The Transplantation Society

Four Decades of International Cooperation, Innovation, Growth and Progress

1966 – 2006

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Nicholas L. Tilney has been involved in both clinical transplantation and its biology throughout his career. Trained in surgery at the Peter Bent Brigham Hospital and in cellular immunology at Oxford University, he became involved in the field relatively early during its development. His research interests have involved particularly the definition of the mechanisms of acute and chronic rejection, with special emphasis on antigen-independent, donor-associated risk factors for graft survival. He is President-Elect of The Transplantation Society.

At its closing session early in 1966, participants at the seventh and final Tissue Homotransplantation Conference sponsored by the New York Academy of Sciences, voted to form The Transplantation Society. A constitution was formulated, presented, and approved. Officers were chosen. Bernard Amos, an enthusiastic supporter of the fledgling effort, was elected Past-President, Peter Medawar, the doyen of transplantation biology, was President. John Marquis Converse, the organizer of the meetings, was named President-Elect. The first meeting of the new Society was to be held in Paris the following spring and every two years thereafter.

Forty years later, the Society has assembled 21 times in venues all over the globe (Table 1). There are currently over 3000 members from scores of countries. It has become the major international voice in what has been arguably the most exciting and innovative advance in medical biology during the twentieth century. Formed slightly over a decade after the first successful kidney transplant, it arose from already deepening roots.

A young Oxford zoologist, **Peter Medawar**, joined a plastic surgeon in a burn unit in Glasgow to examine the phenomenon of graft rejection. Confirming that grafts of the patients' own skin but not those of others would heal normally, Medawar embarked on a series of experiments in rabbits to examine the process in more detail. His recognition that genetic variations between donor and host evoked differential tissue responses, that the animal would reject a "second set" of grafts from the same donor in an accelerated fashion, and an emerging appreciation of the existence of transplantation antigens provided compelling evidence that immunological host mechanisms were involved in graft behavior. With his colleagues, Rupert Billingham and Leslie Brent, Medawar then demonstrated that graft rejection could be prevented in laboratory animals after introduction of specific foreign cells during fetal or neonatal life; these animals would become "immunologically tolerant" to the donor antigens upon reaching adulthood. As winner of the Nobel Prize and first President of The Transplantation Society, his contributions continue to influence the entire field.

Born in Paris, **John Marquis Converse** became professor of plastic surgery at New York University School of Medicine. A master surgeon and renowned teacher, he performed distinguished experimental work in transplantation immunology and the genetics of tissue typing. Elected President of The Transplantation Society, he remained one of its strongest proponents.

Prologue

The first formal meeting of research workers and clinicians interested in the new subject of homotransplantation was held in the autumn of 1952 at Arden House in Harriman, NY. Averell Harriman, governor, diplomat, and advisor to presidents, had donated this huge private house to Columbia University as a conference center two years previously. Built before World War I by his father, a railroad magnate, it sits in 8000 acres of woodland and field. A handful of participants attended.

A modest foundation of knowledge was already in place. Although the grafting of bodily structures had been in the mind of man throughout history, actual attempts had been few. Occasional early surgeons had fashioned skin pedicles to close nasal defects. Rarely, they had transferred skin grafts from donor sites to cover superficial ulcers. The results of blood transfusions, another form of tissue transplantation, were so disastrous that further attempts had been virtually outlawed.

Arguably, the modern field was triggered in 1894 by the death of the President of France from an assassin's knife. Energized by the event, a young surgeon in Lyon, Alexis Carrell, devised effective operative means to repair and reconstruct blood vessels. After moving to the Rockefeller Institute in New York in 1908, he gained much notoriety including the Nobel Prize for his techniques in vascular surgery and for transplanting a variety of organs into experimental animals. But discouraged by the inevitable and unexplained failure of the previously well-functioning grafted organs, he turned his attention to other scientific endeavors.

Arden House, Harriman, NY. (Columbia University Archives, NY, with permission)

Year	Congress	City	President	Congress Chair
1966	**Formation of the Society**		D. Bernard Amos (Past-President)	
1967	**I**	Paris	Peter B Medawar	JM Converse, FT Rapaport
1968	**II**	New York City	John Marquis Converse	
1970	**III**	The Hague,	Jean Hamburger	DW van Bekkum, JJ Van Rood, H Balner, JJ van Longhem
1972	**IV**	San Francisco	Paul S Russell	Samuel Kountz
1974	**V**	Jerusalem	Michael Woodruff	Michael Schlesinger
1976	**VI**	New York City	Rupert Billingham	Felix Rapaport
1978	**VII**	Rome	Leslie Brent	Rafaello Cortisini
1980	**VIII**	Boston	Felix Rapaport	Anthony Monaco
1982	**IX**	Brighton	Hans Balner	P.B. Medawar
1984	**X**	Minneapolis	Paul Terasaki	John Najarian
1986	**XI**	Helsinki	Peter J Morris	Pekka Häyry
1988	**XII**	Sidney	Anthony P Monaco	Ross Sheil
1990	**XIII**	San Francisco	Richard Batchelor	Oscar Salvatierra
1992	**XIV**	Paris	Thomas E Starzl	Henri Kreis
1994	**XV**	Kyoto	Roy Y Calne	Kazuo Ota
1996	**XVI**	Barcelona	John S Najarian	Josep Loveras
1998	**XVII**	Montreal	Pekka Hayry	Ronald Guttmann
2000	**XVIII**	Rome	Oscar Salvatierra	Rafaello Cortisini
2002	**XIX**	Miami	Carl G Groth	Camillo Ricordi
2004	**XX**	Vienna	David ER Sutherland	Raimund Margreiter
2006	**XXI**	Boston	Kathryn J Wood	Benedict Cosimi

Table 1

Comparable activity was minimal, although unbeknownst to Carrell the possibilities of suturing vessels together had encouraged a few surgeons in Europe to transplant kidneys between animals, between man and monkey, and between monkey and man. All were unsuccessful. The subsequent cataclysm of World War I put an end to further experiments. With the single exception of a transplant of a lamb's kidney into a patient dying of mercury poisoning in 1923 in the United States and an experience in Russia with cadaver kidneys placed in six individuals with renal failure in the mid-1930s, activity remained static until June 1950 when a single case stimulated interest on each side of the Atlantic. A surgeon in Chicago, Richard Lawler, removed one of the failed polycystic kidneys from a patient, Ruth Tucker, and replaced it with the normal organ of a recently deceased donor. To the astonishment of everyone, the transplant functioned long enough to

David Hume contributed substantially to the early transplantation conferences, although he never became an officer in The Transplantation Society because of his early death. He is included herein as a highly visible and innovative pioneer in the care of patients with renal failure. Becoming Chairman of Surgery at the Medical College of Virginia, he was a major contributor to the new field. Honored and admired by his peers, he was killed in a plane crash in 1973.

Working as a physician in Holland and becoming interested in patients dying of uremia, **Willem Kolff** devised a hemodialysis machine to remove toxins from the blood using thin cellulose tubing and using the anticoagulant, heparin. In 1940 during the Nazi occupation he had been forced to move to a small town in the north of Holland where he treated several patients with his new device. His prototype was later improved and refined by John Merrill and others at the Peter Bent Brigham Hospital so successfully that the treatment became established throughout the developed world. Moving to the United States, Kolff became increasingly interested in the development of the artificial heart and other artificial organs.

Felix Rapaport was a medical student examining the fate of skin grafts in human subjects with Converse in 1953. They noted not only that second set grafts from the same donor were rejected in an accelerated fashion but that those of some third party donors were as well. The "sharing" of tissue groups between unrelated individuals was considered responsible. As Dausset had discovered leukocyte antigens about the same time, Rapaport spent many months with him in Paris grafting skin in over 900 volunteers and their families. Their results evolved into increasing appreciation of HLA. Rapaport fully involved himself with the workings of The Transplantation Society throughout his career as a member of the Council from 1966 until his death in 2003. He also became President and later received the Medawar Prize.

Morten Simonsen noted in 1957 that splenomegaly was a prominent feature of the graft versus host disease (GVDH) that developed in chick embryos following injection of allogeneic lymphocutes. His splenomegaly assay became an important tool in assessing the severity of this condition. Describing various aspects of the responses of dogs to renal transplants, he was an innovative investigator who was later awarded the Medawar Prize for his contributions.

Ruth Tucker, on her discharge from hospital after her kidney transplant in July 1950.

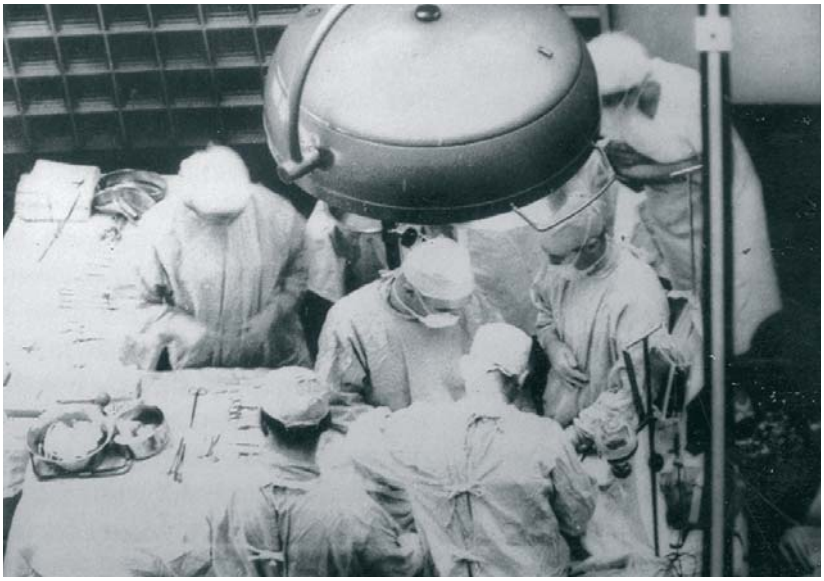
allow the remaining native kidney to recover some function. Mrs Tucker lived for six more years.

