YALE JOURNAL OF BIOLOGY AND MEDICINE 78 (2005), pp. 171-182.

HISTORY OF MEDICINE

The Early History of Kidney Transplantation at Yale (1967–1985): A Personal Memoir

Bernard Lytton

Department of Surgery, Section of Urology, Yale University School of Medicine, New Haven, Connecticut

This is a personal account of the development of the treatment of end stage renal disease (ESRD)† at Yale by hemodialysis and transplantation between 1967 and 1985. These modalities became available after 1960 and were the first definitive treatments for kidney failure. During the ensuing 40 years, they became the standard and most effective treatment for ESRD. Today, a renal transplant provides the best option for a patient with renal failure, and dialysis is used to keep the patient alive until a suitable kidney becomes available or for the long term treatment of those individuals who are unwilling or unable, for medical reasons, to undergo the surgery and immunosuppressive therapy.

Kidney disease was first recognized by its clinical manifestations. Dropsy — the accumulation of fluid in the body tissues leading to swelling of the extremities, rapid weight gain, and diminished urinary output — was thought to represent failure of the kidneys, although in many instances the problem was primarily cardiac failure. Richard Bright, a physician at Guy's hospital in the early part of the 19th century, was the first to distinguish between dropsy of renal origin and other causes by its pathological and laboratory findings, the visible changes in the kidneys at autopsy and albumin in the urine. Bright's disease became the generic name for all types of nephritis until these were later classified into the various types according to the distinctive pathological findings in the kidneys. There was no effective treatment, and the disease generally progressed to renal failure and death from uremia. Early in the 20th century, renal disease became more defined by its physiological manifestations and loss of homeostasis with fluid retention, electrolyte changes, loss of acid base balance, and the accumulation of nitrogenous waste products. Treatment was directed at these problems by the use of diuretics, chemical correction of electrolyte changes and dietary protein restriction. These measures were partially successful in decreasing morbidity and prolonging life, but with the advent of total renal failure, little could be done. The end of the 20th century ushered in a new era.

In 1938 at the University of Gruningen in Holland, a young intern, Dr.

To whom all correspondence should be addressed: Bernard Lytton, M.D., F.R.C.S., Yale University School of Medicine, Section of Urology, P.O. Box 208041, New Haven, CT 06520-8041.
†Abbreviations: ESRD, end stage renal disease.

Willem Kolff, faced with a young patient dying of kidney failure, began experimenting with a sausage casing of cellophane and heparin, a newly discovered chemical that prevented blood clotting. He placed blood that had been anticoagulated, containing a high concentration of urea, in the sausage casing and immersed it in a saline bath. He found that the urea passed rapidly out of the cellophane casing into the bath of saline, thus cleansing the blood by dialysis. Shortly afterward, the German armies marched into Holland, and Dr. Kolff continued working as a staff doctor in a civilian hospital under the occupation. He performed the first dialysis on a patient using this principle in 1943 [1]. He wound the cellophane tubing, through which he ran the patient's blood, around a drum that rotated in a bath of dialysate fluid. Unfortunately, of the first 15 patients he treated, only one survived. After the war, Dr. Kolff visited the Peter Bent Brigham Hospital in Boston, and as a result, a group under Drs. John Merrill and Carl Walter developed the Kolff-Brigham kidney. By 1950, they began to successfully treat patients with acute and chronic renal failure by hemodialysis. This was an essential prelude to the development of kidney transplantation as it provided a method to maintain patients with kidney failure while they awaited the availability of a suitable kidney. During World War II, in Glasgow, Scotland, Drs. Thomas Gibson and Peter Medawar were studying the problem of the rejections of skin grafts in burn patients [2]. Extensive burns had become a major problem for many Royal Air Force pilots and aircrews who survived plane crashes. Their work proved to be the beginning of the modern era of transplantation immunology. Some 10 years later, in 1959, Rupert Billingham, Leslie Brent, and Peter Medawar, presented their landmark experiments on immunologic tolerance to skin homografts in mice at a faculty seminar at University College London, where I was teaching anatomy. They showed that the injection of lymphocytes derived from one strain of mice into another strain of fetal mice *in utero* made these mice, when born, tolerant to skin grafts derived from the mice that had donated the lymphocytes [3].

The interest in transplantation goes back to at least the 15th century. A painting by Fra Angelico in the Museo di San Marco in Florence depicts the saints Cosmas and Damian (who were early Christian martyrs) replacing a devoted church member's leg that had been afflicted by a malignancy with the leg of an African slave.

