Renal Transplantation:

A Twenty-five Year Experience

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Boston has played a significant role in the development of renal transplantation. In Boston was performed the first successful isograft between identical twins (1954) the first successful allograft between fraternal twins (1959) and the first successful allograft from a cadaveric donor (1962). An immunosuppressive drug was also described in Boston by hematologists Schwartz and Dameschek (1959) and modified for renal transplantation in dogs (1961) and used for the first time in a human recipient in March 1962. By 1965 renal transplantation had become a clinical reality. Three hundred and ninety-eight of 589 recipients (68%) since 1950 are still alive, a remarkable figure considering that it includes all the earliest experimental transplants. One hundred and ninety-five of 295 (68%) with living-related donor transplants still have functioning allografts; 104/265 (39%) with cadaveric donor transplants have functioning grafts currently. Since 1968 transplants from living-related donors have an 80% one year survival whereas cadaveric donor transplants have approximately a 50% one year survival. Seventy-nine per cent of all one year survivors have had excellent psycho-social rehabilitation.

ALTHOUGH human renal transplantation had been tried sporadically before 1950, it was the first successful graft between monozygotic twins which gave the impetus for sustained trials. Parodoxically this first success still serves as a model for the desired end result in "spare-parts" surgery, because the recipient achieved normal renal function immediately along with control of hypertension and congestive heart failure.[16] In addition this success was a powerful stimulus for world wide redirection of basic immunological research.[24]

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According to Groth[9] human renal transplantation began in Paris and Boston. This current manuscript is a report of the Peter Bent Brigham Hospital experience since 1950. The development of the artificial kidney adopted from Kolff by Merrill, Walter, and Thorn was a necessary prerequisite for attempts at transplantation in patients with terminal renal disease.[14] Some human unmodified renal allografts, vascularized in the thigh with a cutaneous ureterostomy, survived longer[10] than did laboratory models[28] suggesting that the uremic state per se was immunosuppressive, an observation later confirmed using skin allografts in a clinical study.[6]

Our investigations in dogs with renal autotransplants vascularized in the pelvis with a vesico-ureterostomy demonstrated that a solitary kidney could, contrary to then current observations, sustain normal function indefinitely.[17] This laboratory preparation served as the model for our monozygotic twin transplants.

Our experience with identical twins increased during the 1950's.[18] One twin recipient had a normal pregnancy without impairment of renal function indicating the durability of the transplant.[22] She survives today well and healthy twenty years later, the world's longest surviving renal transplant recipient. She and her sister donor have had 5 children since the transplant. Another twin recipient improved urinary bladder hypotonicity and reflux after transplant.[24]

Renal disease is not easily thwarted, however. Two of

our early twin transplant patients developed glomerulonephritis in the transplant after only a few months of normal function and ultimately died from the second siege of "terminal" uremia. This experience opened the possibility of studying in man the etiology and prophylactic treatment of glomerulonephritis. To date these efforts have been only partially successful.

Ethical and Legal Considerations

New ethical and legal problems were raised. Because the use of living donors involved a major surgical operation for the donor, with certain risk of morbidity and even mortality, the physical and psychological evaluation of each donor was important. Treatment is always a balance between intended good and potential adverse effects. For the healthy donor, however, there is no physical benefit. As physicians educated and motivated to make sick persons well, we had at that time to make a basic qualitative shift in our actions as we subjected healthy normal humans to extensive surgical procedures. To this extent we compromised the injunction "to do no harm." The assumption had to be made that the low risk to the donor was justified by the expected benefits for the recipient.[7] In our first instance involving a potential donor below age twenty-one, the Supreme Court in Massachusetts allowed donation of the kidney by the healthy minor on the grounds that the donor himself would benefit psychologically and spiritually from the act of charity; although in the same decision the court recognized that the child might be psychologically harmed if prevented from donating, at slight risk to himself, when the life of an ill relative is at stake.[13]

Immune Suppression by X-irradiation

The experiences with identical twins generated renewed research by both clinicians and basic scientists in an effort to extend the use of transplants to the general outbred population. Two laboratory methods of achieving successful skin allograft survival were then available, namely "acquired immunological tolerance"[2] and x-irradiation, marrow infused" tolerance.[12] When a few patients were referred to the Peter Bent Brigham Hospital for possible transplantation after removal or injury of a solitary kidney, we already had embarked on a wide range of experiments in mice, rabbits, and dogs using the "x-ray-marrow" concept. We thus adapted as best we could these protocols to the anephric patients.[19]

In the 4 years between March 1958 and March 1962, 12 potential recipients were subjected to total body x-irradiation with or without marrow infusion.[20] Only one survived, a dyzygotic twin who received a transplant in January, 1959. He still survives and is the longest survivor of an allograft in the world. But it was becoming obvious that x-ray therapy as an immunosuppressive agent was too blunt, non-specific and unpredictable.

