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Historic Landmarks in Clinical Transplantation: Conclusions from the Consensus Conference at the University of California, Los Angeles

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Abstract. The transplantation of organs, cells, and tissues has burgeoned during the last quarter century, with the development of multiple new specialty fields. However, the basic principles that made this possible were established over a three-decade period, beginning during World War II and ending in 1974. At the historical consensus conference held at UCLA in March 1999, 11 early workers in the basic science or clinical practice of transplantation (or both) reached agreement on the most significant contributions of this era that ultimately made transplantation the robust clinical discipline it is today. These discoveries and achievements are summarized here in six tables and annotated with references.

The symposium making up this issue of the *Journal* was held at the University of California, Los Angeles (UCLA) and announced by the Department of Surgery hosts as "a unique and historic meeting at which pioneers of transplantation from around the world will present and discuss landmarks in the advancement of transplantation biology." The participants (in alphabetical order) were: Leslie B. Brent (London), Roy Y. Calne (Cambridge, UK), Jean Dausset (Paris), Robert A. Good (St. Petersburg, FL), Joseph E. Murray (Boston), Norman E. Shumway (Palo Alto), Robert S. Schwartz (Boston), Thomas E. Starzl (Pittsburgh), Paul I. Terasaki (Los Angeles), E. Donnall Thomas (Seattle), Jon J. van Rood (Leiden).

Each of these 11 pioneers provided for publication their reflections about their own unique contributions. The ultimate objective, however, was to reach a consensus by the group on what were the most critical historical discoveries that made transplantation a form of clinical therapy. Carl G. Groth (Stockholm) was invited to be the Chairman for these consensus deliberations and to prepare the executive summary.

Historical landmark status was restricted to contributions made at least a quarter of a century ago. By this time it had been established that rejection of organ allografts could be prevented or reversed with immunosuppressive drugs and that variable donor-specific immunologic tolerance of the graft subsequently developed in many patients. Long-term survival of human recipients of organ and bone marrow allografts had been repeatedly obtained, ensuring continuation of such clinical efforts. A large number of HLA antigens had been discovered, allowing efforts at tissue matching to proceed. The scientific articles annotating this progress are listed in six tables under the following headings: transplantation immunology, bone marrow transplantation, renal transplantation, liver transplantation, heart transplantation, and tissue matching. The material presented in these tables, including the citations, originated from the participants of the symposium.

It should be noted that transplantation could not have proceeded without contemporaneous advances in general and thoracic surgery, medicine, and anesthesia, such as open-heart surgery, renal dialysis, antibiotics, and intensive care technology. The

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Table 1. Transplantation immunology.

Author	Discovery or application	Year published	Reference
Gibson	Defined the immunologic nature of skin allograft rejection in humans, confirmed subsequently with controlled rabbit experiments.	1943	1
Owen	Discovered that bovine dizygotic twins with placental vascular anastomoses (freemartin cattle) were red blood cell chimeras.	1945	2
Burnet	Based on Owen's observations and on studies of lymphocytic choriomeningitis virus by Traub, Burnet, and Fenner postulated "the development of tolerance . . . during embryonic life."	1949	3
Anderson	Demonstrated mutual tolerance to skin grafts by freemartin cattle twins and speculated that "actively acquired tolerance" was responsible.	1951	4
Billingham	Produced actively acquired donor specific tolerance to skin allografts in mice injected during late fetal life with donor hematolymphopoietic cells.	1953	5
Simonsen	Independently demonstrated GVHD in chick embryos (manifested as	1957	6
Billingham	pancytopenia) and mice (runt disease) after intravenous injection of adult spleen cells.	1957	7
Starzl	Reported evidence that human kidney allografts under azathioprine-prednisone induced variable donor specific nonreactivity.	1963	8

GVHD: graft-versus-host disease.

cardiopulmonary resuscitation procedures introduced during the 1950s were particularly influential because they mandated redefinition of death in terms of irreversible brain damage rather than the cessation of heartbeat and respiration. While salvaging countless victims of cardiac or pulmonary arrest, the new methods also resulted in brain-dead corpses on physiologic life support.