This unique event served as a catalyst. In January 1951 two Parisian teams removed the kidneys from a guillotined prisoner and transplanted them into two patients. They and their colleagues then carried out six more transplants, one between a mother and her son, the first living related combination. All promptly failed. In April, David Hume, a surgeon at the Peter Bent Brigham Hospital in Boston, encouraged both by his previous placement of a kidney as a bridge to tide over a young woman in acute renal failure and the introduction of hemodialysis to the hospital by Willem Kolff, carried out a series of nine transplants. His results were equally disheartening, with one important exception. The new kidney, by happenstance, supported the final patient in the series for nearly six months. Occasional other attempts and failures were to follow. By the time of the Arden House Conference, clinical transplantation, such as it was, had ground to a virtual halt.

At the same time as these early organ transplants, scientific attention was turning toward the host responses brought into play against foreign tissues, hitherto an area of mystery. The practical possibilities of using skin grafts to cover the extensive burns of soldiers and airmen fighting in World War II had become paramount.

The clinicians and experimentalists interested in the evolving subject presented 22 papers at Arden House. Discussion of the topic continued five months later in London at the *Ciba Foundation Conference on the Preservation and Transplantation of Normal Tissues*. Nearly a year thereafter, two plastic surgeons from New York University organized the first of the seven transplantation conferences at the Barbizon Hotel in New York under the auspices of the New York Academy of Sciences. There were seven of these conferences, held every other year.

John Marquis Converse was the driving force. For the first five meetings, a colleague, Blair Rogers, was co-chair. In 1964, Felix Rapaport, a surgeon-scientist, and Jean Dausset, a French biologist and eventual Nobel Prize winner, joined them. The proceedings, published in the *Annals of the New York Academy of Sciences*, provided a comprehensive compendium of the existing knowledge for an ever-growing coterie of biologists, surgeons and physicians.



Joseph Murray and his team performing the first successful kidney transplant (between identical twins) at the Peter Bent Brigham Hospital, Boston on Dec 23, 1954.

One can easily visualize the development of this still arcane subject in the contents of these conferences. The first, *The Relation of Immunology to Tissue Transplantation*, was held 10 months before the first successful kidney transplant between identical twins in December 1954. Topics included the behavior of skin grafts, wound healing, and details of the antibody responses. Transplantation of the ovary, the cornea, and bone marrow were introduced. A young surgeon working independently in Denmark, Morten Simonsen discussed the concept of acquired immunity in the setting of kidney transplants. Subsequent dialogue was brisk as to whether this phenomenon could really explain the rejection of adult tissue homografts. Rogers was particularly skeptical, feeling that Medawar's more detailed earlier findings about the phenomenon in skin grafts were perhaps peculiar to rabbits and had little relevance to man.

Successive conferences mirrored evolving biologic advances and clinical forays. The second meeting focused on the use of embryonic, fetal, and neonatal donor tissues and, for the first time, potential strategies to alter the host-graft relationship. The third was more international in flavor, with contributions from Czechoslovakia, France, Denmark, England and Scotland. One point of discussion involved the new phenomenon of graft-versus-host disease, described by Billingham and Brent, that developed in x-radiated rabbits following bone marrow transplantation. Another was the subject of acquired immunologic tolerance, based on the earlier descriptions of neonatal tolerance. A session dedicated to organ transplantation was included for the first time in 1960 during the fourth conference.

In addition to his role in defining neonatal tolerance, **Rupert Billingham** showed that corticosteroids could weaken the capacity of a rabbit to reject foreign grafts, another example of the possibilities of host manipulation. He worked in transplantation biology for several years at the Wistar Institute in Philadelphia before moving to Southwestern Medical School where he investigated the immunology of pregnancy. A major figure in the field, he ultimately became President of The Transplantation Society.

Leslie Brent, joining Medawar and Billingham as a graduate student, also became interested in several aspects of the biology, including tolerance, the phenomenon of immunological enhancement following adoptive transfer of viable cells, and the effects of total body x-radiation on skin graft survival. His subsequent definition, with Billingham, of GVHD was an important contribution. His Presidency of the Society began in 1976. He and Billingham were later awarded the Medawar Prize, the highest award that the Society bestows

Sir Michael Woodruff was born in New Zealand. During the 31/2 years he spent as a prisoner of war in a Japanese concentration camp, he carried out novel studies on the effects of prolonged starvation. Also considering the possibilities of grafting foreign tissues, he soon became involved in the behavior of allografts (a term that was replacing the original "homograft") in immunologically privileged sites He coined the term "graft adaptation" to describe the diminished susceptibility of a graft to destruction by the host over time, and was one of the earliest users of anti-lymphocyte serum and globulin in experimental models. A pioneer in clinical transplantation and its biology, his 1960 textbook, *The Transplantation of Tissues and Organs,* remains a classic.

In London, **Peter Gorer** approached the antigenic differences in mice strains using serologic methods. The joint evidence from his serological approach and Snell's genetic experiments cemented the acceptance of H2. His researches in transplantation antigens became a foundation for research in the field.

There was increasing optimism. Sir Michael Woodruff, later to become President of the Society, summarized the prevailing sentiments. "It may well be that we shall succeed in devising methods of making tissues and organs from one human being survive permanently in another, not only when there is some special relationship between donor and host but as a general rule. If so, we shall stand on the threshold of a new era in surgery and we shall have found a new meaning to that excellent motto Nemo sibi nascitur - No man is born for himself alone." Prescient words that still echo loudly.

The final three New York Academy conferences well portrayed the increasing excitement permeating the new field. Topics discussed had a strikingly current air and included effector mechanisms, histocompatibility testing, artificial organs, and details of kidney, heart, liver, and lung transplantation in animals and in man. In a summary of the proceedings, Rapaport and Converse noted that transplantation had moved through the definition phase of research in which the patterns of destruction of a variety of tissues and organs were examined, through a period of accruing information about the rejection phenemon, to a third phase that consolidated existing knowledge. They also noted that individuals involving themselves in the subject, whether clinicians or laboratory investigators, were true biologists trained in experimental techniques. With their special areas of expertise, collaborations and cross-fertilization with those in related disciplines would benefit all. This theme would endure throughout the existence of the Society.

The Beginning

The years between the Arden House Conference in 1952 and the first two Congresses of the new Transplantation Society in the late 1960s exemplified a period of remarkable growth in the topic of tissue and organ transplantation. Clinical experience and biologic knowledge advanced in parallel through the interactions, cooperation, and free exchange of information flowing between the laboratories and the bedside. "The whole period," as Peter Medawar noted was, "a golden age of immunology, an age abounding in scientific discoveries all over the world, a time we all thought it was good to be alive. We, who were working on these problems, all knew each other and met as often as we could to exchange ideas and hot news from the laboratory."

Information increasing from both animal models and man directed attention toward the dramatic and complex series of host imunological responses called into play by and leading to the destruction of foreign grafts. Indeed, the concept that such activity was on an immune basis and moderated predominantly by lymphocytes took much time to develop. The

basic features of inflammation - heat, redness, tenderness, and swelling - had been recognized since ancient times. By the beginning of the twentieth century, investigators had found that leukocytes migrating from capillaries were of central importance in the processes of inflammation and the resolution of tissue injury. Although it had long been clear that resistance to subsequent exposure to the same organism often accompanied recovery from infection, controversy raged as to whether cellular activity or serum-based humoral factors were responsible.

By the time of the first few NY Academy Conferences, Peter Medawar had become the champion of the cellular school, Peter Gorer was the proponent of the role of humoral antibodies. From Gorer's collaboration with George Snell came the concept of histocompatibility genes. These, in turn, opened the possibilities of tissue typing to obtain the most optimal match between donor and recipient. One of Gorer's research fellows, Bernard Amos, was to drive the subject toward clinical applicability.

Medawar's initial descriptions of the "homograft response" involved the sequential gross and histologic changes occurring in rejecting skin grafts. He and others interested in the new biology were also beginning to recognize the importance of the lymphoid system in the phenomenon, although they remained ignorant of the function of the lymphocyte. All that was known in a transplant setting was this cell population gathered in a foreign graft; then its destruction occurred. James Gowans, a cellular immunologist at Oxford University, demonstrated that a long-lived population of lymphocytes recirculated continuously through bodily tissues, lymph, and blood. He and others then confirmed that these cells were immunologically competent, responsible both for allograft rejection and for graft-versus-host disease. A second sessile population could, when stimulated, produce antibodies. Subsequent definition of the structure of immunoglobulins prepared the way for understanding of the role of such antibodies in immunity.

A torrent of immunological investigations on cellular and humoral function began to flow in the 1960s and 1970s. They continue unabated to this day. Differing lymphocyte populations with differing functional behavior were becoming understood. An Australian immunologist working in England, Jacques Miller, showed that the mammalian thymus schooled pleni-potentiary lymphocytes into those responsible for cellular immunity. Robert Good, also working on thymic function, was one of the investigators to study the function of cells in the avian bursa or mammalian bursa-equivalent as mediating humoral activity. Others defined the "help" given by the thymus-derived (T) lymphocytes to bone marrow (bursa [B]) derived lymphocytes in antibody production. The subsequent identification of specific T and B cell markers confirmed the presence of these two distinct subpopulations.

