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Organ Transplantation, Past and Present

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There can no longer be doubt that transplantation of tissues and organs will be practiced with increased frequency and success in the future. The number of patients who have been returned to a useful place in society after renal homotransplantation has risen steadily since 1962.* Clinical transplantations of the liver,^{11, 49, 62, 63, 72} lung,^{17, 40, 88}

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heart,^{16, 32, 33} spleen^{41, 69} and pancreas²⁷ have also recently been undertaken.

Progress in various areas of transplantation research has been summarized in several books, monographs and special issues of journals^{5, 10, 12, 38, 58, 61, 86, 87} and will not be recapitulated here. Instead, attention will be focused upon several specific questions that pertain to transplantation of the kidney and liver, but that probably also have relevance to the transplantation of other organs.

KIDNEY TRANSPLANTATION

The Fate of the Chronically Tolerated Homograft

Between November 1962 and March 1964, 64 patients were treated in Denver with renal homografts obtained from healthy volunteers. The 30 recipients (47 per cent) in this group who are still alive have now been followed for 4 to 5 $\frac{1}{3}$ years.

It was evident from the beginning that the principal mortality was early (Fig. 1) and that a patient who survived with good homograft function beyond the first few postoperative months had an excellent chance of living for a significant although then unknown period. The data now available on these cases permit a much clearer projection of what patients treated more recently and more successfully brought through the early postoperative period can expect in terms of 5-year outlook.

The picture has remained encouraging in cases in which intrafa-

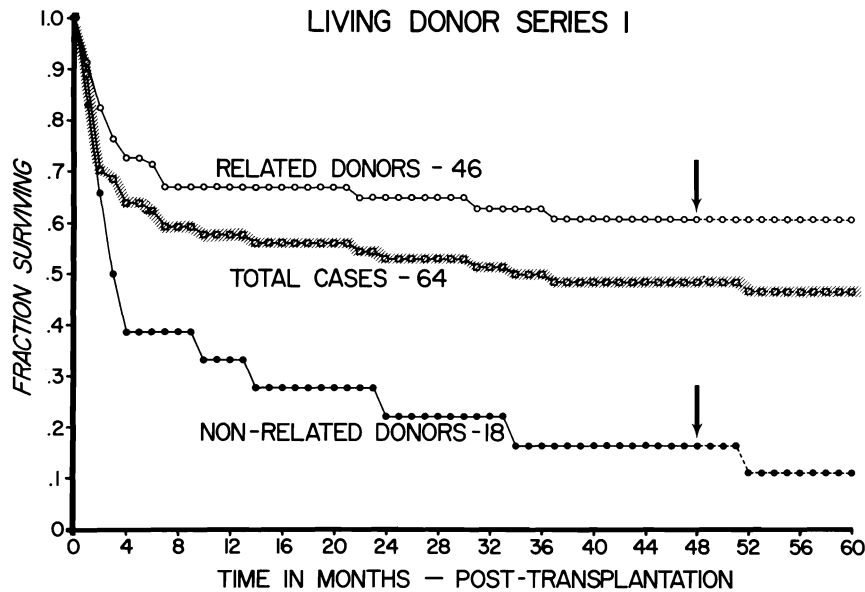


Figure 1. Life survival curves of 64 patients treated in Denver with renal homograft transplantation between November 1962 and March 1964. Preoperative histocompatibility testing was not done. The vertical arrows indicate the time of minimum followup.

mial transplantation was the original procedure. There were 46 recipients of consanguineous kidneys. Of these, 15 died within the first year, but only 1, 1, and 1 were lost during the second, third, and fourth postoperative years (Fig. 1). The present survival after 4 to $5\frac{1}{3}$ years is 28 of 46 (60.9 per cent). None of the 28 patients have received late retransplantation, and none have been returned to dialysis programs. The function of these chronically tolerated homografts has been shown by Ogden⁵³ to be generally almost as good as the contralateral kidneys left in their donors.

With recipients of nonrelated homografts, the picture was not as good. There was a higher rate of early mortality inasmuch as 12 of the 18 patients in the series died within the first year. Furthermore, a steady mortality rate continued thereafter. Two more patients died in the second postoperative year, as well as two others who reached 33 and 51 months. Now only two of the original 18 recipients are alive, one by virtue of a second homotransplantation $2\frac{1}{2}$ years after the first. The other patient has had continuous excellent function from his nonrelated homograft for more than 4 years.

The foregoing observations in a large series of transplantations have made it clear that survival for several years can often be attained, particularly if related donors can be found. However, it can hardly be expected that most of these homografts will function for a normal lifetime since the presence in them of serious structural abnormalities is the rule rather than the exception. This conclusion was reached by Dr. K.A. Porter of St. Mary's Hospital and Medical School, London, on the basis of examination of 2-year renal biopsies obtained from all Denver patients who survived this long.^{56, 57}

An occasional homograft was completely normal. However, in the others there were pathologic changes that were not always reflected in impairment of renal function. There were vascular lesions including fibrous thickening of the intima of interlobular arteries often with rupture or duplication of the internal elastic lamina; deposition of a hyaline-like substance in the subintimal layer of afferent arterioles (Fig. 2); and deposition of the same PAS-positive hyaline material in the glomerular capillaries. The last finding has been shown by Harlan et al.¹⁸ to often be associated with a nephrotic syndrome.

The homografts with vascular lesions often had other secondary morphologic changes including fibrosis of the glomerular tufts, spotty periglomerular fibrosis, interstitial fibrosis or tubular atrophy. The majority of homografts also contained focal accumulations of mononuclear cells. Ten to 40 per cent of these cells were pyroninophilic, the variety found in acutely rejecting homografts. In the chronically functioning homografts, the presence of such cells was not incompatible with good or even normal function.

