The modern period of transplantation began in the late 1950s, but two earlier periods of interest in clinical and experimental transplantation were the early 1950s and the first two decades of the 20th century. Hamilton provides a bibliography of the history of organ transplantation. Table 1.1 summarizes landmarks in kidney transplantation.

### Early Experiments

Interest in transplantation developed in the early part of the 20th century because experimental and clinical surgical skills were rapidly advancing, and many of the pioneering surgeons took an interest in vascular surgical techniques as part of their broad familiarity with the advance of all aspects of surgery. Payr’s demonstration of the first workable, although cumbersome, stent method of vascular suturing led to widespread interest in organ transplantation in Europe. Many centers were involved, notably Vienna, Bucharest, and Lyon. The first successful experimental organ transplant was reported by Ullmann in 1902. Emerich Ullmann (1861–1937) had studied under Edward Albert before obtaining a position at the Vienna Medical School, which was then at its height. Ullmann’s article shows that he managed to autotransplant a dog kidney from its normal position to the vessels of the neck, which resulted in some urine flow. The animal was presented to a Vienna medical society on March 1, 1902, and caused considerable comment. At this time, Ullmann was chief surgeon to the Spital der Baumhertigen Schwestern, and his experimental work was done in the Vienna Physiology Institute under Hofrath Exner. Exner’s son Alfred had already tried such a transplant without success. In the same year, another Vienna physician, Alfred von Decastello, physician assistant at the Second Medical Clinic, carried out dog-to-dog kidney transplants at the Institute of Experimental Pathology.

Ullmann and von Decastello had used Payr’s method, and later in 1902 Ullmann demonstrated a dog-to-goat kidney transplant that, to his surprise, passed a little urine for a while. Neither Ullmann nor von Decastello continued with this work, although von Decastello was noted for his work on blood groups, and Ullmann published extensively on bowel and biliary surgery.

In Lyon, the department headed by Mathieu Jaboulay (1860–1913) had a major influence. In his research laboratories, his assistants Carrel, Briau, and Villard worked on improved methods of vascular suturing, leading to Carrel’s famous article credited with establishing the modern method of suturing. Carrel left to work in the United States, and in the next 10 years he published extensively on organ grafting, successfully carrying out autografts of kidneys in cats and dogs and, showing that allografts, contrary to accepted opinion, eventually failed after functioning briefly, established the existence of “rejection” as it was later termed. He made attempts at tissue matching and demonstrated cold-preservation of tissues. He was awarded a Nobel Prize for this work in 1912.

### Human Kidney Transplants

Jaboulay, Carrel’s teacher, had carried out the first recorded human kidney transplant in 1906, although Ullmann later claimed an earlier attempt in 1902. Jaboulay was later to be better known for his work on thyroid and urologic surgery, but, doubtless encouraged by the success of Carrel and others in his laboratory, he carried out two xenograft kidney transplants using a pig and goat as donors, transplanting the organ to the arm or thigh of patients with chronic renal failure. Each kidney worked for only 1 hour. This choice of an animal donor was acceptable at that time in view of the many claims in the surgical literature for success with xenograft skin, cornea, or bone.

More is known of the second and third attempts at human kidney transplantation. Ernst Unger (1875–1938) (Fig. 1.3) had a thorough training in experimental work and set up his own clinic in 1905 in Berlin, being joined there by distinguished colleagues. He continued with experimental work and by 1909 reported successful
transplantation of the kidneys en masse from a fox terrier to a boxer dog. The urine output continued for 14 days, and the animal was presented to two medical societies. By 1910, Unger had performed more than 100 experimental kidney transplants. On December 10, 1909, Unger attempted a transplant using a stillborn child’s kidney grafted to a baboon. No urine was produced. The animal died shortly after the operation, but postmortem examination showed that the vascular anastomosis had been successful. This success and the new knowledge that monkeys and humans were serologically similar led Unger to attempt, later in the same month, a monkey-to-human transplant. The patient was a young girl dying of renal
failure, and the kidney from an ape was sutured to the thigh vessels. No urine was produced. Unger’s report concluded that there was a biochemical barrier to transplantation, a view mistakenly advocated by the basic science of the day; his main contributions thereafter were in esophageal surgery. (For a biography of Unger, see Winkler.10) These early experiments established that kidney transplants were technically possible. Methods of study of renal function were primitive then; without routine measurement of blood urea and without any radiologic methods, subtle studies of transplant function were impossible. This impossibility plus the uncertainty of the mechanism of allograft rejection led to a diminished interest in organ transplantation after about 10 years of activity. By the start of World War I, interest in organ transplantation had almost ceased and was not resumed in the European departments of surgery after the war. Carrel had switched his attention to studies of tissue culture. Interest elsewhere also was low; in Britain and the United States, scarce research funds were being applied to fundamental biochemistry and physiology, rather than applied projects of clinical relevance. Transplantation immunology faded away after the bright start in the capable surgical hands of Carrel. Murphy’s sound grasp of immunosuppression, and Landsteiner’s awareness of the serologic detection of human antigens. Carrel, Murphy, and Landsteiner all worked at the Rockefeller Institute in New York.

