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Personal Reflections in Transplantation

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The distortions produced by personalized versions of events are well known and particularly well illustrated by a number of articles in both the older and more recent transplantation literature. Consequently, the student of history will be well advised to consult less biased accounts by younger workers such as the catalogue of landmarks in renal transplantation provided by Groth of Stockholm after his study of the written record and after discussions with most of the workers actually involved in the work done from 1950 onward.[14]

Nevertheless, it may be interesting to describe some of the problems of human organ transplantation as they were perceived at the time of our first clinical trials 15 years ago and subsequently. This has been done first by briefly and incompletely sketching the background that had evolved to 1961, the year before the first consistent successes began to be obtained with kidney transplantation. Second, the great advances starting in 1962 are described in the second section. Finally, unsolved or incompletely resolved problems that still exist 15 years later make up the final section.

THE TWENTIETH CENTURY THROUGH 1961

The first known attempts at clinical renal transplantation by vascular anastomoses were made without immunosuppression between 1906 and 1923 with sheep, pig, goat, and subhuman primate donors.† None of the kidneys functioned and the human recipients died from a few hours to nine days later.

Yet, even in these first cases, some principles were clearly delineated despite the climate of ignorance in which the trials were conducted. The applicability of vascular suture techniques, the advisability of perfusion of the heterografts to remove donor formed blood elements, and even the possibility of using pelvic implantation sites were either acknowledged or actually practiced. The efforts to use animal organs were abandoned and no clinical renal heterotransplantations were tried again until 1963.

The first human-to-human kidney transplantation was reported in 1936 by Voronoy[51] who transplanted a kidney from a cadaver donor of B+ blood type to a recipient of O+ blood type in violation of what are now well accepted rules of tissue

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†The literature of these early heterotransplantation trials has been summarized in reference 41 (pp. 262–265).

transfer.[41] Nevertheless, a few drops of initial urinary excretion were observed. The patient's death 48 hours after transplantation was attributed to a blood transfusion reaction. The possibility that there would be an immune barrier to success was apparently not part of the consciousness of early clinicians. This realization awaited the classical studies of Medawar with rodent skin grafts which established the immunologic basis of rejection.[28]

In the 20 years following Voronoy's case, sporadic additional trials were made without the benefit of effective immunosuppression, as recounted 14 years ago by Goodwin and Martin[13] and more recently by Groth.[14] By 1951, Küss et al.[22] and other members of the French school of surgery[11, 40] had virtually standardized the procedure of kidney transplantation to the iliac fossa, anastomosing the renal to the pelvic vessels of the recipient in much the same way as is practiced today. Despite the lack of success with these early patients, other cases were soon reported from Chicago, Boston, Paris, Toronto, London, and Cleveland.* In the meanwhile, the technical soundness of renal transplantation to the pelvic site was unequivocally demonstrated by the identical twin grafting (isotransplantation) experience of Murray et al.[34]

By the middle of the 1950's, the total number of attempts at human renal homotransplantation had reached approximately 30 without any immunosuppression at all, or with adrenocorticotropic hormone (ACTH) or cortisone in a few patients of Küss et al.,[22] Dubost et al.,[11] and Hume et al.[20] Most of the homografts never had significant function, and those that did initially, usually underwent prompt rejection, as was reported particularly clearly by Michon et al.[30] There were three more or less clear exceptions to this generalization. Renal homografts inserted by Lawler,[26] Gordon Murray,[31] and Hume[20] and their colleagues were said to have excreted urine for several months before being rejected slowly. The life of Hume's patient probably was increased thereby by several months. The unexpectedly prolonged survival of kidneys in untreated recipients has been explained since by the loss of immunologic responsiveness that has been shown to accompany uremia.

In the meanwhile, the deliberate obtundation of immunologic reactivity became theoretically feasible when total body irradiation was shown to be immunosuppressive.[10, 25] After that, an intermediate era in renal transplantation was begun in 1958 by Joseph Murray and his associates at the Peter Bent Brigham Hospital using total body irradiation as the primary means to prevent rejection.[33] Although most of the recipients died, two patients are still alive who, in 1958, were given kidneys in Boston[33] and in Paris[15] from fraternal twin donors. Nevertheless, the great risks and highly unpredictable effectiveness of total body irradiation as the sole or main modality of immunosuppression made the undertaking impractical.

The transplantation explosion which eventually occurred from 1962 onward was dependent upon the use of drugs. The first and, as it turned out, most important class of agents was the steroids. The experimental basis for the use of steroids was laid in 1951 by Billingham, Krohn, and Medawar[3] with prompt confirmation by others. The second seminal development was the introduction of the thiopurine compounds, 6-mercaptopurine and its imidazole derivative, azathioprine. These agents were developed by Dr. George H. Hitchings and Gertrude Elion and their colleagues at Burroughs Wellcome and Company, Inc., Tuckahoe, New York, and found by them to inhibit hemagglutinin formation in mice challenged with heterologous red blood cells.[17]

In 1959, the action of thiopurine compounds in blunting the immune response to bovine serum albumin was reported by Schwartz and Dameshek[38] in the journal, *Nature*. By the time of publication, the authors had in press in *The Journal of Clinical Investigation* a second article which documented the effect of 6-mercaptopurine upon rabbit skin homografts.[39] Mean rejection time in 16 control animals was 6.8 days compared to 17.8 days in a group of 17 animals given 12 mg per kg per day of 6-mercaptopurine for 2 weeks, and the same dose every other day thereafter. In this important study, dose response curves were also defined. The work was presented at an international congress in London on September 7, 1959. The findings were promptly confirmed in another institution.[29] A further affirma-