Further studies with immunofluorescence techniques and with ferritin-conjugated antisera by Porter and his associates have shed additional light on some of the foregoing changes.⁵⁶ The deposits in the subendothelial layers of small vessels and glomerular capillaries were shown to contain host antibodies, particularly in the IgM class but also often including complement, IgG and fibrinogen. These were con-

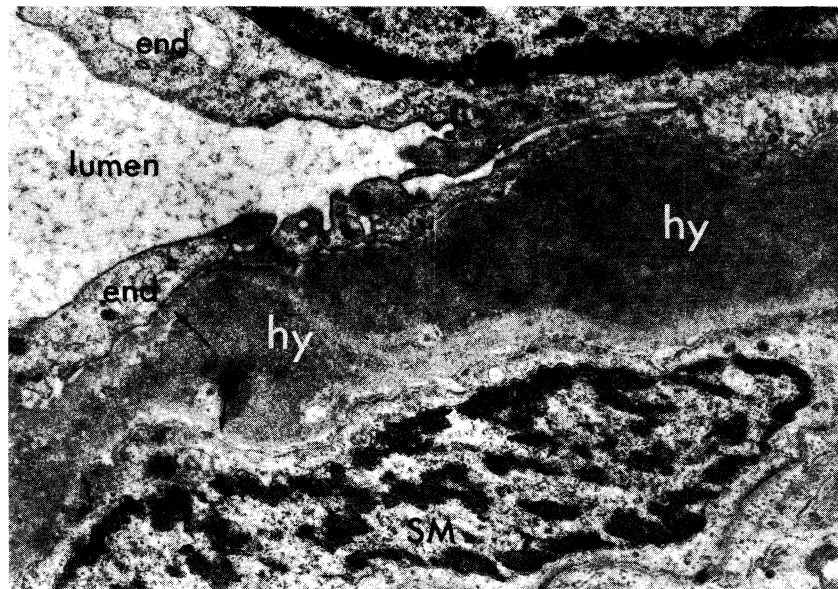


Figure 2. Typical arteriolar lesion in a renal homograft biopsied 1 year and 9 months after the original operation; the patient has had no deterioration in renal function in the subsequent 3 years. The lumen is indicated at the upper left. Granular hyaline material (*hy*) is deposited between the endothelium (*end*) and the smooth muscle (*sm*) of the vessel. Electron micrograph. Phosphotungstic acid ($\times 16,800$). (By permission of *Ann. Surg.*, 162:749, 1965).

sidered to represent the reaction of circulating host antibodies with antigens in the capillary basement membranes of the transplanted kidney.

In three exceptional grafts, the deposits were nodular and were along the subepithelial side of the glomerular capillary basement membranes. The authors suggested that these were caused by the transmission of active glomerulonephritis from the recipient to the homograft.⁵⁶ Morphologic evidence that this sequence of events was possible had previously been published by O'Brien and Hume³² and Petersen et al.⁵⁵ More recently, Lerner et al.³⁶ conclusively showed that anti-glomerular basement membrane (anti-GBM) antibodies present in the serum of a patient with active glomerulonephritis can fix to and adversely affect a subsequent transplanted homograft. Presumably, this complication could be avoided if patients with acute or subacute glomerulonephritis were subjected to preliminary nephrectomy, and transplantation were deferred until recipient serum levels of anti-GBM antibody disappeared.

The possibility that many, or even most, renal homografts will gradually fail is not a serious argument against further clinical transplantation. The degree of social and vocational rehabilitation in the interval of satisfactory kidney function is usually relatively complete. Moreover, it is now known chiefly as the result of Hume's work²³ that retransplantation for the indication of a failing first homograft can be done with reasonable expectation of success. This expedient was considered too late in some patients in our early series who died with diminishing renal function long after operation.

Histocompatibility Typing

During the time that the first Denver series was accumulated, there were no practical methods of predicting the vigor or tenacity of the anticipated rejection process. It was quickly recognized that red blood cell group incompatibilities between donors and recipients could lead to immediate loss of the transplanted kidneys, from which experience the now widely accepted rules were formulated^{61, 67} concerning tissue transfer between people of different ABO types (Table 1). Since other preoperative analyses of donor-recipient compatibility were not available, the transplantation itself became a test system in which, presumably, the recipients of biologically unfavorable kidneys were ruthlessly weeded out by early mortality. It was decided to retrieve the information derived from this unacceptable situation and to use it to try to improve donor selection for future cases. The effort involved collaboration with Dr. Paul Terasaki of Los Angeles and Dr. K.A. Porter of London. In the meanwhile, a six month moratorium on new cases was declared.

For years, Terasaki, Dausset, Payne, van Rood, Ceppellini, Amos, and others²⁰ had worked with a variety of serologic techniques on the characterization of the antigens contained in leukocytes. These workers were convinced that most antigens in renal and other tissue were also present in the readily accessible peripheral lymphocytes. By studying the lymphocytes of prospective donors and recipients, they hoped that an idea could be obtained of their general tissue compatibility. Unfortunately, there was at that time no proof that the antigen systems under investigation had any relationship to histocompatibility, and it was to establish this point that the Denver patients were employed.

First, Terasaki analyzed the antigenic constitution of a number of surviving recipients and their donors using his lymphocyte cytotoxicity test. The quality of the matches was graded and compared with clinical rankings accorded by those caring for the patients. The correlation was imperfect. It was evident that many patients had retained good homograft function for long periods in spite of what appeared to be poor matches with their donors. Nevertheless, most of the really superior clinical results were in patients who had received exceptionally well matched kidneys.^{70, 81} Later, a far more striking correlation was found between the Terasaki results and the degree of histologic injury noted by Porter in the two year biopsies mentioned in the preceding section.⁵⁷ Subsequent reports from other centers have supported the view that lymphocyte antigen determination is an incomplete but potentially useful way of assessing histocompatibility.^{7, 34, 54, 59, 74, 80, 83}

Table 1. Direction of Acceptable Mismatched Tissue Transfer*

O to non-O	Safe
RH - to RH +	Safe
RH + to RH -	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*O is universal donor; AB is universal recipient.