The graft was said to have been successful, probably because they were blessed by divine assistance.* John Hunter, the experimental English surgeon in the 18th century, believed transplanted tissue would live and claims to have successfully transplanted a cock's testis to a hen, apparently without affecting the disposition of the hen. In 1902, Ernest Ullman in Germany carried out the first kidney transplants in dogs [4]. A few years later, Alexis Carrel showed that autotransplantation, a kidney from the same animal replaced into the original animal, could be done successfully, but that homotransplantation, a kidney transferred between unrelated animals, failed within a few days due to a "biological problem" [5].

In 1927, Karl Bauer in Germany showed that skin grafts exchanged between identical twins could survive indefinitely [6]. In December 1954, Dr. Joseph Murray and his colleagues at the Peter Bent Brigham Hospital in Boston performed the first successful kidney transplant between identical twins. About

* Twin brothers martyred in Syria by the Emperor Diocletian in 287 CE. They were crucified, stoned, burned, and beheaded. They subsequently became the patron saints of physicians and surgeons.

1 in 3 twins is identical and occurs in about 1 in every 300 births.

The operation was performed at the suggestion of Dr. David Miller of the U.S. Public Health Service, who called Dr. John Merrill at the Peter Bent Brigham Hospital saying he had a patient with renal failure due to chronic glomerulonephritis who had an identical twin and suggested he might act as a donor. The twin brothers were brought to the hospital in Boston, and skin grafts exchanged between them were found to survive for many weeks. After further consultation, the transplant was performed; Dr. Hartwell Harrison removed the donor kidney, which was implanted in the recipient by Dr. Joseph Murray. After one year with the kidney working well, the operation was reported in the *Journal of the American Medical Association* [7]. They performed seven more such transplants during the next four years. Dr. Murray was later awarded the Nobel Prize for his pioneering work in transplantation. The first patient died after eight years due to development of recurrent glomerulonephritis in the transplanted kidney, a complication that was subsequently found to occur in about 50 percent of recipients, after transplantation between identical twins whose kidneys had been initially destroyed by glomerulonephritis. This problem occurred less frequently with transplants from an unrelated donor as the required use of immunosuppressive agents tended to prevent the development of the nephritis.

The modern era of organ transplantation began a few years later in 1959 with the discovery of a way to suppress the immune response by Drs. Robert Schwartz and William Dameshek at Tufts University Medical School in Boston. They found that the chemical compound 6-mecaptopurine (a purine analog that interferes with the synthesis of protein that induces the immune response) could suppress the immune reaction to a foreign protein (human serum albumin) injected into rabbits [8]. The parent chemical compounds of 6-mecaptopurine were first synthesized by George Hitchings and Gertrude Elion at the Wellcome Laboratories in 1952, when searching for antimetabolites to treat leukemia. They later developed azathioprine (Imuran), a conjugate of 6-mercaptopurine, as an immunosuppressive agent, which was felt to be less toxic [9]. They were awarded the Nobel Prize for their work in 1988. Gertrude Elion visited Yale as a Tetelman Fellow at Jonathan Edwards College in 1993.

Dr. Roy Calne, working with Dr. Joseph Murray, first demonstrated that kidney transplantation between non-identical animals could be performed successfully using 6-mercaptopurine to suppress the immune response to the foreign kidney [10]. He subsequently became Professor of Surgery at Cambridge University and a pioneer in liver transplantation. On his return to London in 1961, he presented his work to a surgical research group to which I belonged and aroused my interest in, and enthusiasm for, renal transplantation.

The first successful human kidney transplant from a non-identical donor using the kidney from a recently deceased person was performed in 1962 using azathioprine to prevent rejection [11]. The methodology and dosimetry for these immunosuppressive agents was worked out in the dog model prior to its clinical application and is one of the prime examples of the value and importance of animal experimentation in the development and establishment of boundary-breaking clinical treatments. The administration of large doses of cortisone to supplement the immunosuppressive effects of Imuran was introduced at that time by the Brigham group.

I came to Yale in 1962 as an assistant professor in Urology and continued some of my work in tumor immunology that I had begun as a British Empire Cancer Fellow at Kings College Hospital in London. Cancer poses the obverse prob-

lem to transplantation: that is why the tumor is not rejected when it exhibits proteins different from those expressed by the host. We had been able to show that the injection of human tumor extracts into the host could elicit an immune response in the form of a delayed hypersensitivity reaction. I also acquired some experience in the technique of kidney transplantation in a study of the vesicorenal reflex in dogs. This required a complete denervation of the kidneys, accomplished by bilateral renal auto transplantation. The initiation of the renal transplantation program had to wait until 1966 when Dr. Jack Cole was appointed as the new chief of surgery. He was committed to a program of organ transplantation and made available the necessary resources and created the favorable political climate needed for the translation of a new idea into clinical practice.