Immune Suppression by Drugs

The advent of drug induced immunological tolerance in 1959 provided a new avenue for study. Schwartz and Dameschek described a specific tolerance to protein in rabbits which were treated simultaneously with 6-mercaptopurine.[27] The animals still could react against proteins not given with administration of drug, indicating a desirable type of specific immune depression. Calne[3] and Zukoski[32] independently applied this drug to the canine renal transplant and the modern era of transplantation had begun.

To try to put this breakthrough in perspective, consider our own experience. For a decade in our laboratory several hundred renal transplants in dogs were performed using varieties of protocols. Our longest survival had been 18 days. Within a few weeks after Calne started to work with us one dog was surviving on a solitary renal autograft for 35 days with 6-mercaptopurine (6 MP) as the only immunosuppressive agent. This was truly a giant step. Protocols for series of dogs were developed in collaboration with Dr. Hitchings and his co-workers at Burroughs-Wellcome Company who had originally synthesized the drug. By 1961 we had reported dogs surviving over 150 days with normal renal function.[4] It was noteworthy that these animals were not sick or debilitated. They ate well, maintained weight, resisted kennel infection, and even procreated normally.

In 1960 two human recipients of allografts received 6 MP with some function occurring. In 1961 two more patients received azathioprine, the imidazole derivative of 6-mercaptopurine, after renal allografts; both had measurable renal function but died of drug toxicity because our drug dosage as extrapolated from our canine experience proved too high for man.[20] In April, 1962 a drug treated recipient of a cadaveric kidney survived for over a year; thus the modern clinical era began.[21]

During 1963 other centers transplanted large numbers of drug treated patients and achieved remarkable success using living-related donors.[11,29] It was immediately evident that drug therapy was more efficient and less dangerous than total body irradiation. An additional advantage was that the dosage could be continually adjusted.

Laboratory Studies

Concomitant with increase in number of clinical transplants a broad scaled analysis of the mechanism of action of immunosuppressive drugs was undertaken in our laboratory. In a large series of replantation and multiple transplant operations keeping the donor animal alive, we observed all animals on prolonged drug therapy

were immunologically competent; that drug therapy could be stopped successfully in some but not all animals; long-surviving kidneys were protected in some way in the new environment because a second donor kidney could be rejected while the first survived; retransplantation of a long surviving kidney back to its original donor did not depress its function; long surviving kidneys successfully retransplanted back to their original donors were rejected when transplanted to third party, non-drug treated recipients; immune paralysis did not account for prolonged survival because the second donor kidney which constitutes a double dose of antigen was rejected while the first continued to survive; absorption or metabolism of the drug did not account for the variation in results because two kidneys, each from separate donors, were rejected differentially in the same drug treated host; and that all hosts were sensitized against the donor and the sensitization continued even in those dogs successfully weaned from drugs.[23]

During the course of these experiments it was apparent that the immunological response to a skin graft did not predict accurately the fate of a renal graft from the same donor. Using the same drug dosage, dogs rejected skin grafts while accepting renal grafts from the same donor. When both skin and kidney grafts were placed simultaneously there was significant prolongation in skin survival and dramatic decrease in renal graft survival. A possible mechanism of this paradox was that skin allografts stimulated the host-immune system to produce individually specific antibodies which are cleared from circulation by the kidney, resulting in destruction of kidney and preservation of skin.[15]

Era of Boundless Optimism

The years between 1963 and 1966 were in retrospect an era of boundless optimism. One year survival of related donor transplants reached 80%; for cadaveric donor grafts 50%. The attrition rate was surprisingly low after one year and most of the mortality and morbidity occurred during the first few months after the transplant. Goodwin had introduced corticosteroids as another immunosuppressive drug[8] and it was only natural to assume that drugs with a better therapeutic index would soon be uncovered. Today the facts are that azathioprine (Imuran) and steroids remain as the basis of immunosuppression in most circumstances.

The early optimism was generated in part by the expectations inherent in the development of tissue typing and matching. Experimentally and clinically the closer the genetic relationship between donor and recipient, the less immune suppression is required. International cooperation was feverishly organized to develop purified sera to delineate the genotypes of man. Terasaki developed a micro-technique for human tissue typing which could service all transplant centers, results were computerized, and kidneys made available over wide geographical areas based on compatibility results.

National Conferences were called to study ways to increase available cadaveric donors. The Uniform Anatomical Gift Act was enacted by practically each state within a few months. Public education programs were started.

An International Kidney Transplant Registry was put into operation so that similar data for every center could be pooled for analyses. Regular reports were sent to participants. Currently the Kidney Transplant Registry has computerized data on over 20,000 transplants starting from the earliest transplants in the 1950's, making kidney transplantation the best documented surgical procedure in history. The formulation of a uniform flow sheet, made available in duplicate on request, allowed the beginning transplant center to start collecting all essential data on their very first transplant.