Becoming interested early in genetics, **George D. Snell** spent his professional lifetime at the Jackson Laboratory in Bar Harbour, Maine. Appreciating quickly that mammalian genes determined the resistance of tumors transplanted into foreign strains of mice, he began his lifetime work defining "histocompatibility genes," identifying antigenic differences between inbred strains through linkage experiments in congenic-resistant animals. His later collaboration with Peter Gorer established the H-2 locus of the mouse, the first major histocompatibility locus (MHC) to be identified.

D. Bernard Amos originally became interested in the immunity of tumors. In 1961, he joined the Duke University faculty to help establish the genetic basis for the new kidney transplant program. Credited as a co-discoverer of the class II products of the HLA gene, his work on phenotyping transplant donors and recipients involved him increasingly in organ procurement and distribution. He was instrumental in organizing an important series of workshops in the 1960s that clarified, compared, and defined human histocompatibility genes. His enthusiasm towards forming the new Transplantation Society culminated in his election as Founding (first Past) President.

James Gowans proved that lymphocytes could be divided up into sessile antibody-producing cells and a long lived recirculating population which, as an integral part of the body's defenses, traverses tissues continuously between blood and lymph. If coming into contact with a foreign stimulus, specifically sensitized lymphocytes could attract other leukocyte populations to produce an inflammatory/immunologic response. Gowans is one of a small group of investigators credited with establishing the cellular basis of transplantation immunity.

Jacques F. A .P. Miller showed that the thymus gland is essential for the normal development of the immune system. Thymectomy of neonatal but not adult animals was associated with a decrease in circulating lymphocytes. The manipulated animals failed to thrive, developed an increased susceptibility to infection and an inability to reject foreign skin grafts. He confirmed his observations by demonstrating that these defects could be reversed by the re-grafting of thymus tissue, or by injecting mature syngeneic lymphocytes from intact donors into the immunologically incompetent host. His studies led eventually to the concept of specific functions of T and B cells and their requirements for mutual cooperation. The Transplantation Society awarded Gowans and Miller its first Medawar Prizes in 1990.

Although the occasional kidneys grafted into unmodified human hosts had, with a single exception, failed summarily, the dramatic successes of the transplants between identical twins convinced many that such an innovative treatment for those in organ failure was indeed possible. But what of the patients seeking help but without an identical twin donor? Medawar and his associates had already introduced the concept of immune tolerance. Could the same state be achieved by depressing the activity of immunologically competent lymphocytes using x-radiation, the only known modifier of immunity available (the word, immunosuppression would not be coined for several more years). Since the beginning of the twentieth century there had been occasional hints about the effects of radiation in depressing the host defenses. In 1930, for instance, Swedish workers had successfully transferred leukemia to immunologically compromised x-radiated rats, an impossibility in normal animals.

The first successful kidney allograft in an immunologically modified recipient. Above, the Riteris brothers before the transplant in 1959; Below, after the transplant. The recipient, John was immunosuppressed with total body x-radiation and survived in good health for another 25 years.

Knowledge of the sequellae of severe radiation injury was crystallized by the atomic bombs dropped on Japan. After the war, radiobiology laboratories opened in Europe and the United States to define more closely the influence of this modality on living tissues and to devise means to control or at least temper its effects. GVHD developing in radiated animals reconstituted with allogeneic leukocytes, a model highly significant to those considering transplantation of the bone marrow, posed severe limitations. These data were particularly important to scientists such as Society member, Donnall Thomas, who won the Nobel Prize in 1990 for his work on this specialized subject.

Investigators were beginning to realize that the survival of skin and then kidney grafts could be prolonged in animals receiving total-body radiation. Based on experimental findings, clinical transplant groups in Boston, Paris, and then in London had begun to place kidney allografts into patients who had been treated with total-body x-radiation, with or without the addition of adjunctive donor bone marrow. Occasional patients of the twenty or so undergoing this treatment survived between 1958 and 1962, supported

George Hitchings and Gertrude Elion are shown with Lollipop, one of the earliest successful transplant recipients to receive their new immunosuppressant agent Azathioprime.

by their genetically foreign grafts. Jean Hamburger and John Merrill became particularly involved.

It quickly became obvious, however, that the high risks and uncertainties of total-body radiation made the need for a more specific and controllable means of immunosuppression mandatory. In 1959, two Boston hematologists, Robert Schwartz and Walter Dameshek, showed that antibody responses of rabbits against beef protein could be abrogated by administration of an anti-metabolite, 6-mercaptopurine (6-MP), introducing the concept of chemical immunosuppression to transplantation.

The data caused a flurry of activity among surgeons interested in kidney transplantation. René Küss, one of the early Parisian transplanters, used it to supplement radiation. In England, Roy Calne found that kidney graft survival could be modestly increased in chemically treated dogs. On his way to Boston to join the surgical laboratory of Joseph Murray in 1960, Calne had been given derivatives of 6-MP by Burroughs Wellcome Research chemists and future Nobel Prize winners, George Hitchings and Gertrude Elion. Using one of the agents, azathioprine, Calne and Murray soon noted that several dogs lived normally with their transplants, an unprecedented finding. Investigators in Denver, Minneapolis, and Richmond quickly confirmed their experimental data. Its subsequent clinical results were equally noteworthy.

Despite the hopes for chemical immunosuppression, the decade of the 1960s was a difficult time in transplantation. At a small conference at the National Institutes of Health at the end of 1963, about twenty-five of the most active participants discussed the existing data on 216 recipients of renal allografts. The results were not gratifying: 81% of those grafted with kidneys from cadaver or living unrelated sources and 52% of those with grafts from related donors had died. Only 4% of all the cadaver-donor organs functioned over a year.

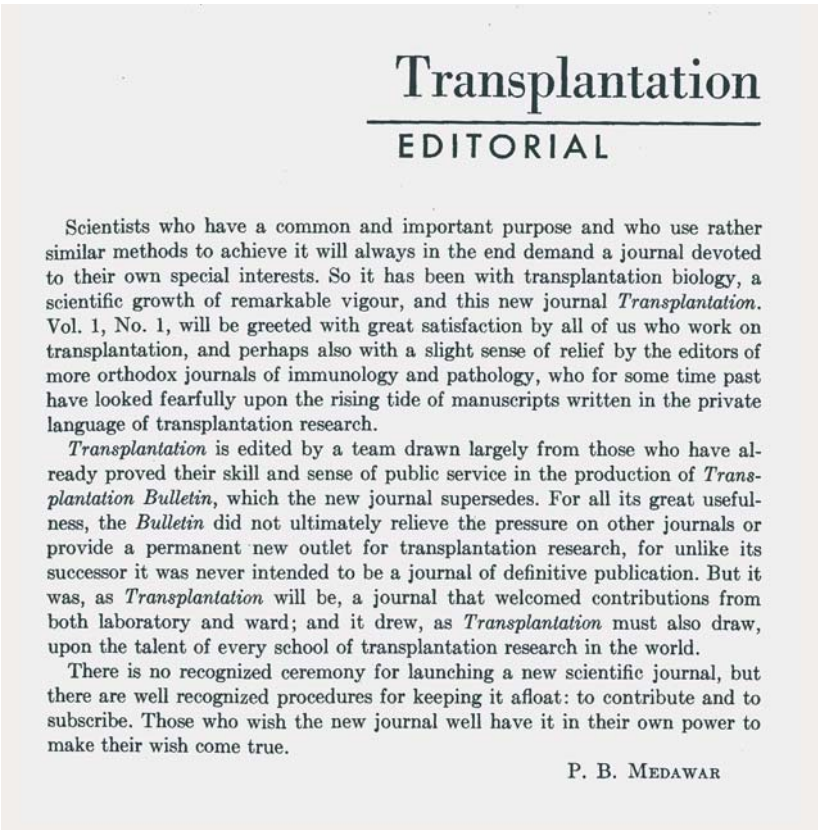
One clinical report, however, relieved the general gloom. Thomas Starzl, a young surgeon from Denver, presented his results with 27 transplants performed over the previous ten months; 67% remained alive with functioning grafts. He and his colleague had used azathioprine plus steroids as maintenance immunosuppression and had reversed the virtually inevitable acute rejection episodes with high doses of prednisone.

The renowned French nephrologist, **Jean Hamburger**, became interested in kidney transplantation in dogs in the late 1940s, presciently suggesting then that successful kidney transplantation in man could only be carried out if: 1) the effects of ischemia could be tempered; 2) tissue compatibility groups could be identified and applied to donor-recipient combinations; 3) anti-rejection drugs were available. Already involved in the original Parisian kidney transplants, he learned about the effects of radiation following a nuclear accident near Belgrade. With the encouragement of John Merrill who had joined him on a sabbatical year, Hamburger quickly began to transplant kidneys into radiated recipients, following the Boston example. A philosopher involved in all aspects of the new field, he accrued many honors over the next decades as one of the premier contributors in the field.

John Putnam Merrill was a young physician at the Peter Bent Brigham Hospital in 1947 when asked to help Williem Kloff refine his dialysis machine. Becoming increasingly knowledgeable about the complexities of renal failure and adept at sustaining afflicted patients using the new hemodialysis technique, he became at the same time a central figure in the establishment of clinical transplantation at that institution. His contributions to the biology of the subject and to the understanding of the pathophysiology of kidney disease are legion.

