunosuppression developed in Denver for kidney and liver transplantation. In addition, the first successful bone-marrow transplantations were finally accomplished in 1968[41] (Table 3).

Table 3 First successful transplantation of human allografts (survival >1 year)

Organ	*City/ref.*	*Date*	*Physician/surgeon*
Kidney	Boston[6]	24 January 1959	Merrill/Murray
Liver	Denver[37]	23 July 1967	Starzl
Heart	Cape Town[38]	2 January 1968	Barnard
Bone marrow	Minneapolis[41]	25 August 1968	Gatti

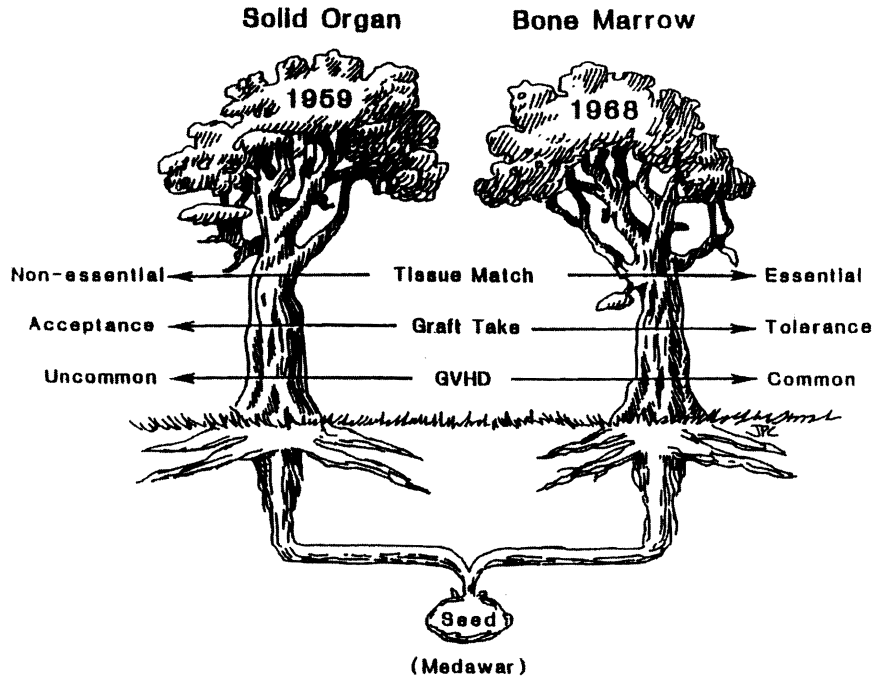

Figure 2 The divergence of the ostensibly unrelated fields of organ (left) and bone-marrow transplantation. The conclusion that the two kinds of transplantation involved different mechanisms of engraftment was the basis for an epistemological collapse in transplantation immunology (see text)

Thus a beach-head of clinical transplantation had been established by 1969, spearheaded by the kidney and liver. This concluded the 16-year phase 1 of the 50-year war. By now, bone marrow and organ transplantation had parted company (Figure 2). Drug-free tolerance that was clearly associated with donor leucocyte chimerism was a clinical reality after bone-marrow transplantation, but only with the use of HLA-matched donors. In contrast, it had become unchallenged dogma that organ recipients did not have such chimerism, implying that organ engraftment involved separate and different mechanisms. Acceptance of this misconception became the dark legacy of phase 1. It was a pervasive error that permeated all levels of transplantation immunology, and immunology in general, for the next third of a century.

PHASE 2

Although the mechanisms of alloengraftment were enigmatic, and would remain so for the next quarter-century, the early successes were construed as a breakthrough; however, the jubilation was short-lived. The succeeding phase 2 was a bleak period that lasted for a dozen years. In the view of critics the heavy mortality, and particularly the devastating morbidity, caused by steroid dependence, made organ transplantation (even of kidneys) more a disease than a treatment. By 1979 the liver programme in Denver and the heart transplant programme of Norman Shumway at Stanford were the only ones of their kind in America. The climate was better in Europe. Swimming against the stream, Roy Calne, Rudolf Pichlmayr, Henri Bismuth, and Rudi Krom kept the liver transplant flame alive in Cambridge, Hanover, Paris, and Leiden. All the while, surviving recipients in these programmes bore silent witness to what some day would be accomplished on a grand scale. A woman, who today is the world record-holder for a non-renal organ, was 4 years old when her liver was replaced in Denver for biliary atresia and a hepatoma in January 1970. Now, more than a third of a century later, she and many other liver recipients close behind have stopped their immunosuppression without rejecting[25].