Dramatic advances in the effectiveness of organ preservation also contributed to the optimism of the early 1960's. With better tissue typing and matching and with kidneys made available by enlightened laws and public interest, the next need was for better organ preservation so that kidneys could be stored while the most suitable patients could be selected and prepared for surgery. Preservation methods are of two types, cold storage after infusion, and continued pulsatile perfusion. Currently kidneys can be maintained for up to three days before being transplanted, but for practical purposes most are used within 24 to 36 hours after harvesting.[1]

Meanwhile, ancillary methods of immune suppression were being pursued. A drug screening program was evaluated and a liaison with the N.I.H. cancer drug screening program established. Localized x-ray therapy over the transplant itself seemed to prolong survival presumably by destroying passenger or infiltrating lymphocytes. Splenectomy and thymectomy were added to reduce total mass of body's lymphocyte pool. Extra-corporeal x-irradiation of circulating blood was tried to use the immunosuppressive effect of x-ray on the lymphocyte without affecting the rest of the host.

The use of anti-lymphocyte serum and globulin as an immunosuppressive agent was developed by Waksman and Woodruff.[9] Widely studied and analyzed it is still used in some centers for selected recipients, but its general usefulness is diminished because the use of animals is required for its production and the purification process is complex.

A new concept of immunosuppression, drainage of lymphocytes by thoracic duct cannulation, was introduced by Franksson[9] and used in some centers, including our own,[25] with beneficial results. This technique

TABLE 1. *Phases of Renal Transplantation (1951–1976) at Peter Bent Brigham Hospital*

1951–1958: (n = 5)	The unmodified host
1959–1967: (n = 126)	Early immunosuppressive trials
	a. Total body x-ray
	b. Drugs—6MP, *Azathioprine, Azaserine, Actinomycin C, Steroids
	c. Adjuncts—Typhoid therapy, extracorporeal irradiation thoracic duct fistula, local x-ray
1968–1972: (n = 257)	Biologic immunosuppression—Antilymphocyte serum
1972–1976: (n = 159)	Steroid pulse

* Mercaptopurine

too was cumbersome, required longer hospitalization and demanded careful management and replacement of proteins and fluids. Its benefits did not seem to justify its universal use.

Unexpected Problems

In this unnatural situation where surgeons are attempting to contravene nature by inserting a foreign protein into an unwilling, albeit needy host, unusual compensatory host mechanisms were bound to surface. Yet in our early days we were naively blind to nature's wiles.

A good example was the unanticipated transplant of a cancer to a suppressed host.[31] An anephric recipient received a kidney in August, 1964 from a patient who died of cerebral metastases from bronchogenic cancer. At donor autopsy there was no other evidence of metastases and specifically the other (non-transplanted) kidney had no cancer. The transplanted kidney functioned well but at 18 months the patient noted a mass over the lower part of the transplant which on biopsy proved to be histologically indistinguishable from original donor cancer. X-ray therapy over the lower half of the kidney transplant did not affect tumor size. Immunosuppression was stopped and patient promptly rejected the kidney without rejecting the tumor. Regional nodes became palpable and were excised along with transplant nephrectomy. Gross tumor was left beyond the limits of the groin dissection. Within months the residual masses melted away. He had a subsequent transplant and still is alive without tumor. This inadvertent transplant of a human cancer argues against use of any cadaver with malignant disease as a potential donor unless possibly the primary is of central nervous disease origin.

Not to be confused with the above transfer of a donor cancer is the development of de novo cancer in immunosuppressed patients. At first suspected to be related to use of antilymphocyte globulin, it is now apparent that any immune suppressed patient is vulnerable. De novo cancers have been reported,[26] about half involving the reticulo-endothelial system with the remainder ranging from basal cell cancers of skin to undifferentiated adenocarcinomas. Presumably the immune surveillance of the host impaired by immune suppression allows cancer virus or cells to become established more readily.

Infections with relatively nonpathogenic viruses, fungi, and protozoa are a direct sequelae of immune suppression and now constitute a major hazard for these patients.

Material and Methods

The entire experience of renal transplantation at the Peter Bent Brigham Hospital between March 1951 and January 1, 1976 has been tabulated and analyzed. All information regarding the course of each patient was collected from hospital and clinic records, from the hospital Transplant Registry and from files in the Transplant Unit and Transplant Clinic. This raw material was then reviewed by members of the transplant team familiar with the particular individuals. Each recipient in the series was listed sequentially in chronological order, then grouped according to donor source.[30] Those persons receiving more than one transplant were listed as a new patient at the time of their next allograft. Followup on all patients was updated to January 1, 1976 by information from the Transplant Clinic which serves about 300 recipients who are seen and examined intermittently. Close contact by letter is kept with the personal physicians of those additional individuals living abroad or at great distances in the United States. Thus, followup information and care of all recipients of renal allografts has been kept as complete as possible.