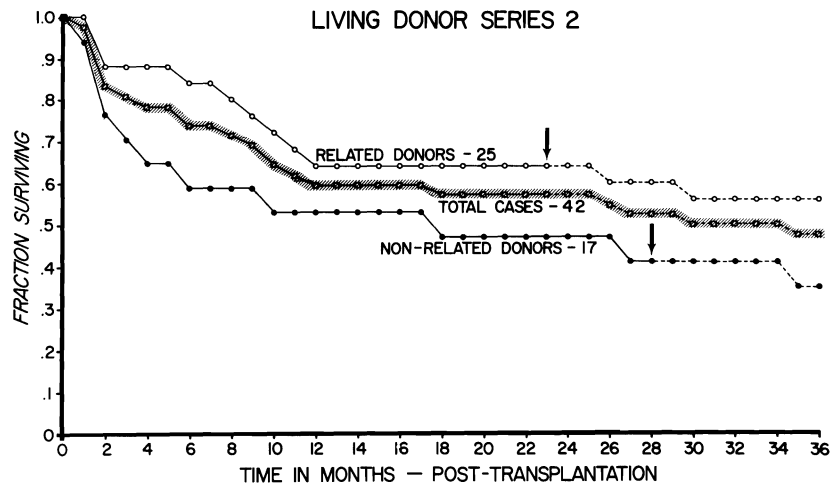


Figure 3. Survival of 42 patients treated with renal homotransplantation between October 1964 and April 1966. An attempt was made by Terasaki to select the most compatible donor among available volunteers. See text for discussion of results.

Although much of the previously cited support for the validity of antigen typing was not available in 1964, there was enough favorable evidence to warrant a prospective clinical evaluation. When transplantation was resumed in October of that year, an effort was made by Terasaki to find the best possible donor among the volunteers available for each patient.

The selectivity was severely limited in most cases of intrafamilial transplantation. In most instances, only one or two blood relatives were willing to donate or were acceptable on general medical or psychiatric grounds. Consequently, the matching was not improved to a statistically significant degree over that which could have been achieved with random intrafamilial pairing.⁷⁸ It was not, therefore, surprising to find that the life survival curve in these related cases (Fig. 3) was almost identical to that defined in the earlier Series I. Of 25 recipients, 16 (64 per cent) were still alive at one year. Two more subsequently died after 26 and 30 months, leaving a residual group of 14 (56 per cent) with a followup of 23 months to 3½ years.

In the 17 nonrelated homotransplantations, the donors were picked from a pool of as many as 80 volunteers. Perfect matches could not be found, but the quality of the pairing was improved over that which could have been expected by chance.⁷⁸ The recipients fared better than those previously observed in Series I. Nine (52.9 per cent) of the 17 recipients were still alive at the end of the first year (Fig. 3). Three more patients were lost at 18, 27 and 35 months respectively, but in two there was life-sustaining renal function until death. Six of the 17 patients (35.3 per cent) are still living with good to excellent function of their original homografts 28 to 40 months after transplantation. The mean creatinine clearance in the remaining group is 83.4 ± 26.2 (SD) ml./min.

In both related and nonrelated cases, observations were similar to those made retrospectively in Series I. Several recipients of poorly

matched kidneys fared surprisingly well. A few patients with good matches experienced vigorous and prolonged rejection. The preponderance of the best results, however, were in patients with close antigen matches with their donors.

The failure to improve survival in the related transplantations or to increase it more in the nonrelated cases was a keen disappointment since evidence from many investigators now suggested more strongly than ever that the tissue typing being used provided a measure of histocompatibility.^{7, 34, 54, 59, 74, 80, 83} It seemed that safer methods of immunosuppression would be required before histocompatibility typing could receive a fair trial. This point was particularly well illustrated by an experiment carried out in our laboratories by Dr. Thomas L. Marchioro. He performed autotransplantation in 18 dogs. Postoperatively, the animals were given immunosuppressive therapy just as if they had received homografts. Despite the absence of an immunologic barrier, the life survival curve of the recipients was similar to that described previously after human renal homotransplantation. There was an early high mortality rate and a later occasional death (Fig. 4); after 1 year, less than half the animals were still alive. Most deaths were caused by infectious disease complications.

It has been recognized for several years that many and possibly most deaths after clinical homotransplantation are due to drug toxicity. At the beginning, bone marrow depression from overdoses of azathioprine was common, but with increased experience this complication is