Robert Schwartz was one of the Boston hematologists who introduced the concept of chemical immunosuppression to transplantation. A productive physician scientist throughout his career, he is widely recognized for his contributions to hematology and autoimmunity. He is currently the book editor of the New England Journal of Medicine and received the Medawar Prize in 2000.

René Küss become interested in the the potential of renal transplantation through experimental work in the 1940s. A urologist, he performed some of the original transplants in unmodified hosts in 1951 in Paris, then grafted the first living donor-recipient combination in the world with Hamburger by anastomosing the host hypogastric artery to the renal artery via a retroperitoneal approach. Quickly following Murray's work in Boston of transplanting kidneys in recipients who had received total body radiation, Küss and his group used this suppressive modality with reasonable success. By 1960 he had added 6-MP and cortisone to the radiation regimen, then led the effort of multi-organ procurement in France. The Society later awarded him the Medawar prize.



Transplantation

EDITORIAL

Scientists who have a common and important purpose and who use rather similar methods to achieve it will always in the end demand a journal devoted to their own special interests. So it has been with transplantation biology, a scientific growth of remarkable vigour, and this new journal *Transplantation*. Vol. 1, No. 1, will be greeted with great satisfaction by all of us who work on transplantation, and perhaps also with a slight sense of relief by the editors of more orthodox journals of immunology and pathology, who for some time past have looked fearfully upon the rising tide of manuscripts written in the private language of transplantation research.

Transplantation is edited by a team drawn largely from those who have already proved their skill and sense of public service in the production of *Transplantation Bulletin*, which the new journal supersedes. For all its great usefulness, the *Bulletin* did not ultimately relieve the pressure on other journals or provide a permanent new outlet for transplantation research, for unlike its successor it was never intended to be a journal of definitive publication. But it was, as *Transplantation* will be, a journal that welcomed contributions from both laboratory and ward; and it drew, as *Transplantation* must also draw, upon the talent of every school of transplantation research in the world.

There is no recognized ceremony for launching a new scientific journal, but there are well recognized procedures for keeping it afloat: to contribute and to subscribe. Those who wish the new journal well have it in their own power to make their wish come true.

P. B. MEDAWAR

President Peter Medawar's editorial in the first issue of *Transplantation*, 1963

The genie appeared to be out of the bottle. This regimen remained the linchpin of immunosuppressive treatment for the next two decades.

The New Society

By the time the First International Congress of the Transplantation Society opened in Paris in 1967, hundreds of kidneys had been transplanted in chemically immunosuppressed recipients in many centers in the United States, throughout Europe and in Australia. There were 425 delegates attending, 200 of whom had become members. The proceedings of the meeting were published in *Advances in Transplantation*.

The Second Congress was held in New York one year later. Converse, the President, introduced an enduring societal tradition of dedicating individual conferences to one or more distinguished contributors to the field; he dedicated the conference to George Snell. As the definition of brain death had just been formulated, the use of kidneys from cadaver donors suddenly broadened. With the burgeoning interest in the enlarging subject, the

Honorees of The Transplantation Society Dedications	
1968	**George D Snell**
1970	**Sir Peter Medawar**
1974	**John Marquis Converse**
1976	**Willem Kolff**
1978	**Samuel L Kountz**
1980	**John P Merrill**
	Joseph E Murray
	Jean Hamburger
1986	**Sir Michael Woodruff**
	Rupert E Billingham
1992	**D Bernard Amos**
	Jean Dausset
	Jon Van Rood

Table 2

Society established a new journal, *Transplantation Proceedings*, for rapid publication of papers from its Congresses, Seminars, and Workshops as well as reviews of current topics in the biologic and clinical aspects of transplantation. Felix Rapaport steered the journal as Editor-in-Chief until his death in 2001. Jean Dausset was named European editor. This complimented the official journal of the Society, *Transplantation*, which had been established a few years earlier in 1963, with Brent as one of the editors.

The Conference dedications proved highly successful (Table 2).

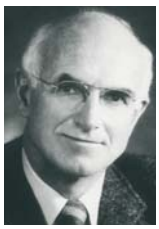
The next ten years were a period of growth and consolidation for The Transplantation Society as more and more experimental and clinical groups presented their findings. Hamburger served as President during the third Congress at the Hague. The plenary talks by notable personalities in the field well exemplified the emerging biologies; these included discussions of tolerance, the H-2 system and the major histocompatibility complex (MHC), tumor immunology, the emerging classification of T and B cells, mechanisms of cellular immunity, and clinical transplantation.

Paul Russell was President at the 1972 meeting in San Francisco. For the first time and as a new departure for the Society, a corporate leader gave an opening address, describing the important collaboration between his company and Willem Kolff in improving hemodialysis technology. This early corporate commitment to research and clinical transplantation and to the biannual meetings opened the way for company sponsorship of the Society that has never waned. The pharmaceutical industry, with their increasing interest in immunosuppression, has become an integral part of the workings of the widening field.

As was becoming clear by the growing successes of the Congresses, the transplantation of organs was beginning to capture the imagination of the world. At the next conference in Jerusalem in 1974, the President of Israel, a renowned biologist and foreign member of the US National Academy of Sciences, emphasized the theme that science was an international effort. Sir Michael Woodruff, the President, noted that for the first

Sir Roy Calne initiated chemical immunosuppression in organ transplantation. In the late 1970s his research team at Cambridge University then showed that another novel agent, Cyclosporin A, had potent immunosuppressive properties in a variety of stringent animal models. Quickly moving to the clinic, Calne's unprecedented results opened the way for universal use of the drug. He and Thomas Starzl are credited with developing liver transplantation into virtually routine treatment for patients with end stage hepatic disease, persisting when all others had failed. He became President of the Society and received the Medawar Prize.

One of the most consistent and productive contributors to the field, **Thomas Starzl** improved the existing results of kidney grafts substantially by combining corticosteroids with azathioprine. His sustained efforts in liver transplantation culminated in the routine use of that organ; with Roy Calne, he is considered the father of that field. He was one of the early proponents of the use of Cyclosporin A and later introduced an important new immunosuppressive agent, tacrolimus, despite initial doubts by his peers. His investigative work on microchinerism as a mechanism of immunological tolerance has been substantial. He became President of The Transplantation Society and was awarded the Medawar Prize.



During his time in the Army, **Joseph Murray** became interested in the possibilities of skin grafting burned patients. Returning to the staff of the Peter Bent Brigham Hospital, he expanded Hume's earlier experience in transplanting kidneys into unmodified human recipients. At the same time he initiated a sustained laboratory effort, improving grafting techniques and documenting for the first time the long-term survival of renal autografts. In December 1954, he carried out the first of several successful kidney transplants between identical twins, then undertook a series of 9 transplants in recipients who had received total body x-radiation. One lived for many years. After Calne and he showed the effectiveness of azathioprine in canine recipients, Murray successfully introduced it as standard treatment in patients. He received the Nobel Prize in 1990, one of seven surgeons in history to have been so honored. He was subsequently awarded the Medawar Prize.

As Medawar's first American research fellow, **Paul Russell** became interested in the subject of tolerance and in the antigenicity of endocrine tissues. Later becoming chief of surgery at the Massachusetts General Hospital, he was a continuously productive contributor both in the clinic and in the laboratory, and as teacher and mentor to generations of leaders in transplantation. He was later awarded the Medawar prize.

time the expanding numbers of contributions had been organized into Symposia, Simultaneous Sessions, and Workshops, a format that has endured and been embellished at all subsequent meetings.

By the Sixth meeting in New York City, the membership of the Society approached 1000. Delegates attended from over 30 countries. Rupert Billingham, the President, summarized the progressively increasing knowledge in his introduction. Gowans discussed the cellular mediators of immunity in a detailed address. Baruj Benacerraf, soon to become a Nobel Lauriate, described his work on the immune response genes. Other speakers summarized the data emerging about the relationship between in vitro and in vivo findings, the connection between HLA and disease, antiidiotype antibodies, suppressor cells, macrophages, cooperation between lymphocyte populations, and the role of blood transfusions in the pretreatment of recipients of organ grafts. Attempts to transplant several extra-renal organs were discussed.

In 1978, the Society was 12 years old. The field had broadened considerably. All Presidents before Billingham had opened their Congresses with brief introductions. Leslie Brent was the first to deliver and publish his Presidential Address, dedicating the meeting to Samuel Kountz for his contributions. The strengths of the organization, Brent noted, were two fold, the interaction between clinicians and biologists, and the bringing together of friends and colleagues (He also added – "no doubt some do not necessarily answer that description!"). He also addressed another important point; the apparent divergence between advances in immunologic research and clinical results. Do experiments on esoteric animal models relate to "real life?" It was after all, 23 years since the first description of tolerance and ten years after the introduction of chemical immunosuppression.

This conundrum continues to plague and enliven not only the field of transplantation but virtually all areas of applied biology. Perhaps the most cogent comment about this issue had come from Medawar himself, speaking a decade previously. "The study of transplantation taught us (and still has much to teach) a great deal about immunology in general, about genetics and developmental mechanisms, and about the natural defenses of the body against malignant disease. A lifetime of research could be spent in any one of these areas of transplantation without any sense of confinement or lack of purpose. But for some of us, now the majority, the compulsion behind our research has always been the determination that one day the transplantation of tissues and organs should become an ordinary clinical procedure." While the same dialogue currently relates to stem cell research, cloning, and other emotive issues, the success of clinical transplantation has enhanced 's Medawar sentiments and tempered many of Brent's worries.