In 1914, in a remarkable lecture to the International Surgical Society, Carrel did anticipate the future development of transplantation. His colleague at the Rockefeller Institute, J. B. Murphy, had found that radiation or benzol treatment would increase the “take” of tumor grafts in rats, and Carrel realized the potential of these findings:

*It is too soon to draw any definite conclusions from these experiments. Nevertheless it is certain that a very important point has been acquired with Dr. Murphy’s discovery that the power of the organism to eliminate foreign tissue was due to organs such as the spleen or bone marrow, and that when the action of these organs is less active a foreign tissue can develop rapidly after it has been grafted. It is not possible to foresee whether or not the present experiments of Dr. Murphy will lead directly to the practical solution of the problem in which we are interested. The surgical side of the transplantation of organs is now completed, as we are now able to perform transplantations of organs with perfect ease and with excellent results from an anatomical standpoint. But as yet the methods cannot be applied to human surgery, for the reason that homoplastic transplantations are almost always unsuccessful from the standpoint of the functioning of the organs. All our efforts must now be directed toward the biological methods which will prevent the reaction of the organism against foreign tissue and allow the adapting of homoplastic grafts to their hosts.*10

**The Middle Years**

Until the revival of interest in transplantation in the 1950s, the 1930s and 1940s were a stagnant period in clinical science. The great European surgical centers had declined: in North America, only at the Mayo Clinic was there a cautious program of experimental transplantation without building on Carrel’s work, notably failing to make attempts at immunosuppression. In transplantation circles, such as they were, there was not even the confidence to counter the vivid claims of Voronoff to rejuvenate human patients via monkey gland grafts, and the endless reports of successful human skin homografts were not examined critically.

The main event of this period was an isolated and little-known event—the first human kidney allograft. It was performed in the Ukraine by the Soviet surgeon Yu Yu Voronoy.11 Voronoy was an experienced investigator, and he eventually performed six such transplants up to 1949. Voronoy (1895–1961) trained in surgery at Kiev under Professor V.N. Shamov and obtained experience there with serologic methods of blood transfusion, then in their developmental stage. He used these methods to detect complement-fixing antibodies after testis slice transplants, and later he had some success with the same methods applied to kidney grafts (Fig. 1.4). In 1933 Voronoy transplanted a human kidney of blood group B to a patient of blood group O with acute renal failure as a result of mercuric chloride poisoning. The donor kidney was obtained from a patient dying as a result of a head injury and was transplanted to the thigh vessels under local anesthetic; the warm time for the kidney was about 6 hours. There was a major mismatch for blood groups, and despite a modest exchange transfusion, the kidney never worked. The patient died 2 days later; at post-mortem, the donor vessels were patent. By 1949, Voronoy reported six such transplants, although no substantial function had occurred in any. (For a biography of Voronoy, see Hamilton and Reid12 and Matevosian and colleagues.13)

**Post World War II**

The sounder basis of transplantation immunology, which followed Medawar’s pioneer studies during World War II, led to a new interest in human transplantation. In 1946 a human allograft kidney transplant to arm vessels under local anesthetic was attempted by Hufnagel, Hume, and Landsteiner at the Peter Bent Brigham Hospital in Boston. The brief period of function of the kidney may have helped the patient’s recovery from acute renal failure: it marked the beginning of that hospital’s major interest in transplantation and dialysis.14