*A complete listing of all original articles is provided in reference 46 (p. 4, Part I).

tion of the antirejection qualities of 6-mercaptopurine came shortly afterward when it was tested by Calne[4] with the canine kidney model. Two mongrel dogs in this latter study survived for 21 and 47 days after renal transplantation from nonrelated donors and after bilateral recipient nephrectomy. The number of experiments were not stated nor were there controls. Further information was provided in later publications by Calne for 6-mercaptopurine and azathioprine.[5]

As recounted by Groth[14] a number of patients in Europe and the United States were given one or the other of the mercaptopurine drugs between 1959 and 1962, usually with a fatal outcome. However, two French recipients survived for prolonged periods of time. One who lived for 17 months was treated in 1960 by Küss and his colleagues[22] with 6-mercaptopurine after initial total body irradiation, and the other was managed similarly by Hamburger and associates[16] in January, 1962. By 1973, Hamburger's patient, whose donor was a cousin, had become the longest surviving non-twin recipient in the world. Murray et al.[33] reported the first patient in whom prolonged survival was achieved under primary immunosuppression with azathioprine alone; this recipient of a cadaver kidney lived for almost 2 years.[35] However, even well into 1962, there was little evidence that drug therapy would yield results substantially better than those obtained with total body irradiation. Such improvements would await the administration of drugs in combination (see next section).

My own involvement in transplantation began in the summer of 1958 at Northwestern University in Chicago. While a new method for one-stage hepatectomy was being developed in dogs, it was appreciated how easy it would be to replace the liver with a graft using a temporary portacaval shunt with or without an external bypass to decompress the blocked splanchnic and systemic circulations. At about this time, I had decided to remain in university work in preference to entering private practice and had spent several weeks in the medical library trying to decide upon some broad area of research in which to make an investment.

Transplantation seemed a worthwhile challenge, partly because of the deeply pessimistic attitudes that prevailed about the prospects of clinical organ transplantation in any except the most unusual cases such as those involving fraternal twins. Transplantation of the liver was especially appealing at that time because of its technical challenge.

Another factor that gave the liver special interest was speculation by Dr. Jack Cannon of Los Angeles that the liver played an important role in rejection. Because of this, Cannon, who was the first to attempt liver replacement,[7] apparently hoped that a hepatic homograft might suffer a different fate from that of other transplanted tissues since it presumably would not contribute to its own repudiation. As it turned out the liver has seemed to be less susceptible to rejection than any other major organ but for reasons that are still not understood.[42] Between 1958 and 1962 in the experimental liver transplant program which I established in Chicago, a brief attempt was made to irradiate both the graft and the recipient; prolongation of graft survival was not obtained.

THE KIDNEY FROM 1962 ONWARD

The kind of laboratory research with steroids, 6-mercaptopurine and azathioprine mentioned above was applicable in one way or another to organ replacement in man, but the connection was not straightforward. In occasional dogs a protracted life proved possible after renal transplantation with the use of steroids,[33] 6-mercaptopurine,[37] or azathioprine[5, 36, 41] as the sole immunosuppressive treatment. In man occasional similar successes were occasionally achieved solely with 6-mercaptopurine or azathioprine as was mentioned earlier. Nevertheless, the consistency with which really long-term survival was obtained was poor. The obvious reason was that complete control of rejection was rarely achieved.

Thus, both the animal data and the initial clinical experience discouraged further trials. The most important development which made immunosuppression practical was the discovery of the way in which azathioprine and prednisone could be advantageously used together. There were essentially no preceding laboratory data to indicate that the benefit with this now universally accepted combination of

agents would be as great as proved to be the case. Indeed, the first publication on experience in animals[27] was a belated confirmation of the far more convincing observations already made in humans.[45]

Furthermore, it is difficult even in retrospect to ascribe priority for standardization of azathioprine-steroid therapy to any single authority or transplantation group. What is clear is that by early 1963 the two drugs were being used together in one way or other and with varying degrees of conviction about their synergism for the prevention or reversal of renal homograft rejection in at least one British[52] and three American centers.[19, 35, 45] Since then, variations of these regimens have been adopted throughout the world.

The way in which our own initial efforts in renal transplantation evolved was as follows. Shortly before I came to the University of Colorado in late 1961, a 27 year old man suffering from terminal renal disease was seen at the Denver Clinic by Dr. Philip Clarke. Dr. Clarke discussed the case with Dr. William R. Waddell, who had come to Colorado in July, 1961, as Professor and Chairman of the Department of Surgery. After my arrival at Christmastime, 1961, Dr. Waddell arranged for me to see the patient and because of my interest in transplantation he asked me to organize an interdisciplinary treatment team. Fortunately, the recipient had an identical twin. The transplantation was carried out on March 27, 1962. Dr. Robert Brittain performed the donor nephrectomy. I performed the recipient operation with the assistance of Drs. Oliver Stonington, Richard J. Sanders, and William R. Coppinger.