Thus, in the summer of 1967, Dr. Howard Levitin in the section of Nephrology and I began hemodialysis in a few patients with chronic renal failure as a prelude to offering them a kidney transplant. Using two machines in a small room next to his office on the second floor of the Fitkin building and assisted by Helen Feigenbaum and another nurse, we carried out hemodialysis on four patients three times a week. One of the problems in chronic hemodialysis is the need for repeated vascular access. At first we inserted silastic arteriovenous shunts between the radial artery and vein that had been designed by Dr. Belding Scribner in Seattle, Washington. These shunts clotted frequently and occasionally became infected. We soon adapted a new idea to our own use in which we anastomosed the radial artery to the adjoining vein. This increases the pressure and flow in the veins of the arm so they become distended and can be readily accessed for hemodialysis [12, 13].

In the treatment of chronic kidney failure, I have always considered dialysis a holding action in preparation for a kidney transplant as the definitive treatment. Our first patient, who urgently needed a kidney transplant, was a 52-year old Polish immigrant who served in World War II as a fighter pilot with the Royal Air Force. He developed renal failure secondary to chronic glomerulo-nephritis. He had a difficult time on dialysis, as he found the fluid and salt restriction very hard to tolerate. On December 9, 1967, three Yale students were traveling south in a car on Interstate 95 near Exit 10 when the driver's vision was temporarily obscured by smoke from an old incinerator at the side of the road. They lost control of the car, and one of the passengers sustained a severe head injury. On the morning of December 21, it became apparent he had no brain function, and a small committee was convened that had been previously set up by Chief of Staff Dr. Lawrence Pickett to decide whether a person could be declared brain dead while on a life-support system. The committee concluded that the patient had no cerebral function, and permission to remove the kidneys for transplantation was obtained from the patient's uncle, who was a physician. The patient's respirator was turned off, and the intended recipient of the kidney was brought to the operating room.

As we prepared to carry out removal of the kidneys from the donor, I was called to the telephone. It was the president of the hospital, who asked me in an angry voice, "What in the hell are you doing?" and "Who gave you permission to do a transplant in this hospital?" The timing and content of his remarks seemed inappropriate and so, perhaps impolitely, I hung up and proceeded to remove both kidneys. We irrigated the harvested kidneys with a cold anticoagulant solution and placed them in a basin of cold irrigant. We then transferred the left kidney to the operating room and implanted it in the patient's lower abdomen anastomosing the renal artery end-to-end to the divided internal iliac artery and the vein to the side of the

external iliac vein. I was being assisted by Dr. Cole, the chief of surgery, for moral support; Dr. Robert Weiss, who is now Chief of the Urology Service; and two of the residents at that time, Dr. Martin Schiff and Dr. John Libertino, who is now Chief of Urology at the Lahey Clinic. The anesthesiologist was Dr. Luke Kitahata, who had to give the patient K exalate enemas during the operation to reduce the high serum potassium.

The procedure fortunately went well, even though I had never seen one performed in a human before. After completing the vascular anastomosis in about 20 minutes, we removed the vascular clamps and were relieved to see the kidney perfuse well with blood. My relief was short-lived, however, as I realized I put the kidney in upside down. Calm was restored when I remembered from my classes in physiology that peristalsis is not dependent on gravity. This occurred many times subsequently and is of no consequence. The ureter was fortunately long enough so we were able to implant it into the bladder without it becoming kinked. The kidney made urine immediately, and as the patient left the operating room with 200 cc of golden-colored liquid in the drainage bag, I murmured that "happiness today is a little urine." I never lost the thrill of seeing a patient make urine after receiving a new kidney often after months or even years of anuria. This patient, the first kidney transplant in Connecticut, did well, and the newspapers gave us front-page coverage.

I think the president of the hospital enjoyed the publicity as he was very complimentary and never mentioned our phone conversation. The kidney subsequently developed acute tubular necrosis associated with an episode of rejection that was successfully treated with large doses of prednisone. After 16 days, the kidney recovered, his urine output returned to normal, and he had no further problems. A year later, he undertook a journey back to his native Poland for a holiday. On returning to the United States, he described what a wonderful reception he had received, the notoriety he achieved as a kidney transplant recipient, still a rare event at that time, and how he enjoyed all of the previously proscribed salty foods that are so popular in his native country. Almost two years to the day after his operation, he was re-admitted with severe abdominal pain and septic shock due to infection and died within hours from what proved to be a perforation of the rectum. This was probably secondary to a rectal ulcer caused by the large doses of steroids that he had been given to prevent rejection. It took several years for us to learn how to moderate the dosage of steroids, to minimize the serious complications that occurred initially both in the prevention and treatment of immunological rejection.