The Struggle for Legitimacy

Although the 1970s were years of entrenchment in transplantation, new information and innovations, both positive and negative, were reported in the Society Congresses. The marked reduction in patient mortality was one important advance that evolved from a variety of refinements. Improvement in kidney graft function was less satisfactory. While the functional survival of organs from living related sources was 75% at one year, that of cadaver organs had only risen from 25% to 45%, a mediocre figure that was to remain static throughout the decade. In contrast, a handful of long-term recipients had returned to normal lives. Of equal interest, perhaps, was that the accumulated data now came from over 200 centers worldwide instead of from the original handful.

Unforeseen specters also arose. The overly immunosuppressed graft recipients were at high risk for infections, particularly from hitherto obscure fungi and viruses. Another unexpected development was the increased incidence of cancer, not only from tumors transferred with the donor organ itself, but those recurring in the recipient even after years of quiescence or arising de novo often after prolonged time intervals. Implicated causative factors included exposure to sun, the influence of viruses, and chemical inhibition of the natural immune surveillance function of the lymphoid system that destroys potential neoplastic mutations in rapidly dividing cells.

Because of the obvious limitations of the available agents, many in the field investigated a variety of adjunctive strategies to inactivate or destroy additional immunologically competent lymphocytes. As some experimental data had suggested that bulk removal of lymphoid tissue by splenectomy, thymectomy, or prolonged drainage of the thoracic duct could prolong graft survival, patient series were initiated. Another approach involved pumping the patient's blood around a cobalt source to destroy radiosensitive lymphocytes. The ill-conceived concept of "antigen competition" came into transient vogue, based on the notion that a powerful immunogen such as typhoid might compete with the host immune responses specific against the transplanted organ. Despite positive effects in animal models, none of these adjuncts were successful clinically.

A more lasting strategy involved the administration of xenogeneic antibodies against human leukocytes. Antilymphocyte serum (ALS) and its various permutations, introduced in experimental animals by Woodruff a decade previously, engendered much interest as potentially potent immunosuppressive adjuncts to the chemical agents. While the results in laboratory models were hopeful and early clinical experiences optimistic, within a few years most agreed that although these preparations reduced the number and severity of early acute rejection crises but did not materially affect

The grandson of a slave, **Samuel Kountz** took most of his surgical training at Stanford University, eventually becoming Professor of Surgery at Downstate Medical Center in New York. Highly regarded by his peers, he developed a lasting interest in both the clinical and experimental aspects of renal transplantation, leading a group of active and able research workers. His final lecture tour in 1977 was in South Africa - a black American professor lecturing during the time of Apartheid. Developing a hypertensive crisis upon his return, he died in 1980.

Jon Van Rood has been an enduring and honored presence in immunogenetics and the clinical importance of HLA. First understanding that prior pregnancies could evoke the presence of leukocyte antibodies in women, he turned to new computer technology to unravel their complexities. Encouraged by Woodruff, his investigations led to the appreciation that HLA matching could influence kidney graft survival. A founder of Eurotransplant, his work on the importance of histocompatibility in transplantation has been of the greatest import. He and Dausset received the Medawar Prize in 1996.

Paul Terasaki was one of Medawar's first research fellows. Developing an abiding interest in the importance of human histocompatibility, he devised the micro-lymphocyte cytotoxicity test to the new area of HLA typing in 1964. He and his colleagues widened its utility in assessing the cross match between donor and recipient. Its subsequent use in detecting cytotoxic antibodies by the panel reactive antibody (PRA) test, and the associated demonstration that graft survival in recipients sensitized against a panel of antigens was inferior to that in unsensitized individuals were critical advances. His enduring efforts in collecting data for the UCLA Transplant Registry has been an important updated source of information for the entire field. Terasaki became President of the Society and was awarded the Medawar Prize.

Peter Morris has been a productive presence in transplantation for decades. From Melbourne, he trained in surgery in Australia, then became increasingly interested in histocompatibility in transplantation through fellowships with Russell and Hume. With Terasaki, he noted that cytotoxic antibodies against human histocompatibility antigens could be found in the sera of graft recipients and that hyperacute rejection would occur if they were specific against the donor. As the long-serving chief of surgery at Oxford University, he has directed a highly visible clinical and research effort. He is an editor of *Transplantation* and of major surgical textbooks.

long-term graft survival. Perhaps the major contribution of these proteins was to act as forerunners of monoclonal antibodies directed against selective lymphocyte populations, their receptors, and their effector products. Several of these refined agents are currently gaining clinical acceptance as induction therapy.

There were also substantial practical advances. Tissue typing was one example. As noted, Dausset had previously defined a system of leukocyte antigens responsible for differences between donor and recipient. Rapaport had joined him in Paris to assess the differential rate of rejection of skin allografts in a large series of human volunteers, confirming Medawar's experimental observations some years before. Numbers of tissue typing laboratories involved in organ matching and distribution were formed as the names of different histocompatibility antigens became standardized and the availability of sera of recognized anti-HLA specificities became available. Van Rood was an important contributor to the influence of HLA on allograft survival. Terasaki introduced computer analysis of serological reactions to leukocyte donors and devised a plastic microcytotoxicity tray for accurate and reproduceable determinations. The availability of molecular techniques has allowed even closer definition of this complex genetic system intrinsic to host discrimination between self and non-self and differentiation between individual members of the same species.

Appreciation of the importance of antibodies circulating in the recipient before placement of a donor allograft was a critical related advance. Based on several cases of almost immediate graft destruction after placement, Terasaki, Peter Morris, and others developed the standard cross-match to prevent such catastrophies. This test and its refinements, now used universally in clinical transplantation, has made the phenomenon of hyperacute rejection extremely rare.

The prospect that a satisfactory tissue match between donor and recipient would improve the results of transplantation also implied that a kidney could be shipped to an optimal recipient throughout regions or between countries. Before the acceptance of brain death in the late 1960s, the interval between removal of an organ from a non-beating cadaver and its placement into a new host needed to be as short as possible. Folkert Beltzer, working in San Francisco, opened a new chapter and universally accepted concept in clinical transplantation by continuously pump-perfusing kidneys with a cold physiologic solution. Other methods of cold storage also became popular.

In contrast to the modest clinical gains, immunology and its related sciences made substantial progress during the 1970s. Appreciation of the differential function of T and B cells opened a variety of experimental possibilities. The increasing availability of monoclonal antibodies facilitated characterization of the intricate cellular cascade mediating allograft

rejection; their virtually unlimited specificity has continued to increase definition of the actions, interrelationships, influences, and contributions of cell populations, subpopulations, and their products. More recent refinements in molecular biology are allowing further identification and definition of a myriad of inflammatory and immunologic mediators in both experimental and clinical settings.

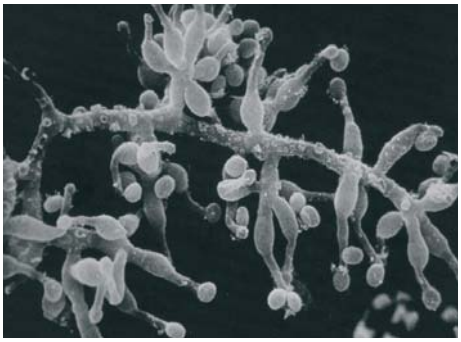
Cyclosporin A: A New Departure

The 1978 Congress in Rome represented the beginnings of a watershed in the field. Although thousands of kidneys had been transplanted plus small numbers of hearts, livers, and pancreases, clinical progress was relatively slow There were, however, occasional points of interest. The efficacy of blood transfusions before transplants became a subject of debate. A Tumor Registry had been formed. Investigators described the immunosuppressive effects of total lymphoid irradiation. And some recipients had been so rejuvenated by their successful allografts that they competed in the new Transplant Olympics, organized in England and continuing internationally to the present time.

Associated biologies ran further ahead, with increasing definition of the MHC complex, the importance of DR matching, mechanisms of rejection and host unresponsiveness to allogeneic tissue, and the relationship between transplantation and cancer. The phenomenon of immunologic enhancement remained a puzzle. The role of suppressor cells was a subject of especial interest.

This meeting also received unprecedented numbers of abstracts. Pope John Paul I endorsed the effort and the attendees acclaimed that their growing clinical and experimental knowledge was influencing and enriching its many associated disciplines. Despite the general enthusiasm, however, Rapaport, the incoming President, sensed problems. During the previous year he and his colleagues were given the responsibility of raising monies from the National Institutes of Health, primarily as travel stipends for young investigators to attend this and future meetings. While the reviewers eventually approved the application, they warned rather sternly that they did not feel that the subject was active enough to

Cyclosporin A is an extract of a primitive fungus, Tolypocladium inflatum



Folkert Belzer began a cadaver transplant program at the University of California in San Francisco in 1966. Means to preserve kidneys were urgently needed. Developing and refining a pulsatile perfusion pump in the laboratory to preserve canine kidneys, he soon began to use the apparatus in humans. The increasing reliability of the evolving techniques and equipment and the development of appropriate electrolyte storage solutions opened a new chapter in organ transplantation. Belzer continued this work throughout the remainder of his career at the University of Wisconsin.

Norman Shumway spent his career at Stanford. Working with congenital heart defects in the 1950s, he began to conceptualize means to correct transposition of the great vessels by removing the heart and rotating it 180˚, subsequently examining the physiologic effects of denervation, lymphatic interruption, and cooling of the myocardium. Transferring his attention from autografts to allografts, he and his team gained increasing facility with actual heart transplantation. Their experiments bloomed into clinical attempts, eventually achieving such beneficial results that transplantation of these organs has become widely accepted. Shumway received the Medawar Prize from The Transplantation Society for his critical innovations.