In the early 1950s, interest in experimental and clinical kidney transplantation increased. With a growing certainty
that immunologic mechanisms were involved, the destruction of kidney allografts could be reinvestigated. Simonsen, then an intern in Ålborg in Denmark, persuaded his surgical seniors to teach him some vascular surgery; using dog kidney transplants, he reported on the mechanism of kidney rejection. Dempster in London also reexamined this question. Both workers found, like Küss in Paris, that the pelvic position of the kidney was preferable to a superficial site, and both concluded that an immunologic mechanism was responsible for failure. Dempster found that radiation, but not cortisone, delayed rejection. Both workers considered that a humoral mechanism of rejection was likely.

In the early 1950s, two groups simultaneously started human kidney transplantation. In Paris, with encouragement from the nephrologist Jean Hamburger, the surgeons Küss (five cases), Servelle (one case), and Dubost (one case) reported on kidney allografts without immunosuppression in human patients, placing the graft in the now-familiar pelvic position. The Paris series included a case reported by Hamburger of the first live-related kidney transplant, the donor being the mother of a boy whose solitary kidney had been damaged in a fall from a height. The kidney functioned immediately, but was rejected abruptly on the 22nd day. In the United States, the Chicago surgeon Lawler had been the first to attempt such an intraabdominal kidney allograft in 1950; it was met with the intense public interest and professional skepticism that were to characterize innovative transplantation thereafter.

A series of nine cases, closely studied, was recorded from Boston, using the thigh position of the graft, and for the first time hemodialysis had been used in preparing the patients, employing Merrill’s skill with the early Kolff/B Brigham machine. David Hume (Fig. 1.5) reported on this Boston experience in 1953. Modest unexpected survival of the kidney was obtained in some of these cases and served to encourage future careful empirical surgical adventures, despite advice from scientists to wait for elegant immunologic solutions. Although small doses of adrenocorticotropic hormone or cortisone were used, it was thought that the endogenous immunosuppression of uremia was responsible for these results, rather than the drug regimen. Many of Hume’s tentative conclusions from this short series were confirmed later, notably that prior blood transfusion might be beneficial, that blood group matching of graft and donor might be necessary, and that host bilateral nephrectomy was necessary for control of posttransplant blood pressure. The first observation of recurrent disease in a graft was made, and accelerated arteriosclerosis in the graft vessels was noted at postmortem. Other cases were reported from Chicago, Toronto, and Cleveland in the early 1950s, but because no sustained function was achieved, interest in clinical and experimental renal allograft transplantation waned, despite increasing knowledge of basic immunologic mechanisms in the laboratory.

The technical lessons learned from the human allograft attempts of the early 1950s allowed confidence in the surgical methods, and in Boston, on December 23, 1954, the first transplant of a kidney from one identical twin to another with renal failure was performed. From then on, many such transplantations were performed successfully in Boston. Although sometimes seen now merely as a technical triumph, valuable new findings emerged from this series. Some workers had predicted that, in the short term, the activity of the inactive bladder could not be restored, and that in the long term, human kidney grafts would decline in vitality as a result of denervation or ureteric reflux. Other workers were convinced that a single kidney graft could not restore biochemical normality to an adult, and that in any case the existing changes caused by chronic renal failure were irreversible. All of these gloomy predictions were neutralized by the success of the twin kidney transplants, and the greatest triumph came when one such recipient became pregnant and had a normal infant, delivered cautiously by cesarean section, with the anxious transplanters in attendance. Many of the twin recipients are still alive today, although the good results were tempered by failures caused by the prompt return of glomerulonephritis in some transplanted kidneys. This complication was later much reduced by immunosuppression. Other lessons learned were that the hazard of multiple donor renal arteries provided a need for pretransplant angiography of the kidneys in living donors, although it still was not thought necessary to perfuse or cool the donor organ. Lastly, there was the first airing of the legal aspects of organ donation, particularly the problem of consent in young, highly motivated related donors. (For an account of this period, see Murray and colleagues.)