The total clinical experience in transplantation has been divided into four time periods for purposes of comparison (Table 1). These arbitrary divisions allow comparison of sufficient numbers of patients and modes of treatment in each category. Survival curves of kidney grafts and of transplant recipients have been compiled after the life-table method of Cutler.[5] Significance (P values) has been based on the chi square test using Yates' correction. Individual causes of death and incidence of non-fatal complications have been compiled and compared for each group.

Quality of life was assessed for each individual bearing a functioning transplant for one year or more. This information was obtained from physicians and nurses who had followed these patients regularly. Although such standards are subjective, we tried to compare the postoperative rehabilitation of each person with his life before the onset of chronic renal disease. The patient's performance socially, at work, or at school, has been included in this evaluation. Although quality of life evaluation is being reported only on recipients with trans-

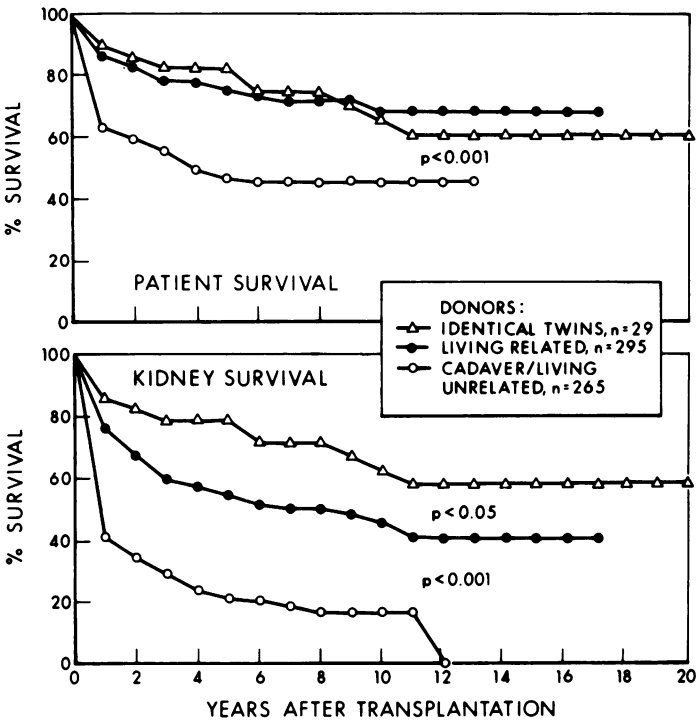

FIG. 1. The overall experience (1951–1976) in renal transplantation is enumerated in life tables. Patient and kidney graft survival are plotted separately.

plants functioning more than one year, many other patients with excellent graft function died within the first year of unrelated disorders.

Results

During the 25-year period of 1951 to 1976, 535 persons with terminal urema received 589 kidney transplants. The 49 patients who received two grafts and the 5 who received three are counted as new recipients with each subsequent transplant. There were 366 males in the group of mean age 34 years, and 233 females of mean age 32 years. While the ages of the patients ranged between 8 and 82 years, the relatively youthful average age in our series emphasizes the early onset of chronic renal failure in a general population. There were 411 of 589 transplant recipients (71%) who survived more than one year postoperatively, 397 of 589 recipients (68%) remain alive as of January 1, 1976. Of those with living-related allografts, 199 (68%) bear functioning grafts, while 33 (11%) have returned to dialysis. There are 63 patients (21%) in this group who have died. Recipients of cadaveric or living-unrelated allografts do consistently less well. Of 265 such patients, 104 (39%) have functioning grafts, 45 (17%) have returned to dialysis, and 116 (44%) have died. Renal transplants have functioned well in 68 patients for over 5 years; 17 over 10 years; 5 over 15 years.

Life tables summarizing the total experience in renal transplantation are enumerated in Fig. 1, and include transplants between 29 pairs of identical twins, kidneys from 295 living-related donors, and those from 265 cadavers or living-unrelated donors. Although the data include those early patients who died following failure of their grafts because of lack of dialysis facilities, it is gratifying to note that the survival of recipients of living-related kidneys is virtually superimposable upon that of recipients of isografts from identical twins. A modest difference remains between related allograft and isograft survival ($P < 0.05$), while that of cadaveric kidneys and of their recipients is consistently significantly worse than the other groups ($P < 0.001$).

The phases of renal transplantation as they have evolved in this program are enumerated in Table 1, while the effects of such therapeutic regimens on patients and allograft survival are noted in Figs. 2 and 3. Although the early experience with allotransplantation in the unmodified human host was small, it was crucial to demonstrate the possibilities of such a venture, both technically and as a therapeutic maneuver in these terminal patients. The survival rates of recipients of living-related organs and of cadaveric or unrelated kidneys have improved steadily as experience with various immunosuppressive measures has been gained, and are significantly better in both groups since 1968 ($P < 0.001$). Since 1972, patient survival, especially among recipients of related kidneys, continues to increase with improve-