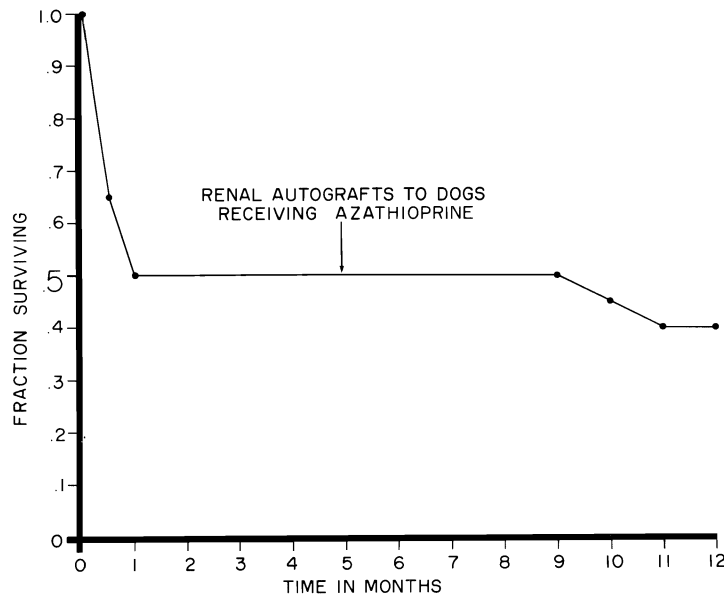


Figure 4. Survival of 18 dogs receiving renal autotransplantation followed by postoperative therapy with azathioprine. The drug doses were similar to those used after experimental renal homotransplantation. There was a high early mortality and an occasional late death. Most of the deaths were the result of infectious complications. Less than half of the animals were alive at 1 year. Note the similarity of the survival curves to those shown in Figures 1 and 3.

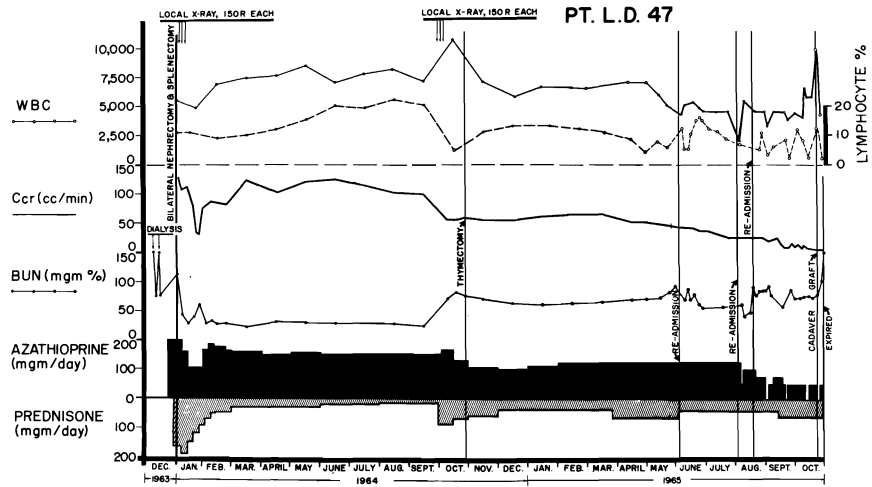


Figure 5. Course of a 37-year-old man (LD 47) who received a kidney from his younger brother. Both were A⁺ blood type. Note the severe late rejection after 9 months and the subsequent slow deterioration of renal function. The late thymectomy did not either induce lymphopenia or make the subsequent management easier; the post-thymectomy changes in lymphocyte counts were related to adjustments in steroid dosage. (By permission of Ann. N.Y. Acad. Sci., 129:605, 1966).

now rarely seen. Avoidance of the hazards of the steroid therapy that is usually combined with azathioprine has not been so simple. In many cases, continued function of a homograft is dependent upon continuation of unacceptably large quantities of prednisone for long periods. The complications that follow are exceedingly troublesome at best and lethal at worst. These include cosmetic deformity, bone demineralization often with spontaneous fractures, muscle wasting, arrest of growth in infants, fatty infiltration of the liver, pancreatitis, and gastrointestinal ulceration and hemorrhage. Most serious, however, is the consequent susceptibility to microorganisms of all types.

If the resultant infections are due to common pathogenic bacteria they can be treated effectively with properly chosen antibiotics. Very often, however, these are caused by fungi, protozoa or viruses for which specific therapy is not available. The tragic consequences are illustrated in Figure 5. This patient, who received a homograft from his brother, had an early rejection crisis followed by excellent renal function for the next 9 months. After the dose of prednisone was reduced to 10 mg./day, he had a delayed rejection, which was controlled by increasing the prednisone dose to a level from which subsequent withdrawals were not possible without further deterioration of kidney function. He died 15 months later but not primarily from renal failure. He had fatty infiltration of the liver, a duodenal ulcer and pancreatitis. There were cytomegalic inclusion viruses in the lungs and liver and diffuse pneumonitis due to *Pneumocystis carinii* and *Aspergillus fumigatus*.

Improvements in Immunosuppression

For the aforementioned reasons, intensive efforts have been made in a number of laboratories to develop new and safer immunosup-

pressive agents. The most encouraging results have been with heterologous antilymphocyte serum (ALS) and its globulin derivative (ALG). These biologic agents were first evaluated in animals by Waksman et al.⁸ and Woodruff and Anderson⁹⁵ for their ability to prevent rejection. Notable contributions have since been made by Monaco and Russell and their collaborators,^{13, 47, 48} Levey and Medawar³ and many others.

In our laboratory, the horse has been used as the source of immune serum.^{22, 68} After immunization with the lymphoid tissue of the species to be eventually treated (Fig. 6), the horses are bled and the serum is separated. Undesirable anti-red cell and anti-plasma protein antibodies are absorbed with donor species red cells and plasma or serum. The antilymphocyte antibodies in the IgG fraction of the horse serum can then be removed with several techniques. Initially, we employed ammonium sulphate precipitation for crude globulin extraction, but more recently pure IgG has been removed in bulk quantities by batch mixing with DEAE cellulose. The ALG can then be given by intramuscular injection.