PHASE 3

What had appeared to be the end of a shattered dream was only the dawn of phase 3 of the 50-year war. Phase 3 began with the clinical introduction of the new drug, cyclosporin, by Calne in England[42] and its combination with prednisone in Denver and Pittsburgh[43,44]. A decade later cyclosporin was replaced by tacrolimus in Pittsburgh[45,46] and eventually elsewhere. The new drugs improved the outlook for all organs, but the stepwise impact was most conclusively demonstrated with liver transplantation (Figure 3). Moreover, it became possible with tacrolimus to develop transplantation of the intestine[47] (a previously forbidden organ). In 1990 the first successful pancreatic islet transplantations in the world were carried out in Pittsburgh[48]. By the end of the 20th century all of the major organs except the brain were being transplanted in every developed country in the world.

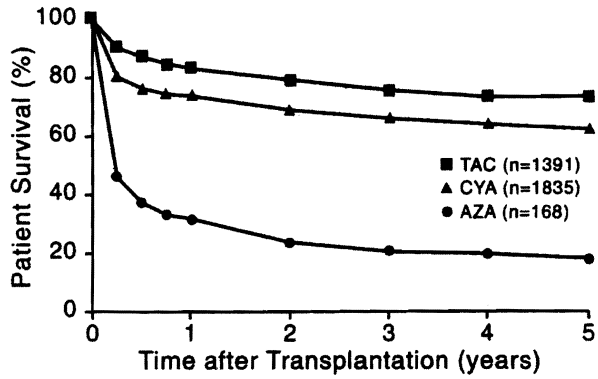

Figure 3 Patient survival: the three eras of orthotopic liver transplantation at the Universities of Colorado (1963–1980) and Pittsburgh (1981–1993), defined by azathioprine (AZA)-, cyclosporin (CYA)-, and tacrolimus (TAC)-based immune suppression. Stepwise improvements associated with the advent of these drugs were also made with other kinds of organs

PHASE 4

There were, however, nagging disappointments. The inherent risks of immune depression and drug-specific side-effects precluded a normal life expectancy. Moreover, the sporadic examples of drug-free tolerance observed earlier with less potent immunosuppression were expected to be more common. Instead, they were almost never seen again. It was obvious that further advances would require elucidation of the enigmatic mechanisms of alloengraftment and tolerance. In 1992 we obtained evidence that bone-marrow and organ engraftment involved the same immunological mechanisms, and were merely variations on the same theme[49–54]. This conclusion was reached when donor leucocyte chimerism was demonstrated in 30 kidney or liver recipients surviving from phases 1 and 2 who had borne functioning grafts for up to three decades. Using sensitive immunocytochemical and/or PCR techniques, donor leucocytes were detected in one or more of the recipient tissues depicted in Figure 4 (or in the blood) of all 30 patients. Because the cells were sparse their presence was termed 'microchimerism'. The presence of microchimerism in these patients signalled a paradigm shift in transplantation that precipitated and defined phase 4 of the 50-year war.

Until this time the events set in motion by transplantation had been largely viewed in the context of an all-or-none immune response, exemplified by the host-versus-graft response that normally proceeds to rejection of the transplanted organ (Figure 5, panel A). After bone-marrow transplantation the recipient either completely rejected the graft or, as shown in panel B, the transplanted bone marrow completely replaced that of the recipient and could reject the recipient (graft-versus-host disease). The dogma depicted in panels A and B was incompatible with our microchimerism discoveries, or with the demonstration by Donna Przepiorka et al. of Seattle[55] that cytoablated bone-marrow recipients always had a small residual population of their own bone-marrow-derived cells.