While this first patient was still recuperating, a second recipient who did not have the advantage of a genetically identical donor was admitted to the hospital in renal failure. The month was May, 1962. Chronic dialysis was not yet a well established form of treatment. On acute intermittent hemodialysis the access vessels were rapidly consumed in this and other early patients. At the same time, desperate efforts to develop effective immunosuppressive treatment with total body irradiation and azathioprine were carried out in the laboratory of the Denver Veterans Administration Hospital. Completely acceptable results in dogs could not be by either irradiation or azathioprine alone or, for that matter, when they were used in combination.

Nevertheless, the decision was made to proceed with transplantation of this 12 year old patient since the prospects of further dialysis treatments were dismal. The plan was to give 300 R total body irradiation preoperatively, 100 R more postoperatively, and to supplement this treatment with azathioprine as the bone marrow depression recovered. The treatment schedule was similar to that used by Murray[33] and Hamburger[15] for their fraternal twin cases. If rejection occurred steroid therapy was planned.

The course of that first patient is summarized in Figure 1. The kidney which was donated by the boy's mother functioned well initially but after two weeks a severe rejection developed in spite of the fact that there were virtually no circulating white blood cells. The BUN rose to more than 75 mg per 100 ml and the creatinine clearance fell to about 5 ml per minute. Prednisone in daily doses of as high as 150 mg was added and daily doses of azathioprine were cautiously added about two weeks later.

Although the rejection was thereby reversed with survival of the patient to the present time, the frightening experience with total body irradiation and consequent bone marrow depression convinced us that the irradiation should be omitted on the next occasion. In the following 44 cases[41] azathioprine was started shortly before operation and continued in the maximum doses that were thought to be possible without the production of leukopenia. Prednisone was withheld until graft repudiation had clearly started. In retrospect, the most important advantage of withholding steroids until a specific indication was that the features of rejection and host-graft adaptation, as well as the influence of drug therapy on these processes (see below) could be delineated with some precision. The greatest disadvantage was that the rejections which developed under treatment with azathioprine alone were sometimes very severe and difficult to reverse with delayed steroid therapy. It was found that their incidence and seriousness were reduced if prednisone was given from the beginning.[41] Consequently, it has been our policy since December, 1963, to immediately treat virtually all recipients of organ homografts with predni-

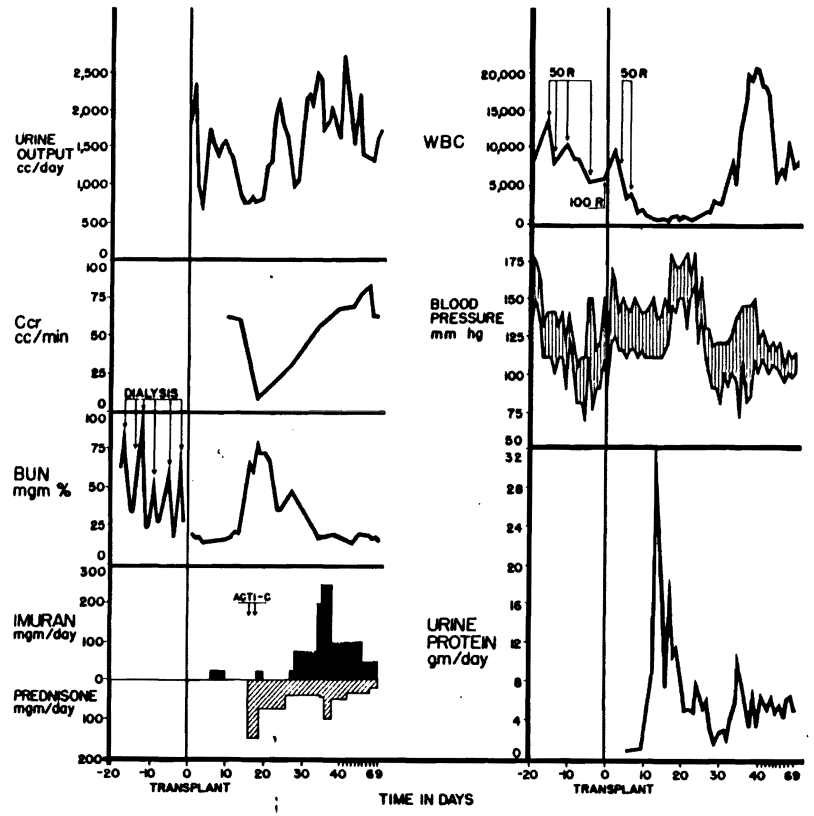

Figure 1. Rejection crisis in patient (LD 1) treated initially with total body irradiation (400 R). Note transient oliguria, depression of creatinine clearance, and elevation of blood urea nitrogen, blood pressure, and urinary protein excretion. The changes were all reversible. The patient previously had undergone bilateral nephrectomy, splenectomy, and thymectomy. R, dose total body irradiation; Acti-C, actinomycin C (each arrow equals 200 μg of actinomycin C administered intravenously). Imuran is synonymous with azathioprine. These general events of rejection have occurred despite treatment with all the therapeutic regimens used at this and other centers since 1962. (*From* Starzl, T. E., et al.: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg. Gynecol. Obstet., *117*:385, 1963, with permission.)

sone and azathioprine (sometimes cyclophosphamide has been used instead of azathioprine), to which in recent years heterologous antilymphocyte globulin (ALG) has been added in a triple drug program.