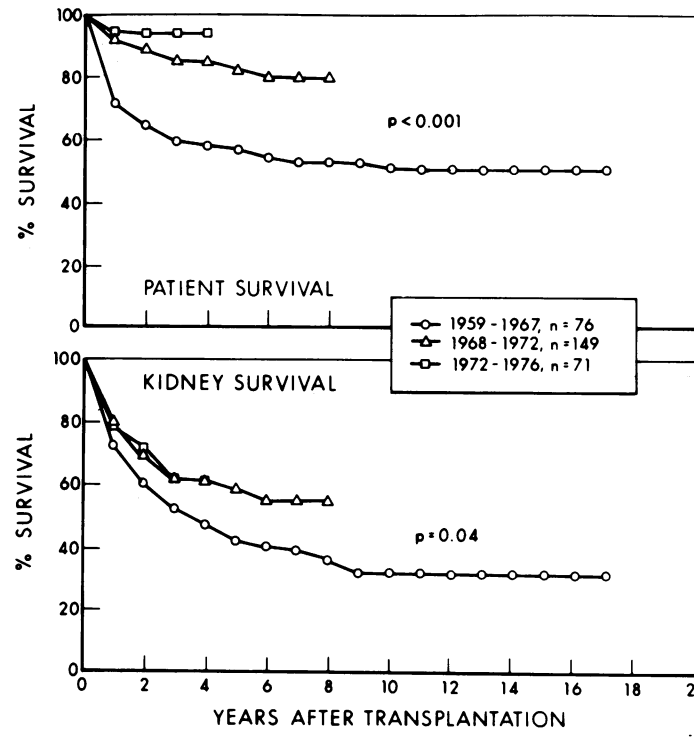

FIG. 2. The survival of renal allografts from living-related sources and their recipients are plotted in life tables. Results of various time periods are compared.

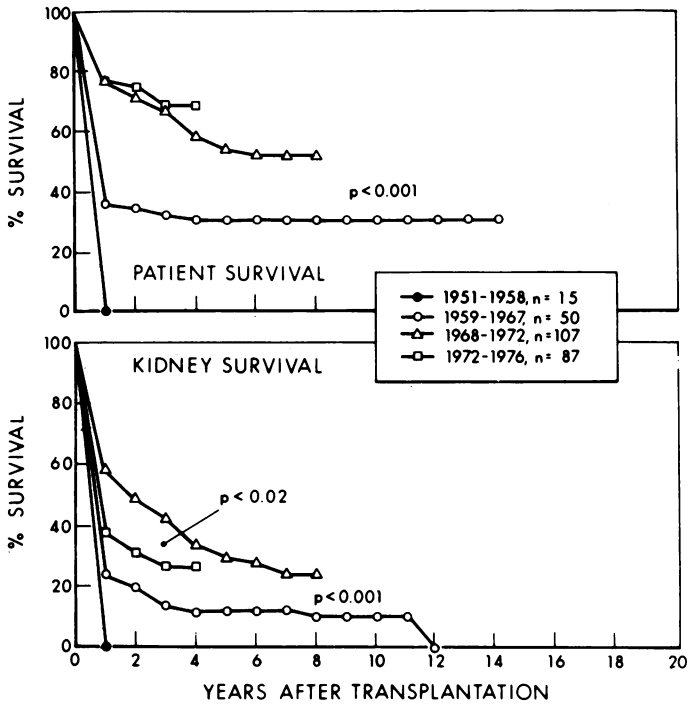

FIG. 3. The survival of renal allografts from cadaveric and living-unrelated donors and their recipients are plotted in life tables. Comparison of the results from various time periods shows little improvement in patient survival from 1968; worsening of allograft survival since 1972.

ments of dialysis techniques and the handling of many of the complications always potential among those on immunosuppressive drugs. However, the survival of kidneys from living-related sources has not increased during the past several years, remaining virtually similar to the period 1968–1972. These results have persisted despite efforts in tissue typing, continued immunosuppressive trials and restless search for newer protocols (Fig. 2). The mortality of those patients receiving cadaveric renal allografts is still high, especially during the first year after operation. Although our present threshold for giving up on a failing allograft by stopping immunosuppression is lower than in years past, appreciable proportions of this high risk recipient population continue to die from sepsis, gastrointestinal or cardiovascular complications. The survival rate for allografts from cadaveric sources has declined during the past three years ($P < 0.02$) probably because of recipient presensitization, use or non-use of blood transfusions, or the preservation and storage of kidneys.

Causes of Death

The causes of death of recipients of isografts (10 of 29 patients, 34%) who have no immunological barriers to surmount are quite different from those of allograft recipients who must remain on powerful immunosuppressive drugs for prolonged periods. An important cause of death among identical twin recipients (5 patients) was the recurrence of nephritis in the transplanted organ, a process which is presently causing progressive deterioration of two additional isografts. Myocardial infarction was fatal to two individuals with excellent renal function 2 and 9 years postoperatively, while three patients died early in the series of technical problems or sepsis.