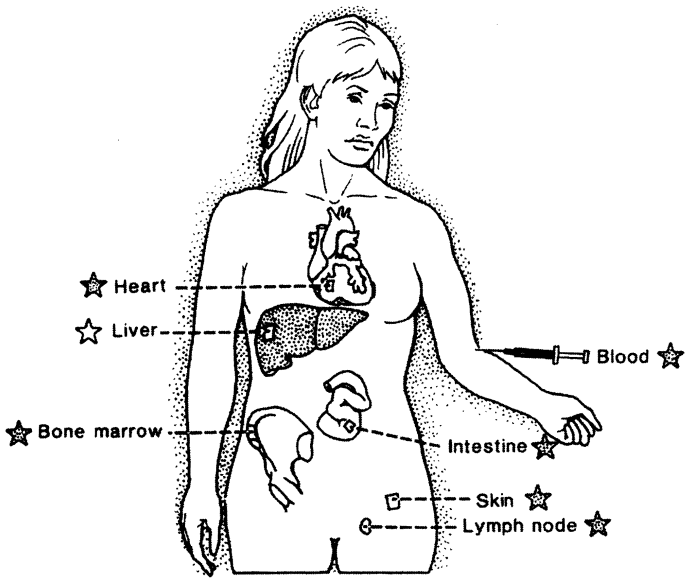

Figure 4 Host sites sampled in studies in 1992 of the longest-surviving kidney and liver recipients in the world. Donor leucocytes were looked for in host blood, skin, and lymph nodes, as well as in the allograft (here liver) of all patients, and in selected cases biopsies were also taken from the heart, intestine, other organs, or bone marrow. The concepts depicted in Figures 5 and 7 were deduced from the finding of low-level donor leucocyte chimerism in all patients, and confirmed in a series of controlled animal experiments

Instead, it was obvious that organ engraftment (Figure 5, panel C) and bone-marrow engraftment (panel D) were mirror images, and that both kinds of recipient had donor leucocyte chimerism.

It now could be deduced that alloengraftment after both procedures resulted from 'responses of coexisting donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion'[49,51]. The passenger leucocytes of a transplanted organ are of bone-marrow origin and include stem cells. Consequently, their haematogenous spread into the recipient was the same as that following a bone-marrow cell infusion. The migration is selective at first to the host lymphoid organs, where the donor cells induce an anti-donor T-cell response. Donor cells that escape destruction begin to spread to ubiquitous non-lymphoid sites after about 30 days.

In clinical practice, and in most experimental models, clonal exhaustion–deletion requires a protective umbrella of immunosuppression to prevent the recipient cell population from destroying the donor leucocytes before deletion can occur. In some experimental models, however, the exhaustion–deletion occurs without treatment (summarized in refs 25 and 26). The usual allograft in these spontaneous tolerance models is the liver, with its large quantity of passenger leucocytes.

Exhaustion and deletion of the dominant response of organ transplantation in the spontaneous tolerance models, or under an umbrella of immunosuppression

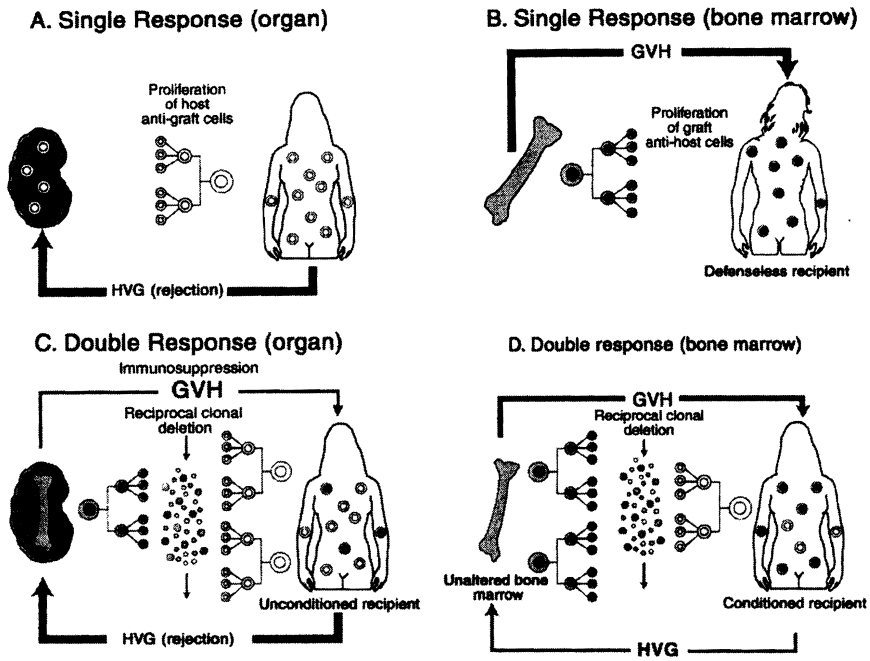

Figure 5 Old (**A** and **B**) and new views (**C** and **D**) of transplantation recipients. **A**: the early conceptualization of immune mechanisms in organ transplantation in terms of a unidirectional host-versus-graft (HVG) response. Although this readily explained organ rejection, it limited possible explanations of organ engraftment. **B**: mirror image of panel **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: i.e. 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 leucocytes of bone marrow origin. **D**: Our currently conceived mirror image of panel **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