By the spring of 1963, the practical possibilities of clinical renal transplantation had already become obvious from observations of our first patients. One reason was the repeated demonstration that rejection was a highly controllable and reversible process. The first report to this effect began as follows:[45]

> "Because of the high failure rate after renal homotransplantation, there has been an air of pessimism concerning the possibility of long term function of the grafted kidney. The immunologic processes subserving rejection are generally thought to be so powerful and persevering that consistent success cannot be expected with the use of any of the currently available methods of antirejection therapy.
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> "Recent personal experience in caring for patients with renal homografts has resulted in alterations in many of our preconceived notions concerning the management of such patients. It has led to the beliefs that the

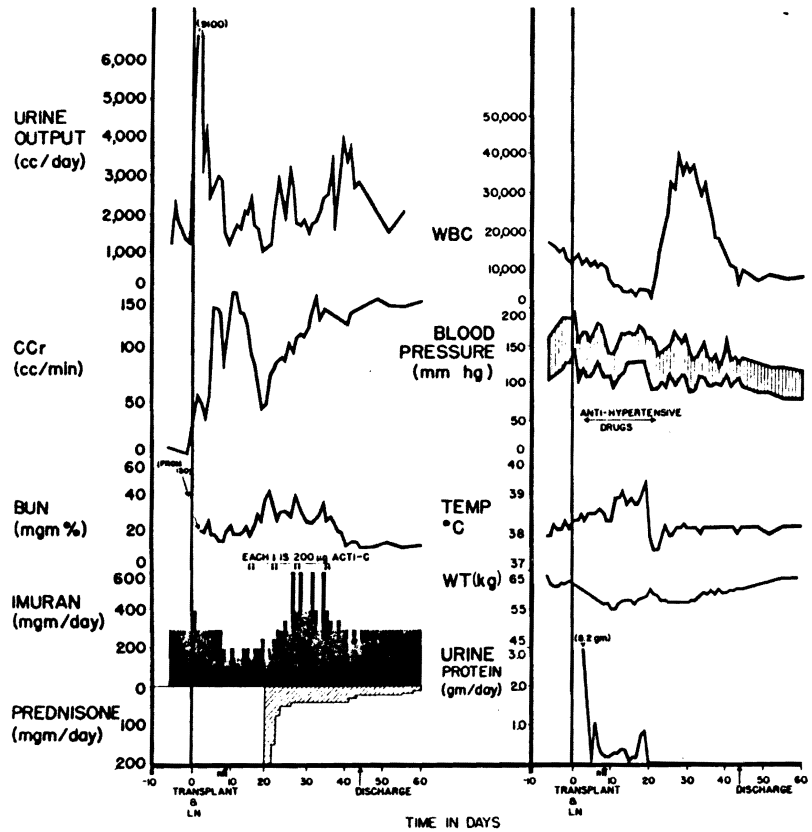

Figure 2. Classic rejection crisis in patient (LD 6) treated with drugs alone. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. Acti-C, actinomycin C; LN, left nephrectomy at time of transplantation; RN, Right nephrectomy. Imuran is synonymous with azathioprine. (*From* Starzl, T. E., et al.: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg. Gynecol. Obstet., *117*:385, 1963, with permission.)

> rejection process can almost never be entirely prevented, but that its effects can be reversed with a high degree of regularity and completeness. Furthermore, the subsequent behavior of patients who have been brought through a successfully treated rejection crisis suggests the early development of some degree of host-graft adaptation, since the phenomenon of vigorous secondary rejection has been encountered only once."

In that series there were 10 patients treated in late 1962 and early 1963. In seven, including the first one treated with irradiation and mentioned earlier, clear cut rejection of variable intensity occurred from 4 to 34 days after operation (Fig. 2), in one case actually leading to anuria. In each instance, the process was reversed by the addition of massive doses of prednisone to the pre-existing therapy with azathioprine (Fig. 2). Three of these seven patients are still alive 14 or more years later and are now among the longest living recipients of non-twin homografts in the world. After the remarkable effectiveness of steroid therapy in this situation had been established from our own experience, but before our findings were published, it was learned that the same kind of observation had been made by Goodwin and his associates[12] in a young woman who ultimately died of sepsis 144 days after receipt of a maternal homograft.

The reversibility of rejection in these patients was only one of the features which established the clinical feasibility of organ transplantation. The quantities of adrenal corticosteroids necessary to achieve reversal were often too large to be compatible with long survival of the recipient if continued indefinitely. Fortunately, another event of equal practical importance transpired coincidentally with the reversal of rejection or shortly afterward. With the passage of time, the need for intensive therapy usually diminished both in patients who did and those who did not pass through a clinically evident rejection. Thus, the patient whose course is depicted in Figure 2 had returned within five months after transplantation to treatment only with azathioprine, a drug which at the outset did not prevent the onset of a moderately severe rejection. An ultimate similar reduction in drug requirement is seen today in almost all new successfully treated recipients and it is probable that some patients could eventually have all therapy stopped. In our laboratory, we have had dogs live for 10 to 12 years after being given treatment with immunosuppressants only for the first four postoperative months.

The foregoing phenomenon of graft acceptance is not understood (see discussion in reference 42, p. 229). However, there is little reason to doubt that a homograft becomes more or less privileged if it can be kept alive through the initial onslaught of rejection. This fact is at least partly responsible for the shape of life survival curves after renal homotransplantation in that the preponderant mortality is in the first few postoperative weeks or months when stringent immunosuppression is required. It has strongly influenced the way in which new therapeutic agents such as heterologous antilymphocyte globulin (ALG) have been used clinically, and it has been a prime stimulus for the extension of transplantation techniques to organs other than the kidney in which both reversal of rejection and "adaptation" are not very different from what they are with the kidney.