Hans Balner, to become President of the Society in 1982, was another important figure in this evolving biology. From Holland, he had become interested early in the phenomenon of GVHD. As long-term Director of the Primate Center in Rijswijk, his studies on leukocyte antigens and matching in chimpanzees paralleled those of Van Rood in humans.

Anthony Monaco, a long serving Editor of *Transplantation*, involved himself in clinical transplantation and its biology throughout his career. Working in Paul Russell's laboratory in the 1960s, he developed an enduring interest in the use of anti-lymphocyte serum as a potential immunosuppressive adjunct. The data he generated in allografts in various laboratory models and the possibilities of creating a tolerant state in recipients with the material, pushed it toward clinical use. As President of the Society in 1988, he inaugurated the Medawar Prize.

XV World Transplant Games, London, Ontario, 2005.
Len Silvester/Stan C Reade Photos

require a biannual Congress and that the chances for further funding might be poor. The relative dearth of federal funds for the subsequent Boston conference, coupled with the virtual disappearance of support for formal training programs in this and other areas of surgery was of continued concern. Fortunately, the increasing generosity of corporate sponsors and the National Kidney Foundation made up the difference.

By the time of the VIIIth meeting in Boston two years later, the theme of which was "A Quarter Century of Transplantation," nearly 700 abstracts had been submitted. More than 1100 delegates arrived from 37 countries. Experience was growing; over 50,000 kidney transplants had been performed. Indeed, replacement of organs was becoming increasingly accepted as part of routine treatment of patients with organ failure. Although federal funding for transplantation research was relatively unfavorable, advances kept coming.

A subject first introduced in Rome and discussed more extensively in Boston was an entirely new immunosuppressive agent. A young scientist newly employed by the Sandoz Pharmaceutical Company in Basel, Jean Borel, had discovered that a metabolite of a newly discovered fungus was markedly immunosuppressive. Within months he had established that this ring of eleven peptides could both successfully treat experimental arthritis in mice and substantially prolong skin grafts. One of Calne's research fellows obtained some of the material and tested it in several organ transplant models. Its potency in several animal species and then in human recipients of kidney and liver grafts was striking. It spread quickly to other units in England and the United States that promptly confirmed its efficacy.

The prospects of substantial improvement in the immunosuppression of allograft recipients engendered tremendous excitement throughout the transplant community. The halls of The Transplantation Society Congress in Rome had been abuzz with discussions about the new agent. Lecture rooms overflowed during the few presentations on the subject. Investigators presented more experimental and clinical data on the subject in Boston. All who had used the drug agreed on its effectiveness.

By the meeting in Brighton two years later under the presidency of Hans Balner, Cyclosporin A (CyA) had become the centerpiece. Extensive discussions of its actions and characteristics culminated in a report from Calne's unit in Cambridge of a one-year actuarial survival of cadaver-donor grafts of over 80%, a figure far superior to that ever achieved before. Other centers soon initiated their own series. Large controlled clinical trials in Canada and Europe enrolled patients. By 1983 it was clear that the use of this drug, usually in combination with steroids, could increase graft survival by 20%. Despite the difficulties in effective dosage in patients and its several sequellae and side effects, Cyclosporin A ushered in a new chapter in organ and tissue transplantation.

A Surge of Extra-Renal Organs

The Tenth Congress in Minneapolis in 1984 saw a substantial increase in numbers of papers on the transplantation of extra-renal organs as most involved felt that the venture had moved from experimental forays to more routine treatment. The clinical results of kidney, liver, and pancreatic transplantation were featured. In contrast, only half the papers on the heart and lung dealt with the results in patients as this organ had become a popular experimental model to study the events of rejection and the pharmacology of immunosuppression. The renewed interest in the practical aspects of transplantation was also mirrored by a surge of papers on organ preservation. One obvious reason for this change in emphasis from laboratory experimentation to clinical series was the increasing availability of Cyclosporin A.

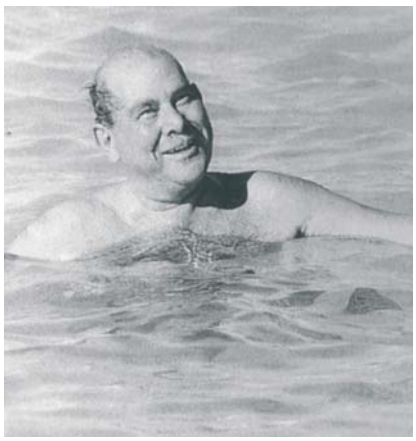
The grafting of extra-renal organs had difficult beginnings. Christian Barnard's dramatic announcement that he had replaced a human heart with the organ from a brain dead donor had burst upon the consciousness of the world in late 1967. A few more such transplants were the prelude to a mercifully brief but frenetic period of clinical activity the following year in which over 100 patients received hearts. The results were so disastrous that several of the principals called a moratorium on further activity until more comprehensive experimental data became available. Only Norman Shumway, who with his colleagues had carefully developed the technique several years

Jean Borel, a young scientist recently hired by Sandoz Pharmaceuticals was asked to screen all new plants found by company botanists for antibiotic activity. He soon noted that one of the extracts of a novel fungus had pronounced immunosuppressive qualities. His determination to continue work with this new substance ultimately changed the face of organ transplantation.

Richard Batchelor trained in research with Gorer after graduating from Guy's Hospital. He spent much of his productive career examining the role of HLA in transplantation and various disease states, and delving into the complexities of tolerance induction. An editor of *Transplantation*, and long interested in various facets of immunology, he has been an important contributor to the biology of the field.

John Najarian developed one of the foremost transplantation units in the world at the University of Minnesota; their production of Minnesota Anti-Lymphoblast Globulin throughout the 1970s became used in many centers to enhance the relatively mediocre results of maintenance azathioprine and steroids. The popularization of the kidney grafting of diabetic recipients, followed by a huge effort in pancreas transplantation by David Sutherland and others on his team, brought these treatment modalities into general acceptance. Najarian's success in transplanting children opened an important sub-specialty. Training scores of transplant surgeons who extend his concepts on an international level, he has become a well-recognized figure. He received the Medawar Prize in 2004 with another major contributor, his long-time colleague, Richard Simmons.

Pekka Häyry has gained worldwide renown as a highly productive leader of both his clinical unit and his experimental laboratory at the University of Helsinki. While a fellow at the University of Pennsylvania, he devised an assay for generating active cytotoxic T cells in the MLC. His subsequent contributions to the understanding of mechanisms of acute and chronic rejection are highly regarded.



Dr Philip Blaiberg "swimming" after his heart transplant in 1968

before, continued their steady efforts. But with the use of the new agent after 1980, information accumulating from a few laboratories and occasional clinical units grafting thoracic organs began to show remarkable improvement. CyA-treated monkey recipients of heart-lungs survived well, for instance, an unprecedented finding. The results of heart transplantation in man began increasingly to resemble those of the kidney.

The replacement of failing abdominal organs followed a similar pattern. Although Francis Moore at the Brigham and Starzl at Northwestern had grafted livers in dogs in the 1950s and then in occasional patients a decade later, their initial efforts were met with uniform failure. Indeed by 1976, only 12 of the 130 human recipients of livers still remained alive. The results were so dismal that only two figures continued to drive the field forward: Starzl in Denver, and Calne in a Cambridge-London unit. While many technical aspects of this formidable operation still remained problematic, clinical progress increased appreciably after the introduction of Cyclosporin A. And as results improved, indications broadened so much that liver transplantation has become routine treatment for a variety of serious and irreversible hepatic conditions. Indeed, this procedure has become so refined that split livers from cadavers and liver lobes from living donors are used increasingly to enhance the supply of these organs. At present over 80% of recipients survive at one year, a remarkable achievement.

Transplantation of the pancreas generally posed even more difficulties than the heart and liver. Reversal of diabetes by replacement of the entire pancreas seemed to be a reasonable course to follow in the 1960s. But the concept took years to mature. Despite the introduction of several technical improvements by the mid 1970s, accumulated clinical data included a total of 57 grafts; only a single individual survived without insulin over the long term. Ductal leaks, pancreatitis, and difficulties in detecting rejection were of continuing concern. Clinical investigators had introduced several methods to drain the powerful digestive enzymes, including tying off the pancreatic duct, leading it through the skin, or anastomosing it to duodenum or bladder. Occluding the entire ductal system with neoprene was a technique that enjoyed some success in the 1980s.

However, the picture gradually improved with more effective immunosuppression, so that within the next decade several thousand pancreas

transplants had been performed in 170 centers throughout the world. It was also becoming clear that graft placement either simultaneously with a kidney transplant or as a separate procedure provided an excellent quality of life for many recipients. It was a prolonged but ultimately a reasonably successful struggle. But while attempts to engraft pancreatic islets have been ongoing for decades, its success, with occasional important exceptions, generally remains elusive.

The Specter of Commercialism

Sir Peter Morris began his Presidency at the meeting in Minneapolis in 1984 and completed it in Helsinki two years later. From the time of the first Congress in Paris it had been the custom for the President to deliver his Address as the final event that closed the meeting. The President-elect, Anthony Monaco and the Council felt it more appropriate that he present his remarks at the beginning of the meeting over which he actually presides. To establish the new cycle, Morris gave a second address two years later in Helsinki. In both, he introduced a theme that was beginning to disturb the entire field, "the rearing of the ugly head of commercialism in transplantation."