**Immunosuppression and the Modern Era**

In 1948, the first patients crippled with rheumatoid arthritis were given the Merck Company’s Cortone (cortisone) at the Mayo Clinic, and intense worldwide interest in the pharmacologic actions of adrenal cortical hormones followed. Careful studies by Medawar’s group in the early 1950s suggested a modest immunosuppressive effect of cortisone,
but when Medawar shortly afterward showed profound, specific, and long-lasting graft acceptance via the induction of tolerance, the weak steroid effect was understandably sidelined and thought to be of no clinical interest. Induction of tolerance in adult animals (rather than newborns) was accomplished by lethal irradiation and bone marrow infusion, and with this strong lead from the laboratory, it was natural that the first attempts at human immunosuppression for organ transplants were with preliminary total-body irradiation and allograft bone marrow rescue. These procedures were carried out in Paris, Boston, and elsewhere in the late 1950s.

This regimen was too difficult to control, and graft-versus-host disease was inevitable. It was found unexpectedly that sublethal irradiation alone in human patients was quite immunosuppressive, however, and this approach was used until 1962, the year of the first general availability of azathioprine (Imuran). In Boston, 12 patients were treated in this way, but with only one long-term survival in a man receiving his transplant from his nonidentical twin.24 In Paris, similar success was obtained with sibling grafts.25,26 These isolated kidney survivals after a single dose of radiation gave further hope and showed again that the immunology of humans, dogs, and mice is different. These cases also showed that if a human organ could survive the initial crucial rejection period, it could be protected or adapted to the host in some way, possibly shielded by new endothelium, by enhancement, or, as suggested later, by microchimeric tolerance induced by mobile cells in the graft.

### Chemical Immunosuppression

In 1958, at the New England Medical Center, attempts were made at human bone marrow transplantation for aplastic anemia and leukemia. To enable the marrow grafts to succeed, irradiation of the recipient was used. Results were poor, and mortality was high. Schwartz and Dameshek27 looked for alternatives to irradiation and reasoned that an anticancer drug, such as 6-mercapto purine (6-MP) or methotrexate, might be of use for immunosuppression in their patients. (For an account of this period, see Schwartz.28) Their important paper in 1959, showing a poor immune response to foreign protein in rabbits treated with 6-MP,27 was noticed by Roy Calne, then a surgeon in training at the Royal Free Hospital, London, and David Hume, new Chairman of Surgery at the Medical College of Virginia. Calne had been disappointed at the failure of irradiation to prolong kidney allograft survival in dogs and, like others looking for an alternative, he found that 6-MP was successful.29 Zukoski and colleagues30 in Richmond found the same effect.

In 1960 Calne visited Boston for a period of research with Murray, and Hitchings and Elion of Burroughs Wellcome, then at Tuckahoe, provided him with new derivatives of 6-MP.31 Of these, BW57-322 (later known as azathioprine [Imuran]) proved to be more successful in dog kidney transplants and less toxic than 6-MP.32 From 1960 to 1961, 6-MP was used in many human kidney transplants. In London at the Royal Free Hospital, three cases were managed in this way, but without success, although one patient receiving a live related transplant died of tuberculosis rather than rejection.33 In Boston, no lasting human kidney function was obtained, but in Paris, Küss and associates34 reported one prolonged survival of a kidney from a nonrelated donor when 6-MP was used with intermittent prednisolone in a recipient who also had received irradiation as the main immunosuppressive agent (Fig. 1.6). This case was the first success for chemical immunosuppression.

This change in approach, giving lifelong, risky medication with toxic drugs, although an obvious development in retrospect, was accepted with reluctance because it meant leaving aside, at least in the short term, the hopes from the work of the transplantation immunologists for the elegant, specific, one-shot, nontoxic tolerance regimen. Many workers thought that entry into this new paradigm was only a temporary diversion.

In 1961 azathioprine became available for human use; the dosage was difficult to judge at first. The first two Boston cases using the drug did not show prolonged survival of the grafts, but in April 1962 the first extended successes with human kidney allografts were obtained.35 Shortly afterward, at the bedside rather than in the laboratory, it was discovered that steroids, notably prednisolone, when given with azathioprine had a powerful synergistic effect. The regular use of both together became a standard regimen after reports by Starzl and colleagues36 and Goodwin and coworkers.37 and this combined therapy continued to be the routine immunosuppressive method despite many other suggested alternatives, until azathioprine was displaced by cyclosporine much later. Use of the combined immunosuppression and the increasing use of live related donors (rather than occasional twin or free or cadaver kidneys), along with the remarkably good results reported in 1963 from Denver16 and Richmond,38 greatly encouraged the practice of transplantation. (For an account of this period, see Starzl.39)