The patterns of death among recipients of allografts have varied somewhat in time, although no relationship between the specific causes and donor source were apparent. As noted in Fig. 4, the incidence of uremia as a fatal complication has virtually disappeared as patients with failed grafts now return immediately to dialysis. Sepsis remains an important cause of death among transplant recipients (26 patients), although it has declined significantly in incidence since 1967. Infection remains predominantly bacterial, although irreversible fungal and viral infection are not uncommon. Death from gastrointestinal (13 patients) or cardiovascular complications (10 patients) or from neoplasia (9 patients) has been relatively constant during much of the transplant experience. Tumors continue to provide a small but steady mortality, usually occurring after months or years of immunosuppression in patients with otherwise excellent allograft function. Two individuals have developed reticulum cell sarcoma of the colon, while other persons have died of various solid tumors including a squamous cell carcinoma of the neck, carcinomas of thyroid, stomach, lung, and cervix, and an intracranial glioma.

Complications

Non-fatal complications developing in patients surviving over one year postoperatively between periods

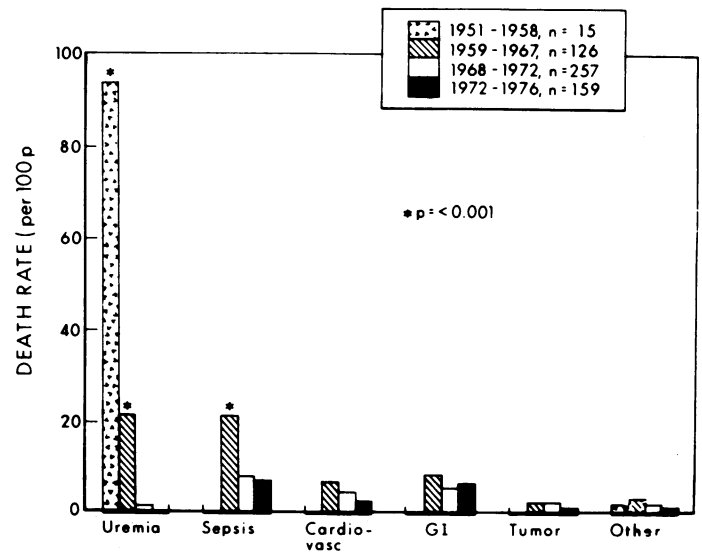

FIG. 4. The mortality rate of transplant recipients among the various time periods are compared. Death from uremia and from sepsis have fallen significantly. There is little change in the incidence of death from other causes.

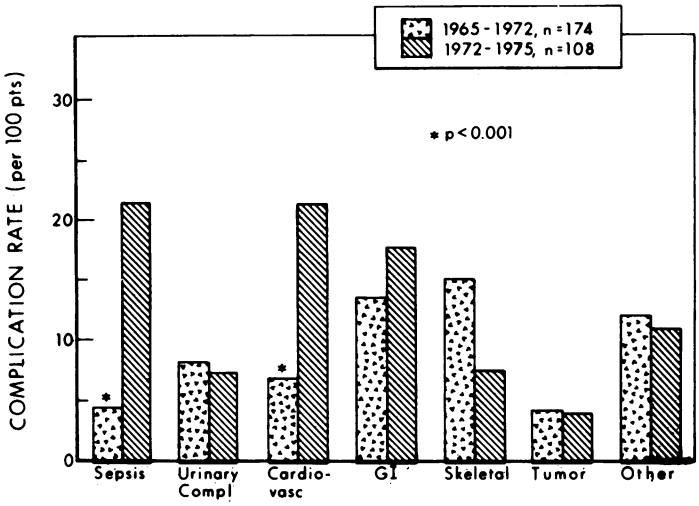

FIG. 5. The complication rate of transplant recipients bearing functioning allografts for more than one year is compared between the four time periods. The incidence of sepsis and cardiovascular complications is more common, although fewer patients than formerly die of these complications.