In 1966, at a symposium on medical ethics in London, G.P.J. Alexandre described the criteria of brain death that had been used in Belgium and France for discontinuing mechanical ventilation of "heart-beating cadavers." It became possible thereby to remove kidneys and other organs from cadaver donors with an intact circulation. The concept was further elaborated in a Harvard-based ad hoc committee report in 1968 in the *Journal of the American Medical Association.* The impact on transplantation of cadaver organs was immediate and lasting.

Transplantation Immunology

The modern age of transplantation immunology (Table 1) [1–8] began with three seminal observations. First, rejection is a host-versus-graft (HVG) immune reaction. Second, a similar immune reaction [graft-versus-host (GVH)] may occur in reverse and lead to lethal graft-versus-host disease (GVHD). Third, it is possible under well defined experimental conditions to avert rejection as well as GVHD and to induce tolerance of alloantigens, which is strongly associated with the persistence in the recipient of donor leukocyte chimerism.

The next step was the recognition that organ allografts are inherently tolerogenic, a property without which their transplantation with long survival in the recipient would not be possible (Table 1). The tolerance induced by organs usually is manifested only under an umbrella of immunosuppression, but it is not a prerequisite in some animal models, particularly if the allograft is the leukocyte-rich liver (see also Table 4).

The discoveries listed in Table 1 were made piecemeal over a period of 25 years, obscuring the fact that all three of the fundamental phenomena studied by early workers (i.e., HVG, GVH, and acquired tolerance) were involved, but to different degrees, in the "acceptance" of organ allografts and the tolerance induced by allogeneic bone marrow following recipient cytoablation. In 1992 the mechanistic linkage of engraftment after these two kinds of transplantation was established with the discovery of donor leukocyte microchimerism in long-surviving human organ recipients.

The clonal selection theory proposed in 1949 by Burnet and Fenner marked the beginning of a new wave in immunology, from which transplantation is often viewed as a mere stream. Instead, transplantation is a mighty tributary. It fostered research into the mechanisms of the destructive antigraft immune response and the control of this response. From these efforts, directly or indirectly, came the discovery of the function of the lymphocyte (1959–1961) and the role of the thymus in the ontogeny of the immune system (1961); delineation (1958–1963) of the human major histocompatibility complex (MHC); distinction of the T and B lymphocyte subsets (1967–1968); and mainly by study of antiviral immune responses, demonstration of the MHC-restricted nature of the adaptive immune response (1968–1974).

Bone Marrow Transplantation

Bone marrow transplantation (Table 2) [9–22] had its roots in radiobiology and hematology, and it was influenced by clinical studies of certain inherited immune deficiency diseases. Early in these efforts it was learned that engraftment of histoincompatible bone marrow can cause lethal GVHD in a recipient rendered immunologically defenseless by cytoablation, a complication also predicted in recipients with immune deficiency disease. Consequently, the preclinical and clinical development of bone marrow transplantation was delayed until reliable methods of HLA typing and matching became available.

The first completely successful bone marrow transplantations were in children with immune deficiency diseases whose family donors were selected with relatively primitive first-generation tissue-matching techniques. Because of their T cell deficiency, these recipients did not require the cytoablation and postgrafting immunosuppression needed with other indications for bone marrow transplantation. With the use of methotrexate as an immunosuppressant in cytoablated recipients, bone marrow transplantation subsequently was applied with steadily improving results in those with an array of benign and malignant hematolymphopoietic dis-

Table 2. Bone marrow transplantation.