The rising success of organ transplantation both in regard to graft function and patient survival, and the increasing availability of health care coverage for those with end stage organ failure at least in the United States, broadened the criteria for acceptance of patients for treatment. As a result increasing numbers of individuals with renal disease in particular sought help, not only those from affluent societies but from those living in less solvent and less medically advanced nations. This quickly created a progressive divergence between organ supply and patient demand, a problem that continues to worsen each year.

Like air rushing into a vacuum, opportunists moved quickly to exploit the need. Irregularities soon surfaced. About the same time that an entrepreneur proposed that kidneys from living unrelated donors in the Third World might be purchased for potential recipients in the United States came the beginnings of a shift in kidney transplantation from university centers to less visible private institutions. The transplant communities of several countries – and the public – began to hear of the brokerage of kidneys from such sources. Notices by impoverished individuals willing to sell a kidney or an eye to those who would buy them appeared in newspapers. Clinics to perform such transplants sprung up, both in poor countries and in some affluent western nations. Clinical groups also advertised for wealthy patients, often from other countries, guaranteeing them prompt and successful transplantation with cadaver-donor kidneys. Well known personalities went to the head of the queue. As a result, local

Fritz Bach, the quintessential scientist, originally introduced the mixed lymphocyte reaction early, an in vitro model of the "homograft response." An extension of this assay was the one-way mixed leukocyte culture (MLC), used first as a test of histocompatibility between donor and recipient. He later involved himself in defining the Class II locus and human HLA. His subsequent contributions to bone marrow and solid organ transplantation, molecular biology and xenografting spanned an entire career.

Oscar Salvatierra popularized deliberate donor-specific transfusion to modify the immunoresponsiveness of histoincompatible recipients. As one of the principals in the emerging field of pediatric transplantation, he described both specialized surgical techniques and important refinements of immunosuppression for that unique patient population. Spending the majority of his career at UCSF and Stanford, he has been particularly active in planning the current national transplantation system in the United States and in promoting federally sponsored research in kidney disease and organ transplantation.

Carl Groth trained in surgery in Sweden then spent time with Thomas Starzl in Denver who credits his substantial contributions to the development of liver transplantation. Innovative throughout his career at the Karolinsla Institute, Groth involved himself particularly in liver, pancreas, and islet transplantation. Highly honored, he served as Chairman of the Nobel Committeee among other important assignments.

David Sutherland has spent his entire career at the University of Minnesota, developing and refining clinical and experimental pancreatic and islet transplantation. As long-time Director of the International Pancreas Transplant Registry, he has done much to develop, perfect, and popularize this field throughout the world.

patients awaiting their chance were bypassed. Some of the cadaver kidneys were exported from one country to another where they were sold to those who could pay.

These and other deviations from standard practice made the headlines. Both the public and the profession were predictably outraged and altruistic donations fell dramatically. Because of these pressures, Governments in Europe and in the United States made the sale of organs illegal. The Council of The Transplantation Society published a set of stringent guidelines for practice in 1985, both for the distribution of cadaver organs and for the procurement of those from living unrelated sources. The statement emphatically condemned such practices, taking the view that altruistic donation of an organ is a gift of extraordinary magnitude and that transplant surgeons hold such an organ in trust for society.

President Morris had opened a subject that reverberates to the present time. Indeed, trafficking of human tissues and organs not only continues but has spread to involve several regions throughout the globe. In some circles, transplantation has become big business for individuals, hospitals, and even governments. In response, the Society has continued to insist that none of its members should condone or join this movement.

Continuing Maturation of the Field

At the XII Congress in Sydney, President Monaco reviewed the life and contributions of Peter Medawar. He then announced that the most prestigious award the Society could bestow, the newly instituted Medawar Prize, would be presented to individuals who, in the opinion of all the Past-Presidents, had carried out the most important work (Table 3). But as Brent had also voiced several years before, Monaco expressed a growing concern among some members that as the results of organ transplantation progressively improve, the field may take on the role of a service rather than a research oriented patient-based discipline. This, he noted, might not only make it less interesting to the young academic clinician but might divide increasingly those individuals from their scientific peers. Conversely, young scientists might view the field as becoming too clinical and direct their efforts into other channels. He stressed that the long-term mandate of the Society is to maximize the interchange between clinicians and scientists, and noted the special emphasis that prior Congresses had placed on basic scientific advances.

And it seemed to be working. At Helsinki, Sydney, San Francisco where Richard Batchelor was President, and the meeting in Paris in 1992, the local organizing committees made special efforts to include large sessions relevant and of interest to the entire professionally diverse membership. A wealth of information was presented including subjects new to the evolving subject:

The Medawar Prize	
1990	Sir James L Gowans
	Jacques F A P Miller
1992	Sir Roy Calne
	Norman Shumway
	Thomas E Starzl
1994	Rupert E Billingham
	Leslie Brent
	Morten Simonsen
1996	Jean Dausset
	Paul I Terasaki
	Jon J Van Rood
1998	Felix T Rapaport
	Anthony P Monaco
	Fritz Bach
2000	Ray Owen
	Robert Schwartz
2001	René Küss
2002	Joseph E Murray
	Georges Mathè
2004	John S Najarian
	Paul S Russell
	Richard L. Simmons

Table 3

particulars about emerging immunosuppressive agents such as tacrolimus and their complications, strategies to induce tolerance, cellular transplantation, long-term outcome of graft recipients, xenotransplantation, and cytokine and receptor biology. The non-heart beating donor was discussed and cumulative results from the growing Organ Registries presented. Indeed, reflecting the increasing basic and clinical knowledge, the 1990 meeting in San Francisco had attracted 2700 attendees, over 1000 more than prior Congresses. That pattern has persisted since.

In Paris, President Starzl noted the death of Professor Hamburger, then described his own novel concept of microchimerism as the cause of long-term graft acceptance. Sir Roy Calne particularly emphasized the importance of the concept of tolerance during his Address at the Congress in Kyoto two years later, reviewing existing knowledge of the phenomenon not only in occasional clinical instances but in allograft and xenograft models as well.

At the Barcelona meeting in 1996, President Najarian reviewed many of the advances evolving over the past three decades of the Society's existence. He noted that there were now over 3000 registrants from 54 countries who contributed a panoply of divergent and interactive disciplines to the field. In fact The Transplantation Society had become the umbrella organization for increasing numbers of affiliated specialty societies throughout the world. Reviewing the overall activity in the subject, he enumerated the vast changes occurring not only clinically and pharmacologically, but in its biology as well. Ever more detailed information of the rejection cascade through appreciation not only of the functions and interactions of leukocyte populations, but by advancing knowledge of a variety of cytokines, chemokines, and adhesion molecules, were becoming defined. Cell surface receptors including the

Georges Mathé early recognized the presence of GVHD in humans receiving bone marrow infusions following a nuclear accident and worked with Hamburger and Küss in the early use of total body x-radiation in renal graft recipients. Returning to bone marrow transplantation, he began to realize some successes but soon moved on to preparing potential recipients with ALG, presaging the pretreatment strategies in tolerance induction being evaluated currently. His interests included non-transplant related immunotherapy for cancer. Honored and respected, he has been an important force in the field.

Richard Simmons played a particularly important role in understanding the influences of viruses in immunosuppressed patients, and the relationship between infection and rejection. Leaving the University of Minnesota to become chief of surgery at the University of Pittsburgh, his influence has been important to the field.

Lady Jean Medawar trained in zoology and experimental pathology at Oxford University, ultimately becaming Director of the Margaret Pyke Trust in London. After marrying Peter Medawar, she co-authored several books with him. In addition to authoring other books, she wrote a highly popular biography of her husband.

R.D. Owen at the University of Wisconsin discovered in the 1940s that each member of a pair of free-martin cattle twins carried both his own circulating red cells but those of his sibling. The chimeras were mutually tolerant. This observation gave Medawar his first clue about the phenomenon of immunological tolerance.

T cell receptor complex were becoming understood. With such definition came understanding of the mechanisms of action of new immunosuppressive agents that, used alone or in combination, improved clinical results. Indeed by the time of the Barcelona Congress, the results were good enough that 400,000 kidneys, 42,000 hearts, 52,000 livers, and thousands of other organs had been transplanted throughout the world.

Nobel Prize Recipients in Transplantation and its Biology

1960	Peter B Medawar
1980	Baruj Benacerraf
	Jean Dausset
	George Snell
1988	Gertrude B Elion
	George H Hitchings
1990	E Donnall Thomas
	Joseph E Murray

Table 4

At the same time Najarian mentioned the areas that continued to lack progress. Tolerance remained a will o' the wisp despite enormous and sustained efforts by many investigators. Xenotransplantation, in spite of the formation of a specific society, two journals, and continuing publicity, was relatively static. While substantial strides had been made in organ preservation and storage, this was still a short-term event. But despite these caveats, the Society was continuing to grow and provide support for the worldwide effort.

The ensuing Congresses continued to be an intellectual and social feast for all participants. Pekka Häyry, President at the Montreal meeting, noted that 85% of the vast numbers of participants were not members of the Society, attesting to its wide appeal to speciaists in related fields. To accommodate their diversity of interests, a record number of invited speakers addressed the Plenary sessions on large themes of common interest. The Early Bird Symposia were introduced, sponsored by different companies and carefully vetted for general interest.

An interesting and novel feature of the Helsinki conference was a review of important aspects of the field as "viewed by the protagonists." Fifteen designates who had played seminal roles in the new subject joined a discussion round table after their brief remarks. Their presence was embellished by an additional personality, Lady Jean Medawar. This unique event was not only nostalgic for older participants but a valuable reminder of the origins of transplantation for the next generation. The Society awarded its Medawar Prize to individuals honored at this special seminar, Fritz Bach, Anthony Monaco, and Felix Rapaport.