The genie was now out of the bottle, and we were soon engaged in doing many transplants. We adopted a somewhat different management style for the transplant program at Yale. The responsibility for the post-operative care of patients was divided between the nephrology service, staffed by two physicians and a nephrology fellow, and the urology service, staffed by four surgeons and two residents. While the nephrologists continued to be the patient's doctor of record, the services made joint rounds each day, and no major changes in treatment protocols were made without consultation and consensus. Although this was a somewhat unique arrangement, it proved to be very successful because of the close collaboration of the physicians concerned. It had the advantage that someone was always readily available for emergencies, especially when the urologists were busy in the operating room, and that patients who had acute tubular necrosis postoperatively were dialysed promptly. Furthermore, their follow-up care as outpatients was more appropriately carried out by the nephrologists as many of the long-term problems in these patients are primarily medical, such as diabetes, fluid

and electrolyte disturbances, and the complications of prolonged steroid administration. It also enabled us to continue to function as a urology service and to provide adequate training for our residents. Although we all participated in performing renal transplants and harvesting kidneys, Dr. Martin Schiff had primary responsibility for the kidney transplants and the establishment of vascular and peritoneal access in patients with chronic renal failure. There were only four or five centers in the United States where the urology service performed the kidney transplants; the majority were under the direction of dedicated transplant surgeons in departments of general surgery. We had good continuity of care as the same urologic surgeons, Drs. Lytton, Weiss, McGuire and Schiff remained in the program for the first 15 years. There were a few more changes among the nephrologists; Dr. Levitin (1967 to 1969) became Dean for student affairs and was succeeded by Dr. Robert Brown (1969 to 1972) who then moved to The Beth Israel in Boston. Dr. Barry Strauch (1972 to 1973) followed for one year before going into practice. Dr. Frederic Finkelstein (1973 to 1978) was director for five years before taking over the dialysis service at the Hospital of St. Raphael and organizing a large home dialysis program. His associate, Dr. Alan Kliger (1978 to 1985), took over and was joined by Dr. Peggy Bia (1983 to present), who succeeded him when he joined Dr. Finkelstein in private practice.

The results of the next few cases were not as good as the first; fewer than 50 percent of the kidneys remained functioning after one year, a little better than the national average at that time. The sixth and seventh patients in the summer of 1968 were the first of what we called "double headers." That is, we used both kidneys from a single cadaveric donor for two recipients. Two young girls, 16 and 14, were the first two recipients from the same donor.

In the case of the first young woman, we had to correct her serious metabolic abnormalities, so the kidney had to be refrigerated for seven hours after being perfused with cold Ringer's lactate solution following removal from the donor. There were no perfusion machines at that time for renal preservation. The young woman did well, and the kidney survived for 17 years, after which it failed as a result of chronic rejection. She has received a further transplant since and is now married and has three children. She is one of the eight early kidney grafts that survived 15 years and was the only one with a kidney from a cadaver that did so.

The other young woman lived nine years and died of a lymphoma. The next patient, our eighth, was a young girl who had been our first patient to receive a kidney from a living donor, her mother. It functioned for six years until it was lost from chronic rejection. She then received a second kidney from a cadaver donor. At that time, a kidney transplant from a cadaver donor involved a period of six to 24 hours to make the logistical arrangements, harvest the kidneys, and perform the transplant.

It was a very time consuming and intensive effort on the part of everyone concerned. Following a call from an outlying hospital about a possible donor, the urologic surgeon on call and a junior resident would drive out to harvest the kidneys, collect blood for tissue typing, and remove a number of lymph nodes to perform a mixed lymphocyte reaction test with the recipients' lymphocytes that helped to define the degree of compatibility. There were always numerous delays and technical problems to overcome, and most transplants were performed at night or in the early hours of the morning. We did not have satisfactory perfusion machines for the harvested kidneys during the first few years, so the transplants were performed whenever a kidney became available, which often stretched the

resources of the section. One Christmas Eve, we harvested four kidneys, transplanted two that evening, and implanted the other two the following morning.

In 1972, we began to perfuse the harvested kidneys to preserve them for up to 48 hours, using a machine designed by Dr. Folkert Belzer, a former Yale surgery resident who had moved to San Francisco to work with Dr. Engelbert Dunphy [14]. A New England Organ Bank was established in Boston in 1972 under Dr. Benjamin Barnes and received kidneys from all over New England; Dr. Schiff was appointed to the board to represent Connecticut. The sera from the donors were typed and matched against sera from patients on the waiting lists for a kidney, and the kidneys were then distributed to the best matched recipient. Since 1991, kidneys are no longer preserved by perfusion machines, but are irrigated with a preserving cold perfusate which enables them to be kept refrigerated for up to 36 hours prior to transplantation.