Author	Discovery or application	Year published	Reference
Jacobson	Protection against lethal irradiation by spleen shielding, mistakenly ascribed to humoral factors.	1951	9
Lorenz	Protection against lethal irradiation by injection of bone marrow, mistakenly ascribed to humoral factors.	1951	10
Main	Protection against lethal irradiation in mouse by infusion of bone marrow cells and subsequent acceptance of skin allograft from the marrow donor (tolerance). Recognized analogy to neonatal tolerance.	1955	11
Ford	Proved with cytogenetic techniques that marrow cells of mouse reconstituted with bone marrow after lethal total body irradiation (TBI) were donor origin.	1956	12
Barnes	First attempt to treat leukemia in mice by bone marrow transplantation after lethal TBI.	1957	13
Thomas	First attempts to treat malignancy in human patients by high dose chemotherapy or TBI and an infusion of marrow, showing safety of the infusion and one example of transient engraftment.	1957	14
Thomas	Two children with leukemia given twice the lethal dose of TBI and bone marrow from an identical twin had benign hematologic recovery. Recurrence of leukemia led to the subsequent addition of chemotherapy to TBI.	1959	15
Thomas	First outbred animals (dogs) to be successfully engrafted with allogeneic marrow; conditioning with TBI and treatment after grafting with a short course of methotrexate. Graft rejection, other causes of graft failure, and GVHD described.	1962	16
Mathé	World's first prolonged engraftment of human allogeneic bone marrow; adult recipient with leukemia conditioned with TBI. Died without disease recurrence after 20 months, probably from complications of GVHD.	1963	17
Storb	After developing dog typing sera, achieved survival of most histocompatibility matched, but not of unmatched, recipients of bone marrow from littermate donors. Recipients cytoablated and treated with a short course of postgraft methotrexate.	1968	18
Gatti[a]	After initial illuminating analyses of the inborn errors of lymphocyte development [X-linked agammaglobulinemia, thymic alymphoplasia, and severe combined immunodeficiency disease (SCID)] as experiments of nature, Good suggested a new two-component concept of immunity and performed the world's first completely successful bone marrow transplant in a child with otherwise uniformly lethal X-SCID. A second marrow transplant from the same donor cured a complicating aplastic anemia in this patient, also for the first time.	1968	19
Bach[a]	This was followed by a partially successful allogeneic bone marrow engraftment in a child with Wiskott-Aldrich syndrome.	1968	20
deKoning[a]	Successful allogeneic bone marrow plus thymus engraftment was done subsequently in a child with lymphopenic immune deficiency.	1969	21
Thomas	Review of bone marrow transplantation, including description of first large series of patients with aplastic anemia or leukemia given allogeneic marrow grafts from matched siblings. Problems with GVHD and opportunistic infections defined, with emphasis on the importance of histocompatibility, and discussion of possible use of matched unrelated donors.	1975	22

[a]These three patients did not need myeloablation or postgraft immunosuppression.

eases, other kinds of malignancies, and numerous inborn errors of metabolism.

Kidney Transplantation

Three factors made the kidney a pathfinder organ in transplantation (Table 3) [8, 23–47]. One was the development of dialysis for the treatment of acute, and ultimately chronic, renal failure. The second was the fact that the kidney is a paired organ, ensuring a supply of surgically removed "free kidneys" and, increasingly after 1953, physiologically ideal live donor kidneys. Third, its technical simplicity and the ease with which allograft function could be monitored made kidney transplantation ideal for laboratory and clinical investigation.

By 1974 kidney transplantation had already gone through the four eras shown in Table 3 defined by: no immunosuppression, immunosuppression with total body irradiation (TBI), the first use of drugs to prevent rejection (azathioprine) or reverse it (prednisone), and the introduction of adjunct anti-lymphocyte antibody therapy. Each major improvement in immunosuppression up to 1974 and subsequently permitted goals in kidney transplantation to be reached that were not attainable before.

Thus the transition from no therapy to TBI corresponded with the step from identical to fraternal twin transplantation. The change to azathioprine-based treatment established kidney transplantation as a clinical service from 1963 onward, especially using kidneys from living related donors. Cadaver kidney transplantation burgeoned with the acceptance of brain death during the late

Table 3. Kidney transplantation during four eras.