### A Time of Optimism

The mid-1960s was a period of great optimism. The rapid improvement in results seemed to indicate that routine success was at hand. Looking to the future, calculations were
made that suggested that enough donor organs would be available in the future if all large hospitals cooperated, and such donations did start to come from outside the transplantation pioneer hospitals. Transplantation societies were set up, and specialist journals were started. The improvements in regular dialysis treatment meant an increasing pool of patients in good health suitable for transplantation, and this allowed for better and planned preparation for transplantation. With a return to dialysis being possible, heroic efforts to save a rejected kidney were no longer necessary. Management of patients improved in many aspects, and the expected steroid long-term effects were met and managed (primarily by the demonstration that low-dose steroids were as effective as high-dose steroids). The need for cooling of donor organs was belatedly recognized, many tests of viability were announced, and transport of organs between centers began. Bone disease and exotic infections were encountered and treated, but the kidney units were affected by a hepatitis B epidemic in the mid-1960s, which affected morale and status. The narrow age limit for transplantation was widened, and in Richmond the first experience with kidney grafts in children was obtained.

Recipients of kidney transplants reentered the normal business of life and became politicians, professors, pilots, and fathers and mothers of normal children. Other good news in the United States came when the federal government accepted the costs of regular dialysis and transplantation in 1968. There were always unexpected findings, usually reported from the pioneer units with the longest survivors. Cautiously, second kidney transplants were performed at Richmond when a first had failed; these did well, and the matter became routine. Chronic rejection and malignancy first were reported in kidney transplant recipients from Denver. As a result of the optimism, experimental heart transplantation started, the first human livers were grafted, and there was a revival of interest in xenotransplantation. Although the attempts of Reemtsma and coworkers, Hume, and Starzl at transplantation with chimpanzee or baboon kidneys ultimately failed, rejection did not occur immediately, and the cases were studied closely and described.

In the search for better immunosuppression, there was great excitement when laboratory studies by Woodruff and Medawar produced a powerful immunosuppressive antilymphocyte serum, and production of versions suitable for human use started. Initial results were favorable, but the whole antilymphocyte serum had an unspectacular role thereafter, added to from 1975 onward by the use of monoclonal antibody versions. Hopes for another biological solution to transplantation were raised in 1969 when French and Batchelor found an enhancing serum effect in the new experimental model of rat kidney transplantation made possible by the development of microsurgical methods, but it proved impossible to mimic the effect in humans.

Tissue Typing

The greatest hopes resided in the evolution of tissue-typing methods, which entered routine use in 1962 (Fig. 1.7). The increasing identification of the antigens of the human leukocyte antigen (HLA) system seemed to promise excellent clinical results in the future from close matching made possible when choosing from a large pool of patients. Sharing of kidneys in Europe started in 1967 at van Rood’s suggestion, and in North America, Amos and Terasaki set up similar sharing schemes on both coasts of the United States. Others followed throughout the world, and these organizations not only improved the service but also soon gathered excellent data on kidney transplant survival. The need to transport kidneys within these schemes encouraged construction of perfusion pumps designed to increase the survival of organs and the distance they could be transported. Much work on perfusion fluids was done until the intracellular type of fluid devised by Collins et al. in 1969 allowed a simple flush and chill to suffice for prolonged storage. Although the hopes for typing were not fully realized, such schemes had other benefits in obtaining kidneys when urgently required for patients with rarer blood groups, for children, or for highly sensitized patients. Such patients had been recognized by the new lymphocytotoxicity testing using a crossmatch between donor cells and recipient serum. First noted by Terasaki and associates and described in more detail by Kissmeyer-Nielsen and colleagues in 1966 and Williams and colleagues, such pretransplant testing explained cases of sudden failure and led to a marked diminution in hyperacute rejection.