In April 1972, we performed a living-related transplant between a pair of 7-year-old identical twins. Kathleen had lost her renal function as a result of hemolytic uremia syndrome, and because of their age, we had to obtain a court order to permit us to perform the procedure. At that time, this was the youngest recorded transplant between identical twins. The psychological and ethical issues were reviewed by Dr. Melvin Lewis, a child psychiatrist, and debated for some time [15]. The graft is still functioning, and both young women are doing well.

Another intriguing problem was the disproportion between the size of the kidney in relation to the recipient. In 1971, we transplanted the kidney from a 6-year-old who died from a motor vehicle accident into an adult man. Over the next year, the kidney almost doubled in size and increased its function steadily during that time. Two years later, we placed a father's kidney into his 3-year-old son, and it filled half of his abdomen It functioned well but did not decrease in size. We also transplanted the kidneys from an anencephalic child into an 18-month-old infant, using a cuff of aorta and vena cava from the donor to accomplish the vascular anastomoses. The kidneys functioned well until the child succumbed to a viral pneumonia after eight months.

At first, we matched patients only by their blood groups, but within a few years, we began tissue-matching using sera from the recipients blood and lymphocytes harvested from the donors lymph nodes in the case of cadaver donors and peripheral blood lymphocytes from live donors. We also tested for direct compatibility between donor and recipient by the use of mixed lymphocyte cultures. Cross matching, to detect preformed antibodies to tissue antigens in the recipient, proved to be very useful as the presence of antibodies resulted in early rejection in 50 percent of recipients as compared to 4 percent if they were absent. Tissue typing was performed in advance so we could allocate cadaver kidneys based on the best match. Matching for two or more histocompatibility antigens showed a significant improvement in graft survival, although a mismatch did not necessarily predict failure of the graft. The mixed lymphocyte reaction, carried out between live donor and recipient pairs, was more helpful in that there was a marked improvement in graft survival when there was less than 20 percent stimulation. Tissue typing began in 1958, when Dr. Paul Terrasaki from Los Angeles went to work with Professor Peter Medawar in London and later with Professor Jean Dausset in Paris, both of whom had been involved in defining the tissue antigens first in the mouse and then in man. He developed a method to isolate peripheral white cells from the blood and a micro test to determine which antigens or markers they carried, to identify the tissue type of the patient [16]. Thus began the era of tissue typing and with it the elaboration

of the human histocompatibility locus. I think Professor Medawar once remarked that from the immunologist's viewpoint, "Man's best friend is not the dog but the mouse."

Many other distinguished immunobiologists contributed to the exciting research on mapping the histocompatibility locus on the 6th chromosome. Among them was Dr. Bernard Amos, an Englishman working at Duke University. In 1969, after doing our first transplant, we developed an immunological advisory panel that included myself, Dr. Fred Kantor, and Dr. Malcolm Mitchell. We visited Duke to learn tissue typing and how to set up a tissue-typing laboratory at Yale. We obtained a number of specific sera, then available both from Dr. Amos and from a newly created serum bank at the National Institutes of Health. We were fortunate at that time to recruit Dr. Nancy Ruddle, now a distinguished professor of immunology at Yale, to help develop and direct this laboratory, which she continued to do for the next five years. She was succeeded by Dr. Marion Zatz for two years and then by Dr. Robert Cohn (1974 to 1983). After Dr. Cohn left, the laboratory was taken over by the transplant surgeons, first by Dr. Wayne Flye and subsequently by Dr. Marc Lorber.

In 1971, we obtained funding of $250,000 from the regional medical program to promote transplantation at Yale, but unfortunately the program was canceled for political reasons after the first year. We also had a very active program of renal transplantation in children, which was ably directed for eight to 10 years by two pediatric nephrologists, Drs. Norman Siegel and Karen Gaudio, who monitored their patients very carefully and had excellent graft and patient survivals that were significantly better than the national averages.

Between 1967 and 1992, the first 25 years, 630 kidney transplants were performed at Yale (Table 1). The number performed each year in the first 15 years averaged only 15 to 20 per year, whereas in the following 10 years, it averaged 30 to 40 per year (Figure 1). In the early years, we received no payment for the majority of cases, because the patients had exhausted their insurance by the time they came to transplantation. In 1973, Congress passed legislation to provide reimbursement for patients with end-stage renal disease as part of the Medicare program, a result of intense lobbying by advocates for patients with chronic kidney disease and the nephrologists involved in their care.