Author	Discovery or application	Year published	Reference
Preimmunosuppression			
Carrel	Developed vascular anastomotic techniques used for organ transplantation today.	1902	23
Lawler	Surgically excised ("free") kidney allograft transplanted to recipient nephrectomy site. Function controversial.	1950	24
Küss	Free kidneys or kidneys from guillotined donors transplanted with surgical techniques still used today.	1951	25
Michon	First use of living related donor kidney (mother to son): good function before rejection at 3 weeks.	1953	26
Hume	Nine cadaveric or free kidneys transplanted, eight to thigh and one to an orthotopic location. One thigh kidney functioned for 5 months.	1955	27
Murray Merrill	First transplantation of identical twin kidney on 12/23/54, reported first in abstract [28] and more completely the following year [29]. Later report of first nine cases included description of first posttransplant pregnancy.	1955 1956	28 29
Total body irradiation			
Murray Merrill	Renal allograft from fraternal twin transplanted (1/24/59) to a recipient preconditioned with sublethal TBI [30] more fully reported elsewhere [31]. This was the first long survival of an organ allograft, an objective not previously achieved in an animal model.	1960	30 31
Hamburger	Second successful fraternal twin kidney transplantation using TBI, performed June 1959.	1959	32
Hamburger	Successful transplantations of two living related but nontwin kidney allografts using TBI; secondary steroid administration mentioned.	1962	33
Küss	Eighteen-month survival of two nonrelated kidney allografts using TBI; secondary steroid and 6-mercaptopurine (6-MP) administration noted, without details.	1962	34
Chemical immunosuppression			
Schwartz	Showed in rabbits given bovine serum albumin (BSA) while also being treated with 6-MP that the 6-MP suppressed the antibody response to BSA and rendered the animals tolerant of the foreign protein. The experiments were driven by the hypothesis that the proliferating immunocytes of an expanding antigen-specific clone would be selectively vulnerable to antimetabolite drug therapy.	1959	35
Schwartz Meeker	Independently demonstrated a 6-MP dose-related prolongation of rabbit skin allograft survival.	1960 1959	36 37
Calne Zukoski	Moved from the skin to an organ allograft model and demonstrated (independent from each other) prolongation by 6-MP of canine kidney allograft survival.	1960 1960	38 39
Calne	Further extensive preclinical studies (in Murray's Boston laboratory) of a report on efficacy in dogs of 6-MP and its analogue azathioprine.	1961	40
Murray	Clinical trials begun with 6-MP and azathioprine.	1962	41
Murray	Report of first 13 patients treated with 6-MP or azathioprine, one of whom reached 1 year with a still functioning but failing kidney allograft on 4/5/63.	1963	42
Starzl	First systematic use of azathioprine and prednisone with long survival of most of kidney allografts.	1963	8
Starzl	Clinical experience summarized with azathioprine/prednisone therapy in recipients of 67 kidney allografts and 6 baboon xenografts.	1964	43
Antibody immunosuppression			
Waksman	Demonstration of anti-lymphocyte serum (ALS) efficacy with skin allograft test model in rats.	1961	44
Woodruff	Showed additive protection of skin allografts in rats using ALS combined with thoracic duct drainage.	1963	45
Monaco	Convincing demonstration of the therapeutic value of ALS in the canine kidney transplant model.	1966	46
Starzl	First clinical trial of anti-lymphocyte globulin (ALG) as an adjunct to azathioprine and prednisone for human kidney transplantation. With the hybridoma technology of Kohler and Milstein (1975) monoclonal antibodies could be raised against discrete immunologic targets. In 1981 anti-CD3 antibody (OKT3) was introduced clinically.	1967	47

Table 4. Liver transplantation.

Author	Discovery or application	Year published	Reference
Preimmunosuppression			
Welch	First mention of hepatic transplantation in the literature, with insertion of an auxiliary liver in unmodified dogs.	1955	48
Moore	Independent studies in Boston and Chicago of liver replacement	1960	49
Starzl	(orthotopic transplantation) in unmodified dogs.	1960	50
Starzl	Transplantation in dogs of multiple abdominal viscera, including liver and intestine, nearly identical to human procedures done three decades later.	1960	51
Immunosuppression era			
Starzl	World's first three attempts at orthotopic liver transplantation in humans (March 1, May 5, and June 24, 1963) with maximum survival of 21 days.	1963	52
Starzl	Discovery that splanchnic venous blood of dogs contained hepatotrophic factor(s), the most important of which was later proved to be insulin; the finding dictated methods of liver allograft revascularization.	1964	53
Starzl	First >1-year survival after liver replacement in any species (here mongrel dogs) with recognition of the liver's unusual ability to induce tolerance under a 3- to 4-month course of azathioprine, or in this canine model after only a few perioperative injections of ALS or ALG [47].	1965	54
Cordier	Observed that liver allografts in untreated pigs frequently were not rejected. This finding of spontaneous tolerance to livers was promptly confirmed by Peacock and Terblanche in Bristol and by Calne in Cambridge.	1966	55
Starzl	First report of prolonged survival of four (of seven) children after orthotopic liver transplantation between July 1967 and March 1968.	1968	56
Calne	Report of first four patients in the Cambridge (England) liver replacement series, including an adult with >4 months survival.	1968	57
Calne	Showed that spontaneous tolerant pig liver recipients also were tolerant to skin and kidney allografts from the same donor.	1969	58
Starzl	Text summarizing experience at the University of Colorado with 25 liver replacements to March 1969 and 8 cases elsewhere.	1969	59
Starzl	Metabolic abnormality of Wilson's disease corrected, first of more than two dozen liver-based inborn errors cured or ameliorated with liver replacement. These liver recipients and patients cured of mesoderm-based inborn errors by bone marrow transplantation were the first examples of effective genetic engineering.	1971	60