The guidelines for the clinical use of heterologous ALG were provided by extensive investigations in dogs. The ability of the antidog-lymphocyte globulin to mitigate homograft rejection was easily and unequivocally demonstrated.^{66, 68} Nevertheless, protection was incomplete. In about a fourth of the animals, rejection proceeded as might have been expected in untreated animals. Its onset was delayed or occa-

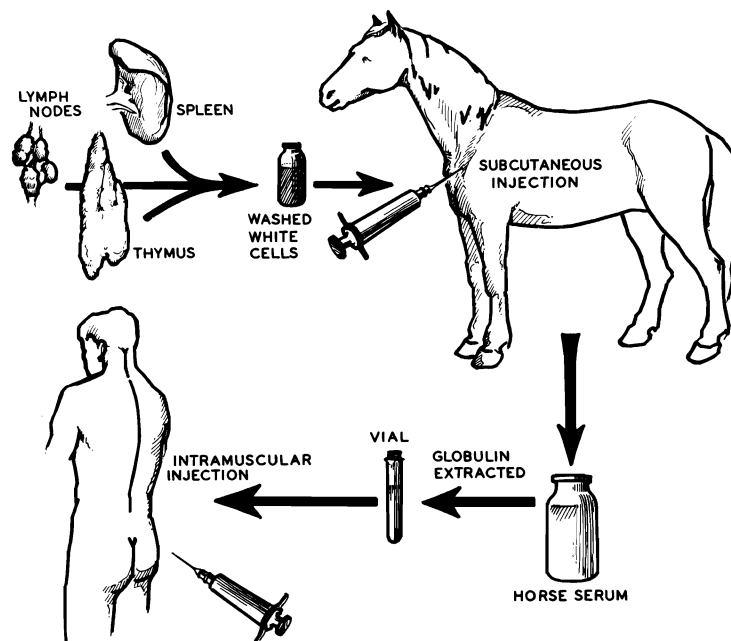


Figure 6. Schematic representation of the preparation of antilymphocyte globulin (ALG). The most convenient source of lymphocytes is the cadaver spleen. An adjuvant is not used for the horse immunization. There are several methods of globulin extraction as discussed in the text. The desired equine antibodies are thought to be in the IgG (7S) fraction of the horse serum.

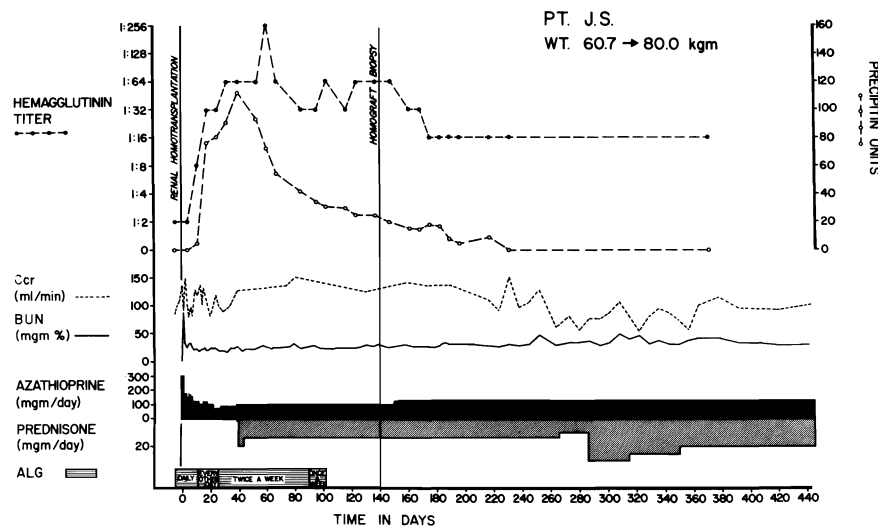


Figure 7. The course of a patient who received antilymphocyte globulin (ALG) before and for the first 4 months after renal homotransplantation. The donor was an older brother. The Terasaki match was a good one. There was no early rejection. Prednisone therapy was started 40 days postoperatively because of the high rises in the serologic titers, which indicated a host response against the injected foreign protein and which warned against a possible anaphylactic reaction. Note the insidious onset of late rejection after cessation of globulin therapy. This was treated by increasing the maintenance dose of steroids. This delayed complication was seen in only 2 of the original 20 patients whose survival is shown in Figure 8. (By permission of Surg. Gynec. Obstet.).

sionally prevented in the rest of the animals. However, survival of as long as 4, 8 or 12 months was observed in the minority of recipients of kidneys or livers. This spectrum of results was similar to that which can be obtained in dogs with other potent immunosuppressive agents such as azathioprine.

Other factors concerned with the toxicity of ALG influenced the therapeutic program finally adopted.^{24, 64, 68, 73} After long-term administration of ALG, the animals usually developed antibodies against the injected horse protein. Many of these dogs ultimately had microscopic renal lesions that consisted of deposits of horse protein, with host gamma globulin and complement; the findings were characteristic of serum sickness nephritis.²⁴

For these reasons it was decided to use ALG only as an adjunct to the standard immunosuppressive agents azathioprine and prednisone. The regimen ordinarily followed is shown in Figure 7. ALG was started a few days in advance of transplantation and continued daily for the first 10 to 14 postoperative days, then every other day for 2 weeks, twice a week for 2 months and once a week for a final month.

The first patient was treated in this way in June 1966. From then until the following December, 19 patients were added to the series. One patient died during the second postoperative month as the direct consequence of a technical surgical accident. The others are alive with good renal function from their original homografts 15 to 21 months later for a current survival of 95 per cent.

All these ALG-treated recipients received kidneys from blood relatives. The results are shown graphically in Figure 8 and compared with those obtained in previous intrafamilial transplantations in our institutions. For the latter purpose the consanguineous transplantations in the original Series I were divided into 2 consecutive groups, now termed Series IA and IB, to evaluate the effect of increased experience upon results. The intrafamilial homotransplantations described in the previous section on histocompatibility typing were Series II. In each of the consecutive earlier series the mortality rate in comparable followup intervals had been 28 to 31 per cent.