There followed a rapid proliferation of dialysis capability during the next few years associated with a strong financial incentive to keep patients on dialysis. This became known as "the golden age for nephrologists." Patients needing dialysis were rapidly recruited to the program once there was adequate funding. It became the conventional wisdom that dialysis was better and safer than transplantation, and patients were discouraged from undergoing transplantation. The nurses on the dialysis units developed personal ties with the patients and would discourage them from undergoing further treatment based on anecdotal news of what had happened to some patients who had undergone transplantation. They did not acknowledge that patients on dialysis undergo accelerated degeneration of their blood vessels and there was a considerable mortality rate, primarily from heart disease and strokes.

About 50 percent of patients on dialysis died during the first five years. Death while on dialysis was attributed to "natural causes," while a death following transplantation was a surgical mortality. We undertook a study to compare the results in patients undergoing dialysis with those undergoing renal transplantation over a three-year period. It was found that while survival rates were the same, the quality of life with a kidney transplant was a great deal better as judged by the ability to work, a sense of well being, and sexual activity [17]. In the early years. not only

Table 1. Transplantation at Yale: 1967-1992.

Cadaver donors	454 (72 percent)
Living related donors	176 (28 percent)
Total	630
Adult	541 (86 percent)
Pediatric	89 (14 percent)

was the graft survival only 50 percent after one year, but the patient mortality was unacceptably high. A review of the first 100 cases indicated that by decreasing the dose and the length of time of administration of steroids used for immuno-suppression and by not persisting in the treatment for rejection when there were unmistakable signs that it was irreversible, patient mortality and morbidity could be significantly reduced without further decreasing graft survival [18]. Improved methods for the diagnosis of rejection at an earlier stage, such as serial nuclear scanning, devised by Drs. Gerald Freedman and Martin Schiff, allowed for prompter treatment that also contributed to an improvement in patient survival [19] (Table 2). Cyclosporin, which was introduced in the early 1980s, proved to be a much more effective and less toxic agent for suppressing the immune response. This led to a dramatic improvement in results; 70 to 80 percent five-year survivals for cadaver renal grafts and up to 90 percent for living related donor grafts (Figures 2 and 3). Thus renal transplantation is now without a doubt the preferred treatment for chronic renal failure and is widely practiced. The limiting factor is the availability of suitable kidney donors, and this has resulted in long waiting lists for kidneys in most transplant centers.

In 1983, Dr. Schiff decided to relinquish his position on the transplant service and Dr. Arthur Baue, then Chief of Surgery, used this opportunity to recruit a surgeon dedicated to transplantation to fill his position as he wished to expand the program to include other organs. Dr. Wayne Flye, from Duke University, who had extensive experience in immunology and clinical organ transplantation, was appointed. Dr. Schiff continued to assist him with the program. By 1983, there was sufficient dialysis capacity to accommo-

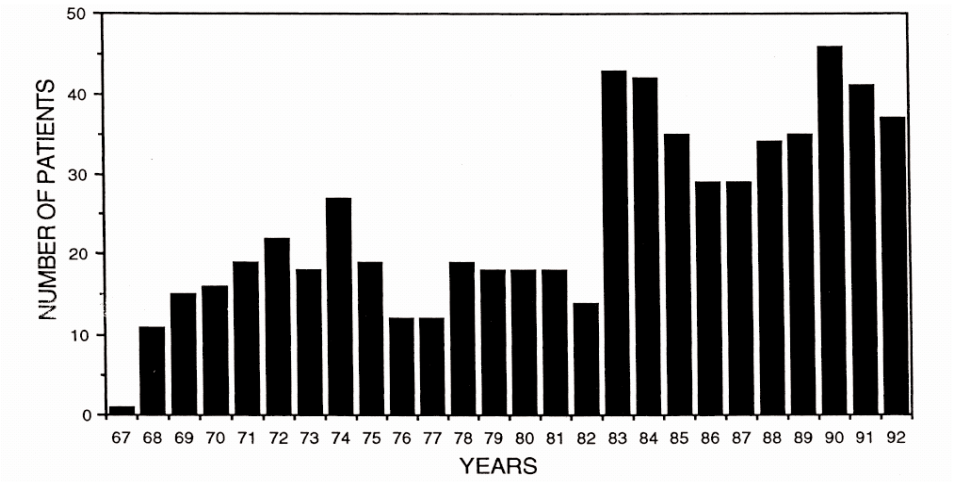

Figure 1. 630 renal transplants at Yale 1967-1992.