1965–1972 and 1972–1976 were compared to detect differences in patterns in time (Fig. 5). No variations were noted when comparing donor source. While the incidence of sepsis (17 cases) and cardiovascular (14 cases) complications were higher ($P < 0.001$) in the later period, the death rates from these conditions is significantly lower (Fig. 4). Thus, increasing numbers of transplant recipients recover from such hitherto fatal episodes. The generally improved control of complications has been maintained through a more aggressive approach to earlier diagnosis and treatment. Fiberoptic bronchoscopy, coupled with transtracheal lung biopsy has been of aid in the prompt diagnosis of cytomegalovirus, pneumocystis, or fungal pneumonias. A full course of appropriate therapy can be instituted quickly with concomitant reduction, but not complete cessation of immunosuppressive medication. Barium enema is performed immediately with any hint of lower abdominal tenderness, and perforation of sigmoid diverticula handled by exteriorization of the afflicted segment, resection and later reanastomosis. Mortality from this condition was total in the past in such patients; survival has been almost complete since the institution of this mode of treatment. Ultrasound has been of significant aid in the detection of collections of fluid around the transplant, within the abdominal cavity, or in the retroperitoneal space following nephrectomy of the native kidneys, as the technique is able to detect abscesses or cavities as small as 2 cm in diameter. Immediate drainage of such collections has decreased mortality from subsequent sepsis. Similarly, if there is a question of urinary tract obstruction or leak as suggested clinically or demonstrated on intravenous pyelogram or ultrasound, rapid exploration of the transplant with repair is initiated. It is interesting that the incidence of other non-fatal complications has not changed appreciably in the time periods under review. Upper gastrointestinal hemorrhage has occurred in 8 patients despite our insistence upon pretransplant pyloroplasty and vagotomy in patients with any previous history of peptic ulcer disease. Aseptic necrosis of the hips has necessitated hip replacement in 25 patients and remains a persisting problem for those receiving long-term steroids. The incidence of tumors, (10 patients) especially squamous cell carcinomas of the skin, has been relatively constant. The development of skin lesion in general—warts, keratoses and papillomata—have been surprisingly high in this immunosuppressed population. In contrast to the high incidence of recurrence of nephritis in isografted kidneys, this condition has recurred relatively infrequently in allografts, but has caused three patients to return to dialysis. Patients whose original disease was membrano-proliferative glomerulonephritis may be especially at risk. One individual in our series developed classic glomerulonephritis in his well-functioning allograft following a streptococcal illness. The progression of this condition led ultimately to failure and loss of the previously well-functioning kidney.

Rehabilitation

The quality of existence engendered by a functioning transplant was assessed in 365 patients surviving one year or more postoperatively (Fig. 6). It is gratifying that the preponderance of individuals (76%) in this series have achieved as satisfactory an adjustment to life as they had before the onset of chronic renal failure. Only 6% became so incapacitated following transplantation as to be unable to cope with their own care or to require multiple hospital admissions. The remainder

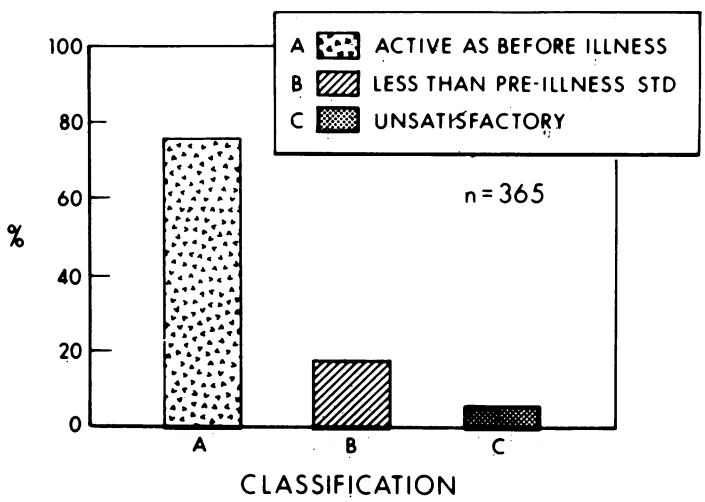

FIG. 6. Despite the potential for complications and risk from chronic immunosuppressive therapy, satisfactory rehabilitation of patients with functioning transplants is generally achieved.

(18%) were able to manage their lives, but were undeniably worse than before the onset of their original illness. As recipients of renal allografts comprise a group of patients whose previously normal existence has been altered permanently by the onset of a progressive and life-threatening illness, it is remarkable how many patients can adjust to pre-illness standards despite powerful medications and the ever present threat of hazardous and sometimes irreversible complications. The ability to return such individuals with successful transplants to relatively productive lives, unquestionably can offer them results more superior than that of permanent hemodialysis with its inconvenience, discomfort, and continuous dependency upon others.

Discussion

In 25 years clinical renal transplantation has become a major form of treatment for terminal renal disease. Born almost unnoticed it received wide exposure during early life because of the dramatic success with identical twins. Supported intellectually and financially during the lean years it became therapeutic rather than experimental after the discovery of drug induced immunological tolerance. Its maximum growth occurred between 1963 and 1968; since then progress has been slower, but better understanding of the immune process is slowly emerging. Compensatory complications are appearing of great variety. Yet overall it has proven to be remarkable therapy with good psycho-social rehabilitation for most patients.

During these past 25 years certain decisions and patients stand out in memory. One was a young man who needed a mitral valve replacement but was considered too far advanced in his uremic state for cardiac surgery. Six months after a successful cadaveric transplant he had mitral valve replacement and today 10 years later, is more active than ever. A second noteworthy recipient of a cadaveric kidney was a 68-year-old biochemist considered unsuitable because of his age for a transplant at other transplant centers. After the transplant, he finished his scientific work and presented it at a national meeting. The fact that he died 18 months after transplantation of a de novo colonic cancer does not detract from the quality of life enjoyed during his final years.