1960s and the subsequent establishment of organ procurement agencies, usually associated with clinical immunology laboratories for tissue (HLA) matching. By 1974 renal transplantation had become a government-financed component of health care in most Western countries.

Liver Transplantation

After a failed trial in 1963, liver transplantation was successfully performed in humans in July 1967 (Table 4) [48–60]. Hepatic replacement was initially viewed as too difficult to be technically feasible, particularly in terminally ill patients for whom artificial organ support comparable to renal dialysis was not available. Instead, challenges generated by its surgical difficulty and physiologic complexity made liver transplantation the co-leader after 1963 (with the kidney) or the leader in the development of broadly applicable advances of surgical technique, immunosuppression, and means of multiple organ procurement and preservation.

Despite a high mortality rate during the first year after liver transplantation, nearly two dozen recipients from this early era have been stable for 20 to more than 29 years using immunosuppression with azathioprine, prednisone, and antilymphocyte globulin (ALG). The proof of the liver's unusual tolerogenicity (Tables 1, 4) is that most of these patients have been able to discontinue immunosuppressive therapy without rejecting their grafts.

The ripple effects of liver transplantation included discovery of the first hepatotrophic factors (beginning with insulin) that are involved in hepatic growth control and regeneration. More than two dozen liver-based inborn errors of metabolism have been corrected by liver transplantation, with clarification of disease mechanisms in some.

Heart Transplantation

The landmarks of heart transplantation are summarized in Table 5 [61–69]. Studies of heart transplantation were carried out at Stanford University in dogs and subhuman primates from the late 1950s to 1967. The results justified the decision by this group to proceed clinically, as announced by interview in the November 20, 1967, issue of the *Journal of the American Medical Association.* On December 3, heart replacement was carried out in Cape Town following an extended visit by the South African team leader to Stanford and other American transplant centers. The first South African recipient died from infection after 18 days, but the second patient (January 2, 1968) lived several years. On January 5, 1968,

Table 5. Heart transplantation.

Author	Discovery or application	Year published	Reference
Cass	Described standard current practice of combining the multiple pulmonary venous and venacaval anastomoses into two large atrial anastomoses. No dogs survived the operation.	1959	61
Lower	Independently developed same procedure as Cass/Brock, preserving allografts with immersion hypothermia. Dogs recovered.	1960	62
Lower	Technically successful canine heart-lung transplantation in nonimmunosuppressed dogs with 5-day survival. With long survival the same operation was done under cyclosporine two decades later, first in monkeys and then in humans.	1961	63
Lower	Immersion hypothermia of canine allografts at 2°–4°C adequately preserved dog hearts for 7 hours.	1962	64
Dong	Demonstrated normal heart function and reinervation of cardiac autografts 2 years after transplantation in dogs.	1964	65
Hardy	Transplantation of chimpanzee heart to human recipient. The heart was too small to support the circulation and failed after 2 hours.	1964	66
Lower	First long survival (up to 9 months) of heart allografts in any species (here dogs). Azathioprine-based immunosuppression was guided by electrocardiogram (ECG) voltage changes, especially R-wave diminution.	1965	67
Barnard	Description of the world's first transplantation of a human heart in Cape Town on 12/3/67, with 18 days survival. A second attempt in New York on 12/6/67 failed after 6 hours. A third recipient, operated in Cape Town on 1/2/68, survived for several years.	1967	68
Stinson	The world's fourth human heart transplantation at Stanford on 1/5/68 was successful and inaugurated the long-standing thoracic organ transplant program at that institution.	1970	69

the Stanford program recorded its inaugural human case, which was successful.