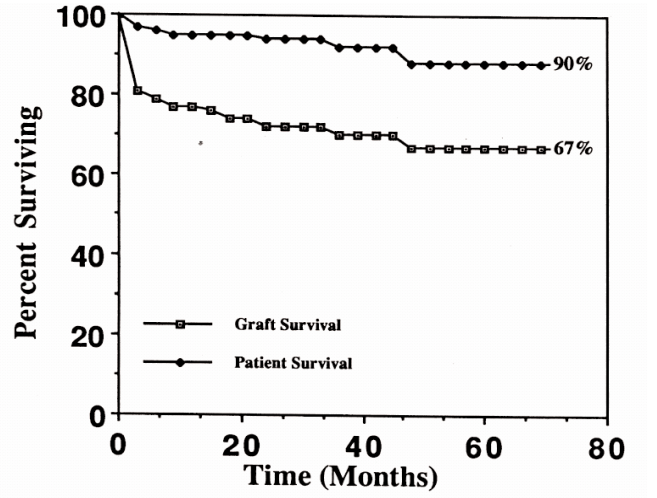

Figure 2. Yale-New Haven organ transplant center, cadaveric renal transplantation 1987 to 1992.

date all those who needed it. This coupled with the marked improvement in the results of renal transplantation following the introduction of cyclosporin, a more effective and less toxic immunosuppressive agent, the list of patients awaiting transplants grew from 20 to 30 patients to over 90 (Figure 4). The combination of these factors resulted in a significant increase in the number of kidney transplants performed each year after 1983. The limiting factor became the shortage of suitable kidney donors, and this has remained a major problem to this day. As a result there has been a significant increase in the number of living donors.

In 1983, the first liver transplant was performed at Yale by Drs. Wayne Flye and Richard Gusberg. Flye and Schiff flew down to Florida to harvest the liver. In November 1984, Drs. Alex Geha and John Elefteriades performed the first heart transplant at Yale. Dr. Elefteriades remembers that after harvesting the heart in Bridgeport, he was returning to Yale in an ambulance with the heart in a cooler when the engine failed as a result of excessive speeding by an overly zealous driver. Dr. Elefteriades got out and thumbed a ride on the highway. Fortunately, the car that stopped for him was a police cruiser that completed the high-speed journey, with sirens blaring, to the hospital. The heart was successfully implanted.

In 1985, Dr. Flye left to become the head of transplantation at Washington University in St. Louis, and Dr Marc Lorber, who trained at the University of Michigan and Baylor University in Houston, joined the faculty as chief of the transplant service. He expanded the program of renal and liver transplantation and in 1987 recruited Dr. William Marks, who began transplantation of the pancreas in

Table 2. Mortality after Transplantation (Yale 1968 to 1981).

	No. of transplants	Deaths	Percent
1968-72	84	24	28.6
1973-76	76	11	14.5
1977-81	85	4	4.7

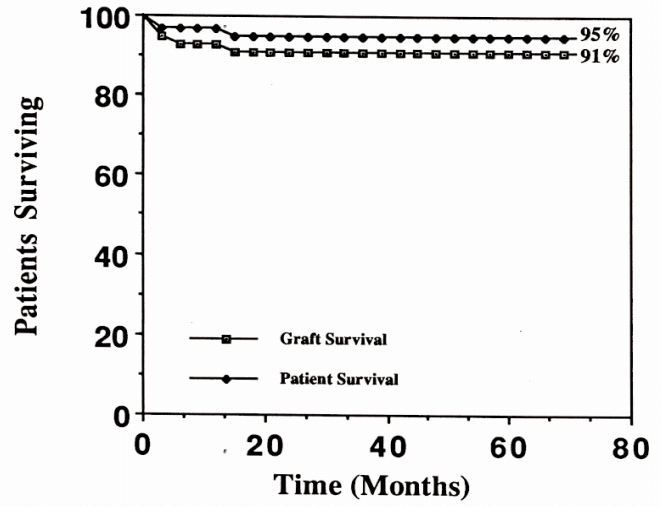

Figure 3. Yale-New Haven organ transplant center, LRD renal transplantation 1987 to 1992.

diabetic patients with anastomosis of the duodenum and pancreatic duct to the bladder. More recently, Dr. Kevin Anderson initiated laparoscopic donor nephrectomy at Yale, with a reduction in morbidity and hospital stay, so the majority of live donors are now managed successfully in this way.

"Life is short, art long, opportunity fleeting, experience treacherous, judgment difficult."
Hippocrates

Acknowledgements: I am indebted to Dr. Marc Lorber for the figure depicting results after 1983 and to Dr. Martin Schiff for reading the manuscript and for his helpful suggestions.