The probable explanation for the improved results in the ALG-treated patients is shown in Figure 9. During the time that the sequential earlier series were being accumulated, there was a progressive tendency to use smaller doses of azathioprine both during the first four and the subsequent six postoperative months. This trend continued into the ALG series. As the average doses of azathioprine were cut, however, compensatory increases in the quantities of prednisone were necessary to maintain a somewhat poorer quality of renal function (Fig. 9, middle and right). The result of the slowly evolving adjustments in policy was a change in the causes of death as described from our institutions by Hill et al.¹⁹ The early mortality from bone marrow depression and pyogenic infections was replaced by a delayed mortality, which was usually due to untreatable infections caused by unusual opportunistic microorganisms.

The situation was drastically reversed in the ALG-treated patients in that the average daily quantities of prednisone could be sharply lowered during the first 4 postoperative months when ALG was being given. Furthermore, the steroid doses remained at acceptably low levels in the next 6 months after the ALG had been stopped. The ability to

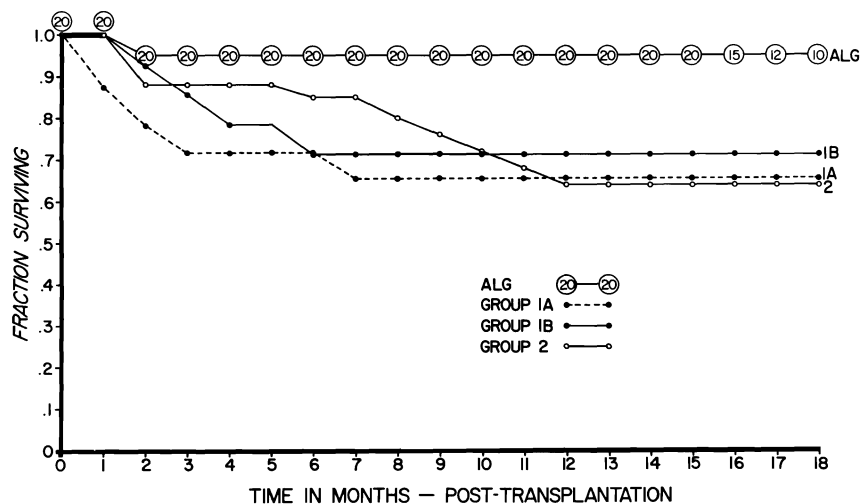


Figure 8. Survival curve of the first 20 patients treated with antilymphocyte globulin (ALG) compared to that in 3 previous series of consanguineous transplantations at our institutions. Follow-ups in the globulin-treated group are 15 to 21 months. The numbers in the upper curve indicate the patients at risk for each monthly interval.

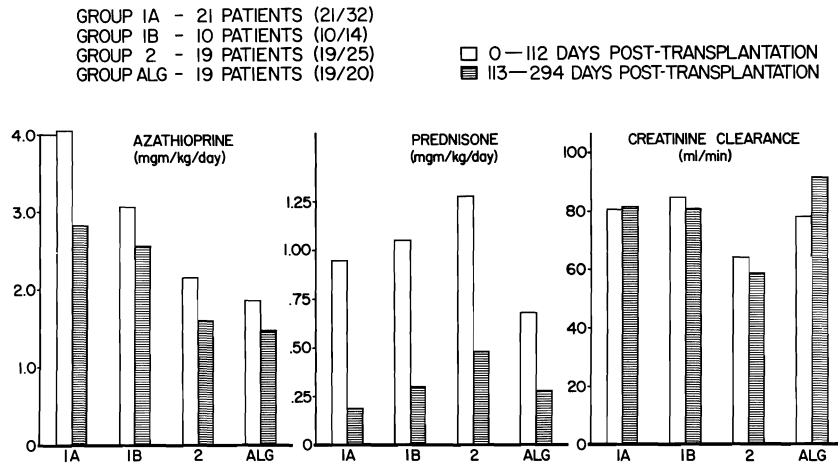


Figure 9. The average azathioprine and prednisone doses per kg. per day and the creatinine clearances for the first 16 postoperative weeks (shaded) and for the subsequent 6 months (solid). Shown are the retrospective control series (Groups 1A, 1B and 2) and the ALG series (Group 3). Inclusion in the analysis was contingent upon survival for 294 days, a condition which was met with the highest regularity in the ALG patients.

reduce the stringency of therapy with both azathioprine and prednisone was not at the expense of loss of renal function since all measures of renal function in the ALG-treated patients were at least as adequate as in the earlier series (Fig. 9, right).

The extremely favorable results of using ALG as compared to earlier series occurred in spite of a sharp bias introduced by the method of analysis. Inclusion of any case in the studies shown in Figure 9 was contingent upon survival for 10 months. A substantial number of the most seriously ill patients in each of the retrospective series were thereby eliminated by their death. Inasmuch as only 1 of the 20 patients in the ALG group was similarly excluded, the latter series was much less selective.

This experience with ALG suggests that its use as an immunosuppressive agent has improved the management of patients after transplantation. There have been a number of side effects, however, which were recently summarized by Kashiwagi et al.²⁶ Sensitization to the repeatedly injected horse protein has in time led to skin rashes. Fever and pain at the injection sites were invariable. In nearly 2 per cent of cases an anaphylactic reaction occurred during the course of therapy. The most serious adverse effects usually were observed when titers of host precipitating antibodies had reached high levels. Interestingly, the easily detectable antibodies were directed against the alpha and beta globulins that were present in small quantities in the ALG; only rarely were precipitins found against the equine gamma G globulin that is thought to be the biologically active part of ALG. Consequently, there is reason to hope that the pure gamma G globulin (IgG) that is now being produced in bulk as discussed earlier will eliminate some of the undesirable features of ALG.