In any event, the numbers of successful cases grew rapidly during the spring and summer of 1963. By the first week of September, 1963, when an international meeting was convened at the National Research Council, 2101 Constitution Avenue, Washington, D.C., to consider the past and future of renal transplantation, our Colorado series of kidney recipients was up to 27. In preparation for this meeting on September 26 and 27, 1963, the 2½ × 3½ foot wall flow sheets from all of these patients were gathered together with the aid of Tom Marchioro, now Professor of Surgery at the University of Washington, Seattle, and bound between soft leather covers like Egyptian scrolls. These were carried by Bill Waddell and me to Washington.

I remember the surprise, if not incredulity, that greeted our report of a very high survival rate (20 of the 27 patients were alive) with so many examples of essentially normal renal homograft function. The book of flow sheets promptly found itself on the center conference table under close scrutiny. The recorded proceedings of the meeting contained much lively, provocative and friendly discussion which would have made interesting reading, but very little of the spirit of that meeting survived to make its way into print.[18]

On the last evening of the conference, Dave Hume of Richmond and Kendrick A. Porter of London came to my hotel room. We spent almost all the night going over each of the Colorado cases. As soon as the meeting finished, Porter and Roy Calne came to Denver where a further exchange of information and ideas took place.

Realizing the unique value of our cases, I had already started to write a book based on the University of Colorado clinical material. Before he left Denver, Ken Porter had agreed to prepare a section on the histopathology of renal homotransplantation. His chapter became a monograph in its own right (see reference 41, pp. 299–359) to which surprisingly little has been added in the intervening years. Porter and I have maintained a fruitful collaboration since then.

By the time the book was finished the following May, the series had increased to 64. Today with follow-ups of 13 to almost 15 years, about one-half of that original group are still alive. A great number of original observations were made possible by the chance to watch this bellwether group of patients and those were summarized in the book. The operative techniques for renal transplantation in adults as well as children were standardized. The rules of acceptable transfer of tissues between donors and recipients of different blood types were established, and it was shown that violation of these rules could lead by the action of preformed recipient an-

tibodies (in this case isoagglutinins) to what later became known as "hyperacute rejection." The first widely used techniques of organ preservation were introduced, consisting of cooling of the excised organs by infusion with cold solutions. More sophisticated methods of preservation, including cadaveric whole body perfusion, were introduced. The requirements and techniques of infectious disease control were standardized. A limited, informative, but ultimately unsuccessful trial of renal heterotransplantation using baboon kidneys was undertaken. A comparison of the fate of these baboon heterografts with that of Reemtsma's chimpanzee heterotransplantations show that the chimpanzee would be a better donor if animals are used for this purpose in the future.

By the spring of 1964, the basic care of kidney recipients under double drug immunosuppression had been standardized in much the mold that is so familiar today. Further developments have occurred. Most importantly, the supply of high quality organs has been greatly increased by the wide acceptance of irreversible brain injury as the ultimate definition of death rather than the cessation of heartbeat.[9]

The importance of these changes in social and legal attitudes has been amplified by research in organ preservation. In 1967, Belzer and his associates in San Francisco described ex vivo perfusion methods with plasma derivatives that allowed the preservation of kidneys for two or three days.[2] Not long after simple flush techniques using cold electrolyte solutions of intracellular composition (containing high potassium and high magnesium) were introduced that allowed successful refrigeration for 24 to 48 hours.[8] With these improvements in organ preservation, renal transplantation became an elective undertaking in comparison to the urgent conditions which had been necessary before.

In tissue typing, there were great expectations in the middle and late 1960's. The first retrospective as well as the first prospective attempts at HL-A tissue typing in kidney recipients were inaugurated in a collaboration with Dr. Paul Terasaki of Los Angeles.[50] Unfortunately, the fuzzy correlations of HL-A matching and the outcome in all except perfectly matched sibling cases indicated that the tissue typing issue was much more complex than had been appreciated. The use of tissue matching to identify good sibling combinations has been useful. But from a practical standpoint the most important matching procedures today are the direct crossmatches which avoid placing a kidney into a recipient who possesses preformed antigraft antibodies. The first lessons about the harmful effects of preformed antibodies were learned with blood group mismatches in which antired cell isoagglutinins triggered hyperacute rejection.[41] Not long after, the devastating effects of preformed cytotoxic antibodies were described by Terasaki et al.[49] and Kissmeyer-Nielsen et al.[21]

In 1966, we introduced what has since been called a triple drug program of immunosuppressive therapy adding antilymphocyte globulin (ALG) to azathioprine and prednisone. ALG consists of antibodies raised in animals against human lymphocytes. The regimen of ALG which was used in man was guided by several general conclusions that emerged from the experimentations with large animals in our laboratories and elsewhere.[24, 43] These can be summarized as follows: (1) ALG had potent but imperfect immunosuppressive qualities when used alone; (2) with continued administration of the heterologous serum derivatives there was a highly significant risk from a variety of foreign protein reactions; and (3) ALG could be used effectively and probably with increased safety in combination with other drugs. Each of these factors contributed to the initial decision to employ heterologous ALG as an adjuvant agent added to therapy with azathioprine and prednisone and to limit its use to the first four postoperative months. It was hoped that the predictability and safety with which homograft rejection could be prevented would thereby be improved and that the hazards of immunologic reactions to the serum products would be accordingly reduced with the efficient level of immunosuppression to which all three agents would contribute.