The XVIII Congress was appropriately celebrated in Rome with the opening of the new millennium. For the second time, the Pope, this time Jean Paul II, addressed the participants. As his predecessor had before him, he strongly endorsed the altruistic and legitimate donation of organs to

offer a chance of health and life to those ailing.

In his Presidential Address Oscar Salvatierra explored the ongoing role and contributions of The Transplantation Society to the overall field, emphasizing its world wide mission, legacy, and its future. He noted that the specialty sections the Society sponsors, now included two new Sections, the International Xenotransplantation Association (IXA) and Transplant Infectious Disease (TID). In subsequent years the Cell Transplant Society (CTS), The International Pancreas and Islet Transplant Association (IPITA), the International Society for Organ Donation and Procurement (ISODP), and the Intestinal Transplantation Association (ITA) have gathered under the umbrella of the parent Society.

An important addition to the Congress was the introduction of the biennial Basic Sciences Symposia, organized by Kathryn Wood and her committee, and designed to bring together young investigators from all over the world. These participants would not only hear cutting edge science but would interact closely with principal figures in immunobiology. A series of corporate sponsored Young Investigator Awards added to the appeal. Salvatierra also announced the formation of a Central Business Office in Montreal and the creation of a website for all members, unique additions to the workings of the Society. One Medawar Prize, he announced, was awarded to Ray Owen, who had introduced Medawar and his colleagues to the concept of chimerism in freemartin cattle, an observation that had indirectly opened the entire subject of immunologic tolerance. Robert Schwartz received the second, for his introduction of chemical immunosuppression.

Members of the Society had voted to hold the 2002 Congress in Buenos Aires. However, due to unexpected political and economic upheaval in Argentina, the venue had to be changed rather abruptly to Miami. Carl Groth, the incoming President, working closely with the local organizing committees on both continents, created under stringent logistical and time constraints one of the most informative conferences. It was an organizational tour de force.

Groth introduced a novel departure for the Society, the Global Alliance for Transplantation. Decrying the striking disparities in transplantation throughout various areas of the world, he suggested that the Society should create an alliance to include all international societies interested in the field, the pharmaceutical industry, and the World Health Organization. Representatives of these groups would work together to increase information gathering and data analysis on the grafting of organs and cells, maintain global professional guidelines in the field, and establish educational links among all involved. Although recently initiated, this fledgling effort has already garnered much enthusiasm. Groth also announced at the Congress that kidney transplant pioneers, René Küss, George Mathé, and Joseph Murray had been awarded the Medawar Prize.

Kathryn Wood was educated at Oxford University and has spent her entire career there. An Editor of *Transplantation*, she is a professor of immunology in the highly productive Nuffield Department of Surgery, working closely with the clinical transplant team in applying biologic approaches to treatment of organ graft recipients. Her ongoing interests in tolerance and other aspects of transplantation biology have been important additions to the field.

The XX Congress was held in Vienna, impeccably organized and highly successful. Under the leadership of David Sutherland, the President, and the efforts of several previous presidents, the Society continued to grow in breadth and scope. The bylaws had been extensively revised. The geographical regions of the Society have been broadened from an Eastern and Western Hemisphere division to include six regions throughout the world; a member from each will sit on the Council. Sutherland emphasized the continuity of the ethical guidelines for Society members, first enumerated in 1985, embellished in subsequent congresses, and reconfirmed in published form in 1999. He then announced that the Medawar winners were John Najarian, Paul Russell and Richard Simmons.

The XXI Congress of The Transplantation Society, its Fortieth Anniversary, is held in Boston in 2006, for the first time in conjunction with the American Society of Transplant Surgeons and the American Transplantation Society. A fitting venue for this medical, scientific, and social feast, the city has been closely associated with the gestation, birth, and maturation of the entire field. Kathryn Wood, our productive and indefatigable President officiates. The importance of this joint congress is a tribute to her efforts on the part of the Society, its sections, and its role throughout the world in innovation, the dissemination of ethical principles, and education about the subject of transplantation and those involved in it.

The New Decades

When I was asked by the Council to summarize the origins, activities of the Society and its leaders over its four decade history, I was additionally instructed to consider its course over the next years and decades. In his Presidential address in 1978, however, Leslie Brent aptly quoted George Eliot who had written that "among all forms of mistakes, prophecy is the most gratuitous." I can only agree but will offer some thoughts about the years to come.

The success of transplantation has transformed the dreams of a few visionaries into an innovative and continuously improving form of therapy for thousands of patients with failure of various organ systems. Indeed, it has been one of the most remarkable evolutions of biomedicine of our time. But its very success has produced profound problems, the most compelling of which is the ever-broadening divergence between the supply of tissues and organs and the demand of those requiring them. In response, the acceptance of less than optimal deceased donors with concurrent conditions has risen slightly, while the increasing use of organs from living sources, both related and unrelated, has improved the lot of many seeking help. Indeed, for the first time in the United States, numbers of living

donors have transcended those from deceased individuals. But supply remains the largest challenge for us all, as the inadequate numbers of organs has opened a panoply of often irregular and unrelenting commercial interests while successful use of those from other species remains a tantalizing hope for the future.

New approaches and developments are also helping. Laparoscopic removal of kidneys and some extra-renal organs, split livers, and the slowly accruing success of pancreatic islets are causing optimism. The propagation of cultured autologous hepatocytes on biological struts may produce enough liver substance to sustain patients in hepatic failure. The temporary placement of ventricular assist devices or extra-corporeal hepatic perfusion are promising techniques that may provide time for a failing organ to recover enough function to sustain the life of the patient and preclude transplantation. This strategy may free up available organs for others.

The possibility that stem cells may repopulate dying cells with healthy ones is an exciting vision for the future. Indeed, there are already some efforts to produce myocardial patches from these pleuri-potential cells that can be used to repair non-functioning portions of the heart. Indeed, experimental evidence that stem cells may transform into neurological cells to improve such conditions as Parkinson's Disease and spinal cord injury is compelling. The induction of immunologic tolerance still remains generally elusive although it has been achieved in a small number of recipients. Selective suppression of specific areas of the immune cascade is slowly becoming reality using refined chemical agents and precise monoclonal antibodies, alone or in combination.

So it appears that cellular, tissue, and organ transplantation will flourish over the next decades, driven though the cooperation and collaboration of an international coterie of innovative clinicians, clinician-scientists, and applied biologists.

On a broader front, The Transplantation Society will play a major facilitatory role in tackling ongoing educational, legal, regulatory, ethical and public health challenges. As clinical success has stimulated such demand for transplantation services that we are unable to meet even a reasonable proportion of the need for donated organs, The Society will continue to work with the World Health Organization, with national governments, industry, charitable foundations, and with our colleagues in international, regional and national Societies to manage the consequences of the burgeoning global demands and limited number of available organ donations to deliver the benefits of transplantation therapy globally. Enhancing scientific understanding through research, open dissemination of that knowledge, appropriate educational programs, support and development of global professional standards and the measurement of outcomes, will remain the cornerstones of the Society's mission. Long may it last!

Time Line:
Landmark Events in Organ Transplantation and The Transplantation Society

1952	Arden House Conference Skin grafts and the phenomenon of rejection Introduction of hemodialysis Kidney transplantation in unmodified hosts
1953	Ciba Foundation Symposium
1955-1966	NY Academy of Sciences Conferences
1950s	The concept of acquired and immunological tolerance
1960s	Histocompatibility genes and the definition of HLA The importance of the cross match The lymphocyte as an immunologically competent cell T and B cells Humoral immunity Successful transplantation between identical twins Immunosuppression of animals and man x-radiation chemical immunosuppression addition of steroids to azathioprine the steroid pulse Definition and acceptance of brain death Transplantation of extra-renal organs Xenografts
1967	First International Congress of the Transplantation Society and biennial Congresses thereafter

1970s	Tissue typing DR matching Transplant Registry The Tumor Registry The specter of cancer Organ preservation and distribution Decreasing patient mortality Anti-lymphocyte antibodies Monoclonal antibodies T cell subclasses Cell receptors and effector products
1980s	Cyclosporin Controlled clinical trials Resurgence in the transplantation of extra-renal organs Tacrolimus Commercialism of organs
1990s	The Transplantation Society as an umbrella organization for specialist societies Chronic rejection Novel immunosuppressive strategies mycophenolate mofetil rapamycin induction therapy with monoclonal antibodies Tolerance MHC antigen peptide – T cell receptor interaction
2000s	The Global Alliance Stem cells Construction of organs Ethical concerns

Acknowledgements

The author is grateful for the help and encouragement of Professors Jeremy Chapman, Barry Kahan, Oscar Salvatierra, David Sutherland, Megan Sykes, and Kathryn Wood in the preparation of this project. I am particularly endebted to Drs Salvatierra and Terasaki for the use of their portrait slides.

My thanks go also to Lucy Felicissimo for initiating this project, to Werner Arnold, the graphic designer who brought it to fruition, to my secretary, Joan Garrido, for her patience and technical expertise, and to Gillian Hobbs for her friendly cajoling and coordinating the contributions of everyone involved.

Front cover and title page images from left to right:

1) Pores formed by killer T-cells.
   (Wellcome Trust Medical Library with permission)
2) Successful kidney transplant patient, Richard Herrick,
   with his donor twin brother, Donald, on his discharge from hospital in 1956.
3) Heart transplant operation in progress.
   (Wellcome Trust Medical Library with permission)
4) XV World Transplant Games, London, Ontario, 2005.
   (Len Silvester/Stan C Reade Photos)