Graft survival after heart transplantation using triple-drug immunosuppression (azathioprine, prednisone, ALG) was essentially equivalent to that of cadaver kidney transplantation. As with kidney and liver transplantation, many of the pioneer cardiac recipients enjoyed an excellent quality of life, ensuring prompt acceptance and widespread application of all these operations when better immunosuppression became available.

Tissue Matching

The ABO blood groups, the compatibility of which was later found to be a requirement for transfusion and for bone marrow and organ transplantation, were discovered in 1901 [70]. Similarly, it was necessary to develop methods to type human tissue antigens and then to determine which were compatible or incompatible with those of the donor (Table 6) [70–94]. This was made possible with the discovery in transfused patients, and in women who had been pregnant, of leukoagglutinating and lymphocytotoxic antibodies that recognized alloantigens.

The introduction of computer-assisted search systems allowed delineation of families of antibodies that reacted with individual alloantigens and also made feasible the grouping of alloantigens into the two closely associated series that are now called HLA-A and HLA-B. The demonstration of crossover of the A and B antigens established HLA as a closely linked supergene. After 1964 use of the microcytotoxicity test greatly facilitated the standardization of HLA typing and the search for HLA antigens. The method was adapted for donor-recipient crossmatching and subsequently for the detection of pretransplant sensitization to HLA alloantigens.

HLA matching has been a stringent requirement for bone marrow transplantation (Table 2). For organ transplantation, the lymphocytotoxic crossmatch has been of crucial importance. Although there is clear evidence that the HLA system contains the dominant histocompatibility antigens, it has not been possible to identify which mismatches would result in failure. Nonetheless, HLA-identical sibling kidney allografts provide the highest graft survival rates. These are approached by survival rates of zero HLA-mismatched cadaver kidneys, justifying kidney sharing.

Quarter Century after 1974

The advent of cyclosporine two decades ago was a watershed for both bone marrow [95] and organ [96] transplantation. When the new drug was substituted for azathioprine, allograft survival and the quality of recipient life improved dramatically. In particular, the transplantation of cadaver organs was upgraded from a frequently feasible but unpredictable service to a reliable one. The results of organ transplantation were further enhanced after another decade with the introduction of tacrolimus [97]. Other promising drugs and monoclonal antibody preparations have been introduced more recently or are in various stages of preclinical or clinical evaluation. However, the therapeutic principles have remained essentially the same as were originally developed with azathioprine, prednisone, and ALG.

With more potent immunosuppressive agents, the field of transplantation has expanded continuously over the last 25 years. Heart–lung and lung transplantations were extensions of the heart procedure. Although survival of a lung recipient for 10 months had been accomplished as early as 1969 [98], the first examples of survival exceeding 1 year were not reported for heart–lung transplantation until 1982 [99] and for lung transplantation until 1987 [100]. Efforts at transplantation of abdominal organs expanded from the liver-only to the liver combined with small bowel [101]

Table 6. Tissue matching.