These basic tenets have been used in all the modifications of the triple agent program that have been used since that time. The original trial of the ALG was given intramuscularly but the intravenous route is usually used now. Questions are incompletely answered about the best kind of lymphoid antigen and the most appropriate animal in which to raise the antilymphocyte antibodies as well as the

Table 1. *Experience with Renal Transplantation at the University of Colorado, 1962–1975*

SERIES	NO. OF CASES: Related	NO. OF CASES: Unrelated*	DATES	FOLLOW-UP TO AUG 1976 (YEARS)	MAIN FEATURE
1	46	18	Nov 1962 to Mar 1964	12⅓–13¾	Azathioprine/prednisone; good risk
2	25	23	Oct 1964 to Apr 1966	10⅓–11⅚	Azathioprine/prednisone + typing; good risk
3	60	17	June 1966 to Feb 1968	8½–10⅙	Azathioprine/prednisone/ ALG; good risk
4	122	15	Mar 1968 to Mar 1971	5½–8½	Azathioprine/prednisone/ ALG; all risk
5	44	28	Mar 1971 to Aug 1972	4–5½	Cyclophosphamide/prednisone/ALG; all risk
6	65	49	Aug 1972 to Aug 1974	2–4	Azathioprine/prednisone/ ALG; all risk
7	27	17	Sept 1974 to Aug 1975	1–2	Azathioprine/prednisone/ ALG; all risk

*Since late 1965, all unrelated kidneys have come from cadavers. Before then, nonrelated volunteer donors were used.

correct dose and timing of the ALG (see discussion in reference 42, pp. 207–216). For that matter, a number of authors have contended that ALG does nothing in improving immunosuppression that could not be achieved equally by the clever manipulation of steroid and azathioprine doses.

In spite of this skepticism, most of the reports of controlled studies with ALG have shown a higher rate of kidney survival, fewer rejections and at least equal patient survival. At the International Transplantation Society meeting in September, 1976 (New York City), there was a stronger consensus than at any time in the preceding decade that ALG was a useful clinical adjunct.

The only other major immunosuppressive agent that has been used extensively has been cyclophosphamide. In 1970 and 1971 we showed that in large series in which cyclophosphamide replaced azathioprine as part of a double or triple drug program, the results were essentially the same with either drug.[48] Although the results were no different from those obtained with azathioprine, we have since returned to the routine use of azathioprine because of our much greater experience with it and because of our high degree of satisfaction with its use.

Table 2. *Actual Survival at One Year and Thereafter in Patients Given Primary Related Grafts from 1962 to 1975*

SERIES	NUMBER OF CASES	PER CENT SURVIVAL: 1 Year	2 Years	4 Years	8 Years	10 Years
1	46	67	65	61	57	52
2	25	64	64	52	40	40
3	60	92	88	78	67	
4	122	76	73	68	—	
5	44	86	80	74	—	
6	65	77	75	—	—	
7	27	89	—	—	—	

Table 3. *Actual Survival at One Year and Thereafter in Patients Given Primary Nonrelated Grafts from 1962 to 1975*

SERIES	NUMBER OF CASES	PER CENT SURVIVAL 1 Year	2 Years	4 Years	8 Years	10 Years
1	18	33	22	17	11	11
2	23	52	43	30	17	13
3	17	82	76	41	29	—
4	15	80	80	80	—	
5	28	75	75	61	—	
6	49	82	71	—	—	
7	17	94	—	—	—	

The immunosuppressive protocols developed at the University of Colorado and the patients treated are listed in Table 1. The results of this experience brought up to date to August, 1976, were presented at the 1976 meeting of the International Transplantation Society, have been recently published, and are summarized in Tables 2 and 3. The greatest improvement in recent years has been survival after cadaveric transplantation (Table 3) and, in turn, this is explained by a greater willingness to abandon an initial homograft and to consider return to dialysis or retransplantation. At the present time, recipients of either related or unrelated homografts are surviving for one year at about an 80 to 90 per cent rate and about three-fourths are still alive at the end of 4 years.

CLINICAL LIVER TRANSPLANTATION

Looking back at the Colorado scene of the early 1960's, it was inevitable that transplantation of the liver would be performed. Optimism was high because of the success of double drug immunosuppression in controlling renal homograft rejection. The assumption was made that the same therapy would be applicable for other organs, a view that was proved correct both in animals and man.[42] Finally, the ability to carry out liver transplantation had been assiduously developed in research involving hundreds of dogs during the preceding 5 years and was known to be within our technical capability. Thus, a policy decision was made in early 1963 to proceed with orthotopic liver transplantation, an operation which requires removal of the diseased native organ and its replacement with a cadaveric graft (Fig. 3).

The first 4 attempts were made in 1963 on March 1, May 5, June 24, and July 16. A fifth patient was treated by Francis Moore in Boston on September 16, 1963, followed by another in Denver on October 4, 1963 (all early cases in Denver and elsewhere are catalogued in reference 42, pp. 530–532).