The 1970s Plateau

The 1970s was a period of consolidation, of improvements in data collection such as the valuable European Dialysis and Transplant Association surveys, and increased sophistication in HLA typing methods and organ-sharing schemes. Cadaver organ procurement generally increased as a result of wider involvement of the public and medical profession, although the number of patients waiting for transplantation persistently exceeded the organs available, and donation declined transiently during times of public concern over transplantation issues. Governments took initiatives to increase donations; in the United Kingdom, the Kidney Donor Card was introduced in 1971, becoming a multi-donor card 10 years later. In hospital practice, methods of resuscitation and intensive care improved, and the concept of brain death was established to prevent prolonged.
pointless ventilation, although its immediate application to transplantation provoked controversy. Despite many new claims for successful methods of immunosuppression, such as trials of splenectomy, thymectomy, thoracic duct drainage, and a new look at cyclophosphamide, no agent except antithymocyte globulin became established in routine use.

Although patient survival after kidney transplantation continued to increase, the 1970s did not show the expected increase in cadaver graft survival. Some groups reported decreased survival figures: this paradox was solved partly by the demonstration that blood transfusion during regular dialysis, which had been discouraged because of the risk of sensitization, was beneficial to the outcome of kidney transplantation, an observation made some years earlier by Morris and coworkers. The 1970s ended with two innovations that revived hopes of reaching the goal of routine, safe, and successful kidney transplantation. Ting and Morris reported the successful clinical application of HLA-DR matching, and Calne and associates revived memories of the excitement of the early days of the use of azathioprine by introducing into clinical practice the first serious rival to it in 20 years, cyclosporine, which had been discovered to be a powerful immunosuppressive agent by Borel. Cyclosporine replaced the earlier drug regimens and was the dominant agent in use until the 1990s. Transplantation had grown to a sufficiently large clinical service that it was worth the attention of the pharmaceutical companies, and in the 1990s steady production of new agents occurred—tacrolimus, mycophenolate mofetil, rapamycin, FTY720, brequinar, and others. Any drug with promise was marketed aggressively, and sponsored trials became a routine part of clinical life.

The improved results of transplantation meant that the shortage and procurement of organs became a more dominant issue. Living donors were encouraged, to which were added occasional altruistic donations, with use later of “kidney chains” to pass on locally incompatibile organs. There was a return to using possibly damaged “marginal” kidneys and organs removed rapidly after cardiac death (DCD). Comparisons of transplantation practice throughout the world showed remarkable differences in attitudes to use of live related donors and cadaver organs, depending on regional and cultural traditions. Kidney transplantation had started as a difficult surgical and scientific challenge confined to a few academic centers in the developed world, but its success had led to the technique becoming a routine service in all parts of the world. In some nations not sharing Western attitudes, the donor shortage meant the appearance of undesirable commercial developments in renal transplantation, such as the purchase of kidneys from living unrelated donors (discussed in more detail in Chapter 41).

Waiting for Xenografts

As the demand for kidney transplants continued to exceed supply, other initiatives appeared and included study of nations and areas with high donation rates (e.g., Spain). As all attempts to increase donor supply fell short of the ever-rising target, the radical alternative of the use of animal organs was examined afresh. Profound immunosuppression alone was ineffective and, at first, methods of removing natural antibody from recipient plasma were tried to deal with the hyperacute phase of xenograft organ rejection. Although the traditional hopes for xenografting of human patients had assumed that “concordant” species such as the monkey would be used, a new strategy using genetic engineering methods first used a line of transgenic pigs, a distant species discordant with humans, with a modified endothelium that reduced the complement-mediated immediate reaction. Hopes continue that these early developments will evolve into a sophisticated successful routine. Meanwhile, the kidney transplanters can only watch, with detached interest, the emergence of stem cell use in cellular transplantation.

These new hopes for xenografts raised old fears among the public and legislators, notably regarding disease transmission. Although this had been a familiar problem in human-to-human transplantation and had been met regularly and dealt with, governments required reassurances about xenotransplantation with the added threat of retrovirus transmission.

Conclusion

Kidney transplantation was the first of the organ transplant procedures to develop because cadaveric donor kidneys revived with time, the availability of live donors increased, and the crucial backup of dialysis was implemented. When radical new ideas are to be tested, pioneers still turn to kidney transplantation. Kidney transplantation is where it all started, with good reason, and it will always be a test bed for major innovation, including laparoscopic and robotic surgery.

Nowhere is the excitement of the early days reflected better than in the recollections of 35 of the pioneers of transplantation gathered together by Terasaki.

References