(the upright curve in Figure 6) coincided with the characteristic reversal of rejection and induction of variable partial tolerance first observed 30 years earlier in our Colorado kidney recipients and eventually in all other kinds of organ recipient. Pretransplant cytoablation of the bone-marrow recipient simply reversed the proportions of the donor and recipient cells, transferring immune dominance to the graft (Figure 6, the inverted curve), thus explaining all of the differences between bone marrow and organ transplantation.

What was not apparent in 1992, however, was how the microchimeric donor cells managed to survive in the organ recipient and why, as we had concluded, their persistence was essential for the long-term survival of a transplanted organ. Answers to these and other questions were provided 5 years later in a review written in collaboration with Rolf Zinkernagel of Zurich[56]. In 1996 and 1997

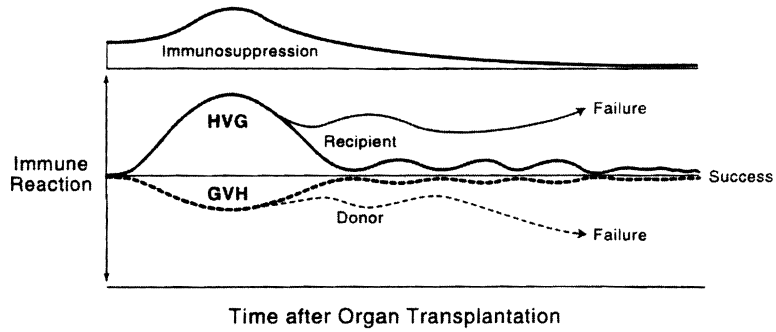

Figure 6 Contemporaneous host-versus-graft (HVG) (upright curves) and graft-versus-host (GVH) (inverted curves) responses following organ transplantation. If some degree of reciprocal clonal exhaustion is not induced and maintained (usually requiring protective immune suppression), one cell population will destroy the other. In contrast to the usually dominant HVG reaction of organ transplantation (shown here), the GVH reaction is usually dominant in the cytoablated bone-marrow recipient. Therapeutic failure with either type of transplantation implies the inability to control one, the other, or both of the responses

Zinkernagel and co-workers had concluded that the adaptive immune response and clinical course after infections by viruses and other non-cytopathic microorganisms were determined primarily by the migration patterns of the pathogen[57–60]. This matched our conclusion that passenger leucocyte migration and relocation were the key events leading to organ engraftment or alternatively to rejection. Except for the different antigens of interest, we were independently describing the same phenomena.

The role of the residual microchimerism in maintaining the clonal exhaustion–deletion, induced at the outset by the flood of passenger leucocytes, was analogous to that of persisting non-cytopathic microorganisms in perpetuating the carrier state following a systemic infection (e.g. by the hepatitis virus). This was only a detail, however, in the concept of immune regulation that we advanced which put transplantation and infection on common ground and was applicable in all other circumstances, including tumour surveillance and self–non-self discrimination. In essence immune responsiveness or non-responsiveness to a given antigen is governed by the migration and localization of that antigen[56].

In this context organ engraftment was by definition a state of variable partial tolerance. Only two mechanisms of immune non-reactivity were necessary: clonal exhaustion–deletion and immune ignorance. Other previously postulated mechanisms of organ engraftment were not essential, singly or in combination. The role of immunosuppression in transplantation was not simply to eliminate the immune response, but rather to reduce it into a deletable range. In a second review we suggested how this tolerance could be made more complete with a different strategy of immunosuppression different from the one in general use[61].