Our first recipient bled to death during the operation; the other 4 first Denver patients survived operation but died from 6½ to 23 days later. Success was nearly achieved in some of these cases.[44] For example, our second patient, a 48 year old male with cirrhosis and a hepatoma, was in remarkably good condition postoperatively. He died 22 days later of systemic and pulmonary infection. At autopsy there were no serious complications in the abdominal cavity. The liver had no unequivocal findings of rejection. Biliary duct reconstruction with choledochocholedochostomy over a T-tube was satisfactory (Fig. 3). Portions of both lungs were necrotic. The pulmonary arteries contained multiple old clots. Apparently, these were deposited at the time of operation from a plastic bypass tubing that had been used to return blood from the vena caval and splanchnic venous pools while these systems were obstructed during the intraoperative anhepatic phase. Ironically, it was later proved that such temporary bypasses are unnecessary because of the well developed venous collaterals in end-stage liver disease.[12]

The series of consecutive early failures caused a moratorium of 3 years to be declared on further cases. Only one more patient was treated at our center until the summer of 1967. The justification to then start another series came from experience with the triple drug immunosuppressive program (including ALG) which by then seemed to be helping the kidney recipients. On July 23, 1967, the chance presented to treat a 1½ year old girl who had a hepatoma. She lived through the operation of liver replacement and for 13 months afterward before finally dying of widespread tumor metastases. Each of the next 8 recipients lived for at least 2 months postoperatively, and 3 of these 8 lived for more than one year with the longest survival of 29 months and 16 days.

The first 25 liver recipients in the Colorado series eventually provided the experience for a text of liver transplantation.[42] Five of these 25 patients lived a year or more. The feasibility stage of human liver transplantation had been passed, but with a one-year mortality of 80 per cent, widespread exploitation of the procedure was a long way off.

Nor was there a quantum improvement in the succeeding 7 years. The patients surviving for one year in the second, third, and fourth groups of 25 patients each were only 6, 8, and 9, respectively. However, one of these recipients is now 7⅓ years postoperative and a total of 6 have lived more than 5 years; 5 of these 6 are still alive.

During a sabbatical leave in 1975 and 1976, I had an opportunity to live in London and to work with Professor K. A. Porter whose collaboration was described earlier in this article. Together, we reviewed the first 93 cases of orthotopic liver transplantation and tried to recatalogue the main reasons for failure. Our conclusions were that:[47] (1) uncontrolled rejection was a relatively uncommon cause of mortality; (2) technical mistakes and mechanical problems with the homografts accounted for the greatest numbers of deaths; and (3) if the complications were of duct reconstruction they frequently caused untreatable infections.

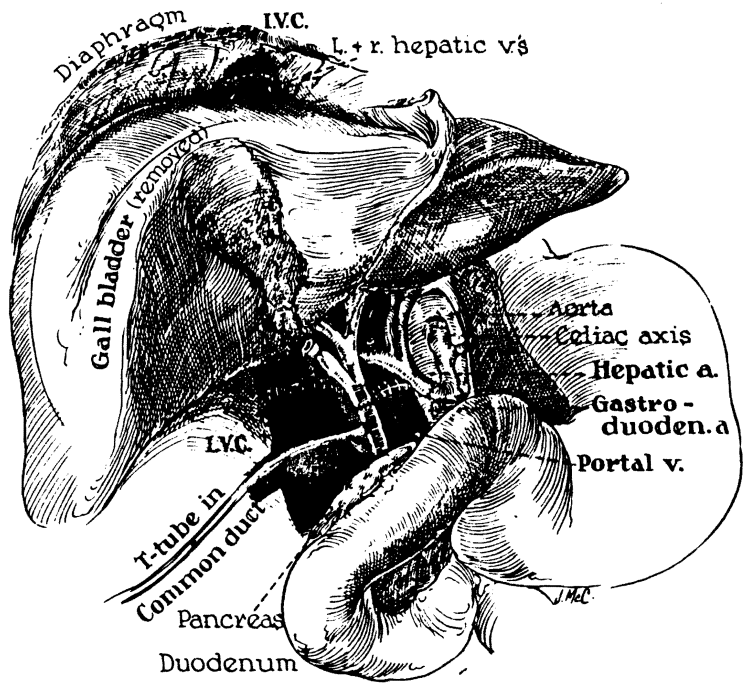

Figure 3. Orthotopic liver transplantation with biliary duct reconstruction by choledochocholedochostomy after cholecystectomy. Other acceptable techniques of biliary reconstruction involve anastomosis of the homograft gallbladder or common duct to a Roux-Y jejunal limb.

Better management guidelines were developed based on more accurate diagnosis with emphasis on frequent needle biopsies and transhepatic cholangiography, avoidance of overimmunosuppression while using the triple drug therapy, and better technical performance at the original operation. The most fundamental technical adjustment was to perform biliary duct reconstruction with choledochocholedochostomy over a T-tube stent (Fig. 3), or by anastomosis of a Roux-y jejunal limb to the graft gallbladder or common duct. The various changes were completed and standardized by late spring, 1976.