REFERENCES

1. Kolff WJ and Berk MJ. The artificial kidney: a dialyser with a great area. Acta Med Scand 1944;117:121-34.
2. Gibson T and Medawar PB. The fate of skin homografts in man. J Anat 1943;77: 294-310.

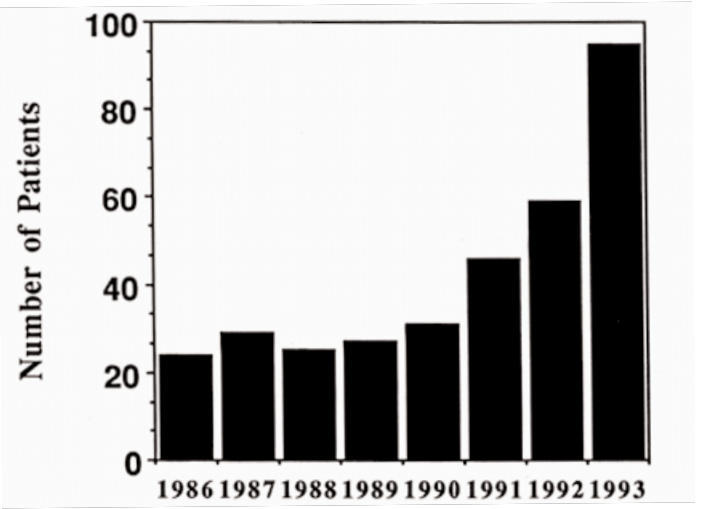

Figure 4. Yale-New Haven organ transplant center patients awaiting renal transplantation.

3. Billingham RE, Brent L, and Medawar PB. Actively acquired tolerance of foreign cells. Nature 1953;172:603-6.
4. Ullmann E. Experimentelle nieren-trnsplantation. Wien Klin Wochenschr 1902;15:281-2.
5. Carrel A. Remote results of replantation of the kidney and the spleen. J Exp Med 1910;12:146-50.
6. Bauer KH. Homoiotranplantation von epidermis bei einigen zwillingen. Beitr Klin Chir 1927;141:442-6.
7. Merrill JP, Murray JE, Harrison JH, and Guild WR. Successful homotransplantation of the human kidney between identical twins. JAMA 1956;160:277-82.
8. Schwartz R and Dameshek W. Drug induced immunological tolerance. Nature 1959;183:1682-3.
9. Hutchings GH and Elion GB. Chemical suppression of the immune response. Pharmacol rev. 1963;15:305-405.
10. Calne RY. Rejection of renal homografts: inhibition in dogs by 6-mercaptopurine. Lancet 1960;1:417-8.
11. Merrill JP, Murray JE, Takae FJ, Hager EB, Wilson RE, and Dammin GJ. Successful transplantation of kidney from a human cadaver. JAMA 1963;185:347-53.
12. Cimino JE, Brescia MT, Appel K, and Hurwich BT. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. New Engl J Med 1966;275:1089-92
13. Lytton B, Goffinet JA, May CJ, and Weiss, RM. Experience with arteriovenous fistula in chronic hemodialysis. J Urol 1970; 104:512-7.
14. Belzer, FO, Ashby BS, Huang JS, and Dunphy, JE. Etiology of rising perfusion pressure in isolated organ perfusion. Ann Surg 1968;168:382-91.
15. Lewis M. Kidney Donation by a 7 Year Old Identical Twin Child. J Child Psych 1974; 13:221-45.
16. Terasaki PI, Mickey MR, Singal DP, Mittal KK, and Patel R. Serotyping for homotransplantation. XX. Selection of recipients for cadaver donor transplants. New Engl J Med 1968;279:1101-3.
17. Bonney S, Finkelstein FO, Lytton B, Schiff M, and Steele T. Treatment of end-stage renal failure in a defined geographic area. Arch Intern Med 1978;138:1510-3.
18. Lytton B, Finkelstein FO, Schiff M, and Black HR. Influence of rejection on graft survival after renal transplantation. Trans. Am Assoc GU Surg. 1975; 67:99-102.
19. Freedman GS, Schiff M, Zager P, Jones D, and Hausman M. The temporal and pathological significance of perfusion failure following renal transplantation. Radiology 1975;114:649-54.
20. Terasaki PI. Antibody response to homographs. II. preliminary studies of the time of appearance of lymphoagglutinins upon homografting. Am Surg 1959;25:896-9.
21. Watnick TJ, Jenkins RR, Rackoff P, Baumgarten A, and Bia M. Microalbuminuria and hypertension in long-term renal donors. Transplantation 1988;45:59-65.