Adherence to two simple therapeutic principles would be required (Figure 7A); the first was recipient pretreatment. The purpose was to reduce the anti-donor response by decreasing global responsiveness before arrival of the alloantigen. The second principle (minimal post-transplant immunosuppression) would require a profoundly counterintuitive departure from conventional practice. Here,

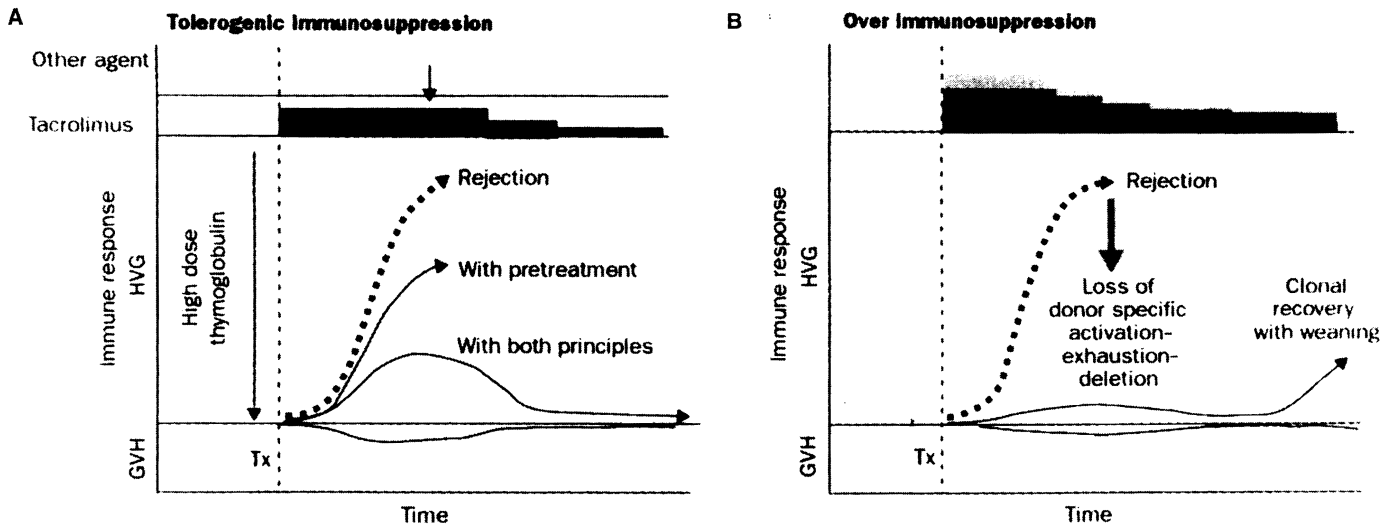

Figure 7 **A**: principles of tolerogenic immunosuppression. Rejection (thick dashed arrow) can be converted to an immune response that can be exhausted and deleted by recipient pretreatment, by minimalistic post-transplant immunosuppression, or by the combined use of both strategies under most circumstances of clinical transplantation. **B**: if the clonal response is eliminated by excessive post-transplant immunosuppression the exhaustion–deletion depicted at the left may be precluded, making subsequent graft survival dependent on unsatisfactorily heavy immunosuppression. GVH = graft-versus-host; HVG = host-versus-graft disease; Tx = transplantation

the objective was to give just enough post-transplant treatment to prevent irreversible immune damage to the organ allograft, but not so much that the seminal mechanism of clonal exhaustion–deletion would be precluded.

The essential point of the second principle was that immunosuppression after transplantation is a two-edged sword. Over-treatment after transplantation can inhibit clonal activation so completely that the derivative event of clonal exhaustion and deletion cannot occur, leaving the patient permanently dependent on high-dose maintenance immunosuppression (Figure 7B). In this view the worldwide practice of starting heavy multidrug immunosuppression on the day of transplantation (so-called induction therapy) systematically closed the window of opportunity for tolerogenesis. It was a treatment policy that had been passed on from generation to generation for the past 40 years.

This practice was introduced after compilation of the cluster of highly tolerant Colorado kidney recipients of phase 1 who have now carried their grafts for 40 years. These pioneer early patients had been managed in accordance with both