Since then, 19 more patients have had liver replacement. With follow-up periods of 3 weeks to 12 months, 14 of the 19 recipients are alive. The 4 postoperative deaths have been due to rejection (one example), inability to revascularize the liver due to recipient portal vein thrombosis (one example), subhepatic infection with erosion into the hepatic artery (one example), bone marrow depression with pneumonitis (one example), and uncontrollable heart failure (one example). The expectation now is that more than one-half and possibly as many as two-thirds of the modern day liver recipients are going to survive to the one-year mark. The same improvement in recent results has been noted also by Calne and Williams working in England.[6]

One of the major by-products of liver transplantation has been new insight about the effect of portal blood and its so-called hepatotrophic constituents on liver structure, function, and the capacity for regeneration. This new area of research was opened during inquiries into the optimum means of revascularizing auxiliary liver homografts while leaving the native organ in place.[23] The essence of portal hepatotrophic concept is that the liver is controlled or influenced profoundly by hormones coming from the venous effluent of splanchnic viscera into the portal vein. Insulin is the most influential of these hormonal factors, although not the only one. From a practical point of view and as it relates to transplantation, the implication is that the portal vein of an auxiliary liver should be supplied with splanchnic venous blood if it is to have an optimal chance of survival.

Auxiliary liver transplantation was first attempted in humans by Absolon et al.[1] and was also given a brief trial at our center.[42] The only person to definitely benefit from this procedure so far has been a child cared for by Dr. Joseph Fortner of New York who is now 4 years after auxiliary transplantation for biliary atresia. We have not performed this operation for several years.

OTHER ORGANS

The dramatic extension of basic transplantation concepts to heart replacement, lung transplantation, and pancreatic transplantation are well known and beyong the scope of this article. We have carried out 7 heart transplantations with the longest survival of 29 months. Several years ago, a decision was made not to do more cardiac cases since our trials did not add to the developmental efforts of the Stanford team headed by Norm Shumway and Ed Stinson.

Unresolved Problems

The great wave of successful renal transplantations in the early 1960's and the prompt demonstration that extrarenal organs could also be transplanted in humans led to a mood of exhilaration seldom tempered by a cautionary note. Although the situation was acknowledged to be imperfect, it was widely believed that new and fundamental developments with which to correct any deficiencies were close at hand. Indeed, as was already stated, many advances were subsequently made in surgical techniques, in organ preservation, and in understanding the complexities and limitations of tissue typing.

However, growth arrest has occurred in the one area that gives transplantation uniqueness and that is central to a myriad of complications which organ recipients must still face. The main problem area remains immunosuppression and from this combined with the impracticality of donor selection by tissue typing stems two therapeutic deficiencies.

First, the predictability of treatment is imperfect. A reasonably accurate prognosis can be offered only to recipients of perfectly matched sibling kidneys. But

even here there is an occasional unexpected graft loss from rejection that cannot easily be explained despite intensive retrospective study. Using relatives other than perfectly matched sibling donors, the predictability of rejection control is substantially less. When cadaveric organs are transplanted, some patients have uncontrolled rejection, others have no difficulty at all, and about half are intermediate between these extremes. Although the exact success rate after cadaveric kidney transplantation is influenced to some extent by the inclusion or exclusion of candidates who have a high risk because of advanced age, coincident disease, or other factors, kidney survival at one year using any of the presently employed regimens is seemingly more or less fixed at about 50 to 70 per cent in all the world's great transplantation centers.

The second general defect is related to the first. At the present time, even patients who eventually achieve a perfect transplant result often must first pass through a postoperative period of significant morbidity. The requirement for intensive immunosuppression is greatest early after transplantation. Because the steroids are the only highly dose-maneuverable component of the immunosuppressive regimens presently employed, the intensification of therapy translates inevitably into larger quantities of prednisone. If high-dose steroid therapy can be avoided or kept to a brief duration while at the same time maintaining good homograft function, the result is apt to be spectacularly successful. If steroids are needed chronically, their well-known side effects depreciate the value of post-transplantation life or may threaten survival itself if the doses are too high.

Although the drug combinations that include azathioprine, prednisone, cyclophosphamide, and ALG have evolved into well standardized double- or triple-drug cocktails that have been used the world over, all are variations on the same theme. Further small adjustments in dosage and schedule are not going to correct the deficiencies of transplantation just mentioned. Some drastic changes in approach are going to be needed. The objective is a foreshortening of the graft acceptance process, so that the transplant passes through the danger period in a few days instead of a few weeks or months.

The first step to accomplish this is to acknowledge that our present methods of treatment represent only a halfway station toward an acceptable final regimen. Some kind of tolerance induction or the effective use of enhancement procedures might be made easier if better drugs were found but no hint of a breakthrough in any of these areas is evident at present.

Nevertheless, a high order of patient service can be provided today with renal transplantation despite the limitations of immunosuppression. The reason is that it is so easy to return patients to chronic dialysis if too much immunosuppression is required to retain homograft function. The same is not true for the liver, heart, and lung, for which artificial organ backup is not available. Using these organs, transplant and patient survival are nearly synonymous.

With the heart, the transplantation itself presents no troublesome technical problems, and in Shumway's magnificent series the life-survival curve reflects very accurately the ability to control cardiac rejection. The one-year survival has edged up to above 50 per cent in the Stanford series. As described earlier, a similar steady improvement has been seen with the immunologically easier but technically more difficult liver. Very little work is now going on with the lung.

With both the liver and lung, it is unlikely that a clear distinction between technical, infectious, and rejection problems will be possible until a much more reliable method is available for the promotion of graft acceptance. Then if something goes wrong it can be assumed that rejection is not the cause. Today the obverse assumption that rejection is responsible must always be made.

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