One of the most disquieting possibilities with the clinical use of het-

erologous ALG was that the renal homografts would become the site of serum sickness or direct nephrotoxic Masugi-like nephritis. This fear has been largely dispelled. The first eight patients treated with ALG received homograft biopsies at the end of their 4-month course of therapy. The specimens were studied with immunofluorescence and ferritin-labeled antibody techniques.⁷³ There was no trace of horse protein. Since then four more kidneys have been studied. In only one was there detectable horse protein, and in that patient there has been no clinical or biochemical evidence of serum sickness nephritis.

Thymectomy in Clinical Transplantation

In adult mice, rats and hamsters complete thymectomy causes a slowly developing loss in immunologic reactivity in otherwise unaltered animals.^{44, 46, 60, 76} The process can be accelerated in skin homotransplantation experiments if immunosuppressive therapy is given with either total body irradiation^{9, 45} or antilymphocyte serum.^{25, 47}

Shortly after the appearance of the first of the above reports eight patients were subjected to thymectomy at our institutions 14 to 85 days before renal homotransplantation. Four patients died within a few weeks or months after receipt of their homografts. The other four are still alive more than 5 years later, all with excellent renal function. They are now four of the longest surviving recipients of renal homografts in the world.

As has been previously stressed,^{70, 71} the role of thymectomy in the attainment of long-term graft function in these cases was essentially unanalyzable. In order to clarify this issue, a formal study of the effect of thymectomy was carried out in 46 more patients who were treated with renal homotransplantation between October 1964 and June 1966. All kidneys were provided by living donors of whom 37 per cent were unrelated. A decision for or against thymectomy was made on the basis of random selection from appropriately marked cards. The spectrum of histocompatibility typing as well as a number of other variables proved to be almost identical in the 22 control cases as compared to the 24 cases in which transthoracic thymectomy was carried out before transplantation.

The duration of followup for these cases is now 21 to 41 months. The results were assessed on the basis of early and late mortality, the dosages of immunosuppressive drugs necessary to retain stable homograft function and the quality of both early and late renal function. There were not statistically significant differences between the thymectomized and nonthymectomized groups in these respects. In all 46 cases samples of the transplanted kidneys are now available for examination as a result of either autopsy or late biopsy. The histopathologic examination has not yet revealed clear differences between the test and control series of kidneys, although the specimens are currently being reviewed for possible subtle differentiating features.

At the moment, however, it can be concluded that an important benefit did not derive from thymectomy. This does not, of course, prove that the thymus has no immunologic function in adult man. At the least, however, it does indicate that other factors are so much more

important in determining survival and homograft function that the loss of the thymus resulted in no detectable changes under the experimental conditions that existed from 1964 to 1966. Conceivably, future improvements in management might permit unmasking of an unrecognizable subtle effect of thymectomy but, at present, there seems to be no justification for the continued use of the procedure in clinical organ transplantation.

Hyperacute Rejection

As mentioned earlier, it was soon learned that renal homografts have had a significant risk of being immediately destroyed if the donors and recipients have different ABO red cell groups in the combinations shown in Table 1. A rational explanation was available since the isoagglutinogens that allow red cells to be typed are also found in other tissues including the kidney.^{22, 75} Thus, if the kidney of an A or B donor were placed in a patient of O blood type, the naturally occurring anti-A and anti-B isoagglutinins respectively in the serum of the recipient could be expected to bind with the renal red cell antigens; serologic studies by Wilson and Kirkpatrick provide strong evidence that this actually occurs.⁹²

In cases in which the homografts were immediately lost, the sequence was typical. After the renal vessels were opened the kidney cortex was not well vascularized although the medulla, pelvis and ureter apparently had a good blood supply. These soft and cyanotic kidneys, which were removed within a few hours, had histologic evidence of widespread small vessel thrombosis.⁶¹ A frank red cell group mismatch did not always lead to this kind of accident. One patient has normal renal function more than 5 years after transplantation under such circumstances.

Recently, there have been reports of similar catastrophes in cases in which there was conformity of red cell types. The first case was described briefly by Terasaki,⁷⁷ and others were added by Kissmeyer-Nielsen,³¹ Williams^{89, 90} and Terasaki.⁷⁹ In the serum of many of these patients preformed antibodies were present preoperatively that reacted against donor white cells. This has resulted in speculation that such antibodies were directly responsible for the homograft destruction by virtue of a high-grade nephrotoxicity.^{31, 89} Our own studies on hyperacute rejection in the absence of red cell mismatching, carried out in collaboration with Richard Lerner and Frank Dixon of La Jolla, California, have led us to a different conclusion.⁶⁵ In five kidneys that sustained rejection on the operating table there was unequivocal evidence of a generalized Shwartzman reaction. With immunofluorescence techniques, Lerner and Dixon found massive fibrin deposition in the small vessels and glomerular capillaries and consequent cortical necrosis exactly as in an experimentally induced Shwartzman reaction. Little or no immunoglobulin deposition was detectable by immunofluorescence,⁶⁵ although eluates of some of the kidneys were later shown by Dr. Felix Milgrom of Buffalo to contain leukoagglutinins. In three of the five instances, the kidney donors had been shown by Terasaki to have a good histocompatibility match with the recipients.

The generalized Shwartzman reaction was first described in 1934, but its significance, as summarized by Lee and Stetson³⁵ and Hjort and Rapaport,²¹ was not understood until the last decade. Classically, it is produced in rabbits by two injections of endotoxin at 24-hour intervals. A generalized coagulopathy is produced. If the animal's reticuloendothelial system (RES) can clear the breakdown products of fibrinogen rapidly enough, the kidney is spared from injury. If not, it becomes a primary target because the specific qualities of the renal microcirculation make it an exceptionally good fibrin filter. The result is cortical devascularization and necrosis.