The influence of surgeons in the area of transplantation biology not only has helped patients but has also been a stimulus for basic scientists of many disciplines to recognize the potential clinical relevance of their research. In addition many current leaders in surgery have emerged through their interest and activity in this area.

One never dreamed that so much would occur in 25 years. The challenges ahead are more difficult but still soluble and will require concentrated analysis of the mechanism of rejection as well as search for safer methods of immune suppression.

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Discussion

Dr. Fuad J. Dagher (Baltimore, Maryland): The outstanding transplant work initiated at the Peter Bent Brigham Hospital a quarter of a century ago opened the doorway to clinical transplantation as a therapeutic modality for patients with end-stage kidney disease. At this Bicentennial Commemoration, the Brigham's transplant contribution should be considered part of the American Heritage.

(Slide) This book *Give and Take*, written by Dr. Francis D. Moore in 1964, illustrates in essence what has been going on in the field of transplantation. The paper we have just heard summarized well the overall transplant experience at the Brigham, i.e. the results of these kidney transactions over the past 25 years.

As shown by the survival curves, the authors recognized that progress in this field is definite, but unfortunately slow.

At the University of Maryland Hospital we are newcomers to this field, and in 1968 we performed our first and only kidney transplant operation for that year. Since then, we have performed 108 transplants in 102 patients, ranging in age between 11 and 59 years, with a mean age of 32 years.

Our results between 1968 and the present time are very similar to those presented here for the same period of time. Approximately 45% of our cadaveric renal allografts were lost within the first year from acute rejection which was nonresponsive to steroid pulsing. An additional 30% were lost in the next two years. Living related transplants, however, particularly those between HL-A identical siblings, have had better results. The 5-year kidney survival in this group is over 75%.

Of the complications we encountered, sepsis led the list. Of interest, we had one patient who developed generalized skin infection with purulent exudates caused by a very bizarre organism of the algae group, named Prototheca. This unusual infection has not been reported in kidney transplant patients but only in a few nonimmunosuppressed patients, particularly those working with marine life. Six patients developed significant polycythemia, requiring periodic phlebotomies; approximately 70% of our patients developed hypertension, with a diastolic pressure of over 100 mm Hg, necessitating the use of antihypertensive drugs for the first year or two. After that, and for some reason, the blood pressure came down to within normal levels.

As to the cause of death in kidney allograft recipients, sepsis remained the major problem. The mortality rate due to sepsis was similar to that shown by the Brigham group.

It is obvious, however, that for further progress and for a major breakthrough in this field we should more closely with the immunobiologists.

Finally, I would like to ask Doctor Tilney the following questions: Has any of your transplant patients shown evidence of polycythemia and/or high blood pressure; if so, how do you explain their development? And what is the status of diabetic patients with end-stage kidney disease? Do you recommend transplantation as a therapeutic modality for them?

Dr. William Stubenbord (New York, New York): We have analyzed our own results from the New York Hospital, where over the past 12 years we have had experience with over 500 transplants. Superimposing our data on Dr. Tilney's, they fit almost exactly. Reviewing 326 cadaver transplants, our three-year graft survival rate is about 30%, and at the present time we see no reason for increased optimism in the near future.

Dr. Nicholas L. Tilney (Closing discussion): We have had no trouble with polycythemia. We have certainly had trouble with anemia. We no longer do routine preoperative nephrectomy of the native kidneys. Even though these kidneys don't work they still make erythropoietin which improves the anemia of the dialysis patient.

We certainly have had our share of patients with hypertension, although most of the hypertension that arises acutely following kidney transplantation seems to decrease after a few weeks or months, and can be controlled more easily with medication. We certainly take out the native kidneys if there is hypertension preoperatively, feeling that this to be an important prophylactic measure.

As to the diabetic population, the Minnesota group has had a vast experience with these patients. They have done kidney transplants in more than 60 diabetics. They transplant the kidney before the diabetics go into dialysis, and thus are presumably dealing basically with a more healthy population than our particular diabetic transplant population, which now numbers about 15 patients.

There are good reasons for transplanting diabetics. It does serve to rehabilitate them and once they have a well-functioning kidney and are on stable doses of steroids, their blood sugar seems to remain a bit more quiescent than on chronic dialysis.

Also, diabetic neuropathy seems to improve rather dramatically. We don't know whether the neuropathy of the uremic diabetic is a combination of uremic plus diabetic neuropathy, but with a well-functioning kidney, often these people who had terrible foot drop and neuropathy before can walk around quite well after transplantation.

Certainly with steroid pulses, their blood sugar may need adjustment and, obviously, the threat of infection, especially systemic fungemias, is always present.

Dr. Joseph E. Murray (Closing discussion): I would like to reemphasize the influence of surgeons in the area of transplantation biology.

There have been ups and downs in our past experience, but I am confident that the next twenty-five years will see continuing, solid progress.