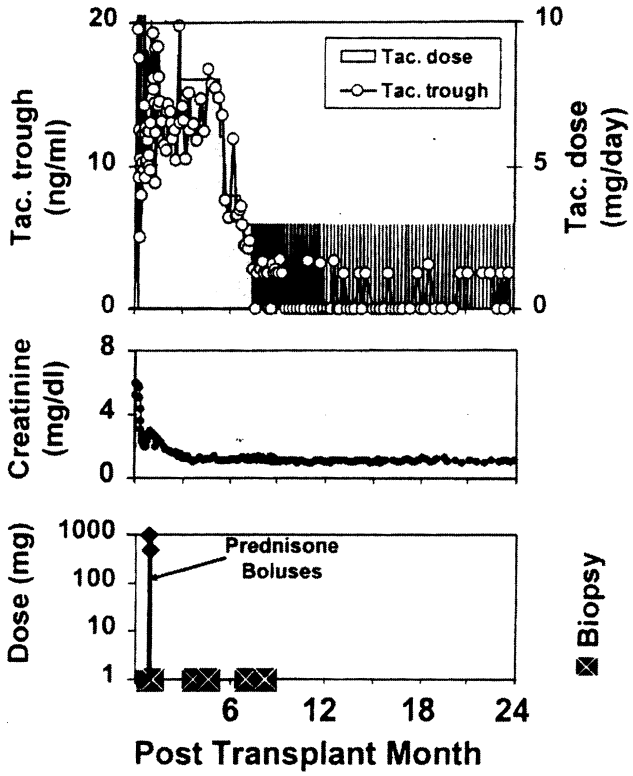

Figure 8 Course of the recipient, in August 2001, of a cadaveric kidney following pretreatment with 5 mg/kg ALG a few hours before transplantation. Biopsy-proven rejection in the third week was treated with infusions of 1.0 g and 0.5 g prednisone. Daily tacrolimus (fully shaded area) was begun on the day after operation. Spacing of tacrolimus was begun after 7 months. Now, $2\frac{2}{3}$ years post-transplantation, treatment has been with one dose per week for almost 2 years

principles: pretreatment with Imuran, and the addition of no other drug afterwards except for prednisone, and then only to treat rejection. In December 1963 the pretreatment was de-emphasized because of preoperative infections. In subsequent cases multidrug prophylactic immunosuppression was begun on the day of operation because of graft losses to non-reversible rejection. Without insight regarding engraftment mechanisms, this antitolerogenic use of immunosuppression became the worldwide state of the art.

With the new insight, and armed with the better drugs available today, we now returned full cycle in July 2001 to phase 1[62,63]. Pretreatment was given with an ALG (thymoglobulin®) similar to the one we introduced in 1966, or with a broadly reacting monoclonal antibody (Campath®). Minimum post-transplant monotherapy was given with tacrolimus (Figure 8) to which other agents were added only in the event of breakthrough rejection. In the patient whose course is shown in Figure 8, a bolus of prednisone was given in response to an early biopsy-proved kidney rejection. After approximately 4 months, weaning was begun from tacrolimus monotherapy by progressive spacing of doses to: every other day, three times a week, twice a week, and in many cases to one dose a week. The depicted patient has been on one dose a week tacrolimus for the past 18 months.

The strategy has been used for the treatment of more than 1000 kidney, liver, intestine, pancreas, and lung recipients. The patterns of treatment and convalescence were the same for all kinds of organ recipients. The quality of life achievable with such treatment exceeds anything ever systematically achieved before. Thus, we are in the waning days of phase 4 in respect to both the controversy concerning the immunological mechanisms of tolerance and their facilitation by the revised use of immunosuppression.

PHASE 5

The same mechanisms and treatment principles are expected to apply for the transplantation of animal organs into humans (xenotransplantation). The recent elimination of the αGal epitope from pig tissues by knockout of the α1, 3-galactosyltransferase gene[64] has been an important step. Thus, phase 5 of the 50-year war may already have begun. It is clear, however, that more genetic modifications are needed. It also is obvious that, if and when xenotransplantation is accomplished with pig donors, the engraftment mechanisms and therapeutic principles almost certainly will be the same as those of allotransplantation. The crucial migratory antigen will be the transgenic pig leucocyte. Even if the immune barrier is surmounted, it is not known whether the numerous metabolic products of the liver will be compatible with the human environment.

POSTSCRIPT

That concludes my chapter, except for a final comment. A third of a century ago (1970), I was invited to this city to receive an important international prize from the Falk Foundation. The prize was given for accomplishment of the first successful

human liver transplantations. Those few autumn days in Germany were a magical interlude in my life that I have cherished ever since. Many things have changed in the ensuing third of a century but, as a constant, the Falk Foundation has continuously supported world hepatology. Thank you for inviting me to this Symposium.

Acknowledgement

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