Author	Discovery or application	Year	Reference
Landsteiner	Discovery of ABO blood groups.	1901	70
Gorer	Described single dominant histocompatibility locus (later H-2) in mouse, analogous to the human leukocyte antigen (HLA) system.	1948	71
Dausset	Discovered first HLA antigen (MAC) using antiserum from transfused patients.	1958	72
Van Rood	Independently demonstrated HLA antibodies in pregnant	1958	73
Payne	women.	1958	74
Van Rood	First use of computers to make sense of the complex reactions produced by human antibodies, allowing identification of antigens currently known as HLA-B 4 and 6, as well as leukocyte antigen grouping.	1963	75
Starzl	Hyperacute rejection of ABO-incompatible kidneys (from host isoagglutinins) and rules to prevent it.	1964	76
Terasaki	Description of microcytoxicity test, critical for further development and practical use of HLA typing.	1964	77
Bach	Independently described mixed lymphocyte culture (MLC) test	1964	78
Bain	of histocompatibility.	1964	79
Payne	Defined allelic system now known as HLA-A 1, 2, and 3.	1964	80
Van Rood	Described antigens now known as HLA-B7+B27 and HLA-B8 as part of a closely associated system.	1965	81
Dausset	Proposed single locus for the HLA system, analogous to the mouse H-2 system.	1965	82
Terasaki	Description of hyperacute kidney rejection associated with	1965	83
Kissmeyer-Nielsen	antigraft lymphocytotoxic antibodies and proposed prevention with cytotoxic crossmatch (Terasaki), confirmed and extended the following year with the leukoagglutinin test (Kissmeyer-Nielsen).	1966	84
Terasaki	First prospective trial of HLA matching for donor selection.	1966	85
Van Rood	Proposal that initiated the first international organ exchange organization.	1967	86
Ceppellini	Coined the term "haplotype" to indicate the chromosomal combination of HLA alleles.	1967	87
Amos	Showed that the MLC reaction was detecting the HLA-D locus.	1968	88
Kissmeyer-Nielsen	Described the first crossover between HLA-A and HLA-B, proving that HLA identified a chromosomal region and not a single locus.	1969	89
Dausset	Demonstrated the importance of HLA compatibility for the survival of skin grafts in unmodified human volunteers.	1970	90
Starzl	Long survival frequently achieved at all levels of HLA	1970–1	91
Mickey	mismatch using a living donor and cadaveric kidneys. However, the best function, histologic appearance of allografts, and survival as well as the least dependence on immunosuppression was with zero-HLA mismatched kidney allografts.		92
Terasaki	Identification of presensitized patients at high immunologic risk using the panel reactive antibody (PRA test).	1971	93
Van Leeuwen	Identified the first sera that could be used for HLA-DR typing. This formed the basis on which HLA-DR serology was developed.	1973	94

and to the more complex multiple abdominal visceral grafts [102]; in the end it resulted in successful engraftment of the small bowel alone [103]. Tacrolimus played a crucial role in making the abdominal procedures involving intestine clinically applicable.

Although pancreas transplantation was offered at first only to diabetic patients who also were undergoing kidney transplantation for diabetes-associated end-stage renal disease [104], pancreas transplantation alone has been performed more recently in nonuremic diabetics [105]. The alternative appealing approach of transplanting the isolated islets of Langerhans only was attempted during the 1970s but did not result in success (defined as insulin independence) until 1990 in a patient with postpancreatectomy diabetes [106] and 1991 in a patient with type I diabetes [107]. Success with this procedure still is achieved only in occasional cases.

Résumé

La transplantation d'organes, de cellules et de tissus a littéralement explosée dans ce dernier quart de siècle, avec le développement d'une multitude de nouvelle spécialités. Cependant, les principes de base qui ont rendu ceci possible ont été établi sur trois décennies, commençant pendant la deuxième guerre mondiale et terminant en 1974. Pendant la conférence de consensus historique tenu à l'UCLA du 25 au 27 mars, 1999, 11 chercheurs sur la transplantation travaillant en sciences

fondamentales et/ou en clinique se sont mis d'accord sur les contributions les plus significatives de cette période et ont donné à la discipline de transplantation sa crédibilité présente. Ces découvertes et accomplissements ont été résumés en six tableaux, dotées de 93 références.

Resumen

En los últimos 25 años se ha producido un auténtico renacimiento por lo que a trasplantes de órganos, células y tejidos se refiere, lo que ha propiciado el desarrollo de múltiples áreas nuevas de especialización. Sin embargo, los principios que hicieron posible los trasplantes se establecieron hace más de 3 décadas, ya que las investigaciones al respecto se realizaron en el periodo de tiempo comprendido desde los comienzos de la 2ª Guerra Mundial al final de 1974. En la histórica conferencia de consenso, celebrada en UCLA, del 25 al 27 de marzo de 1999, 11 investigadores pioneros, procedentes tanto de las ciencias básicas como de la clínica y del tratamiento mediante trasplantes, alcanzaron un acuerdo sobre, cuáles fueron los hitos más importantes de este periodo, que permitieron que la técnica de los trasplantes sea hoy una especialidad clínica bien definida y en continua expansión. Estos descubrimientos y realizaciones se resumen en 6 tablas y 93 referencias bibliográficas.

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