A number of factors besides endotoxin can condition or precipitate a Shwartzman reaction, including antigen-antibody reactions; injection of thorotrast, carbon black, or steroids; or administration of an oxidized lipid diet. Their effects are incompletely understood, but presumably they could be influential either by reinforcing the coagulopathy and/or reducing the efficiency of RES function, or by suppressing counter-regulatory fibrinolysis.

The recipient of a renal homograft could be expected to be a good candidate for a Shwartzman reaction. Before operation, he undergoes multiple hemodialyses with attendant risks from accidental exposure to endotoxin in the extracorporeal circuit,²⁸ from an additional RES load imposed by increased blood hemolysis⁴ and from the rapid changes in coagulation that occur with this procedure.⁸⁴ With multiple blood transfusions, there is an increased chance that he will develop antibodies against antigens in infused white blood cells or red cell subgroups, and that these will later react with the same antigens in the homograft. The operation itself introduces the latter possibility as well as that of a spectrum of other potential triggering antigen-antibody reactions either within or outside the freshly transplanted kidney. Steroids, which can potentiate a Shwartzman reaction by causing RES paralysis,⁸² are commonly used during and after the operation.

Recognition that many, and possibly most, rejections on the operating table are due to Shwartzman reactions has practical implications. Prophylactic measures can be taken. Greater attention can be paid to the details of hemodialysis, including asepsis and hemolysis rates. The value of white cell free blood for transfusion is obvious. Immunologic tests to detect presensitization are available; when such an examination is positive in a prospective recipient, the hazards are predictably increased.^{79, 89} Under these circumstances, it may be advisable to use total body heparinization at the time of transplantation. This was done in 2 of our patients whose previously placed kidney transplants had been immediately destroyed; the final homografts functioned well.⁸⁵ Once a Shwartzman reaction has started, a combination of heparin and fibrinolysin therapy might be worth a trial.

It is probable that most and perhaps even all Shwartzman reactions are ultimately triggered by antigen-antibody unions at the time of transplantation. If these are intrarenal, they may be inherently benign or even undetectable with immunofluorescence studies as in our cases and of significance only by virtue of the devastating secondary effects that they can initiate depending upon a variety of other conditions. If, as

is now thought, the site of the immunologic reaction is not critical to the chain of events, it is conceivable that the Shwartzman reaction may lead to destruction of the kidneys after transplantation of other organs.

Cadaveric Transplantation

A cadaveric renal homograft was first transplanted in Denver in April 1963. This recipient, as well as the next two, died within 39 days. The kidneys functioned either poorly or not at all. No more cadaveric transplantations were performed for more than 2 years.

The program was reopened in November 1965. From then until July 1967, 12 patients received the kidney of a blood group compatible cadaver as their primary homograft. In each case, a minimal followup of eight months is available.

Six of these 12 recipients died after 13, 10, 8, 3½, 3½ and 3 months. The other six are still alive after 27, 24, 15, 10, 9 and 8 months. One of the latter patients, however, required transplant nephrectomy and regrafting one year after receipt of his first kidney; another lost his homograft after a year and is now anephric 15 months post-transplantation.

The last six patients in this series received ALG therapy for the first several postoperative months. In all cases, the donor-recipient histocompatibility matches as determined by Terasaki were poor. Two of the recipients who had received kidneys from a common cadaveric donor died within a one day interval more than 3 months postoperatively. Death was caused by pulmonary emboli. The homografts had little or no evidence of rejection.

The other four patients, including one with preformed lymphocytotoxic antibodies, had good or excellent renal function during the 4-month period of ALG therapy. After its discontinuance, all have had evidence of slow but progressive rejection.

Other groups with much more extensive experience in cadaveric transplantation have repeatedly expressed optimism about the future of this approach.^{6, 12, 23, 29, 30, 39} It is a point of view with which few would disagree, especially since the prospects of transplanting livers, lungs and hearts will depend upon the use of cadaveric organs. Nevertheless, it is worth emphasizing that the costs in mortality, morbidity and rehospitalization have been high in all centers. Furthermore, survival exceeding 4 years with continuous function of nonrelated renal homografts is rare. To our knowledge there are only four patients whose courses have been this long—one of Dr. Willard Goodwin who was treated at UCLA in June 1963, another who has been followed by Dr. David Hume of Richmond since August of that year and two more who were in our Series I.

LIVER TRANSPLANTATION

The first clinical liver transplantations were performed in 1963.⁷² In these cases, the recipients' diseased livers were removed and replaced with cadaveric homografts (orthotopic transplantation). By the summer of 1967, there had been nine such attempts—seven in Denver^{62, 72} and

one each in Boston⁴⁹ and Paris.¹¹ The survival had been from 0 to 23 days.

Since then, six new trials have been made at our institutions with more encouraging results. All recipients survived for at least one post-operative month, and four are still alive after 1, 3½, 6 and 7½ months; the other two patients died after 2 and 4½ months. The improved results were the product of several improvements in care as reported elsewhere.⁶³

First, an efficient technique of preservation had been developed in dogs, which permitted livers to be stored for 8 to 24 hours and then successfully transplanted as orthotopic homografts.² The method that combined hypothermia, low flow perfusion with diluted blood, and hyperbaric oxygenation was used in the clinical cases for several hours after death of the donors and until the recipients could be prepared. Good immediate hepatic function was obtained in each case (Fig. 10).

In each of these cases, the compatibility of the donor and recipient white cell antigens was studied in advance of operation. A good match with compatibility in all six currently recognized components of the recently defined HLA system⁸⁰ was present in only one case. In three, there were breaches in one major antigen group, and in the other two there were mismatches in two of the six groups.

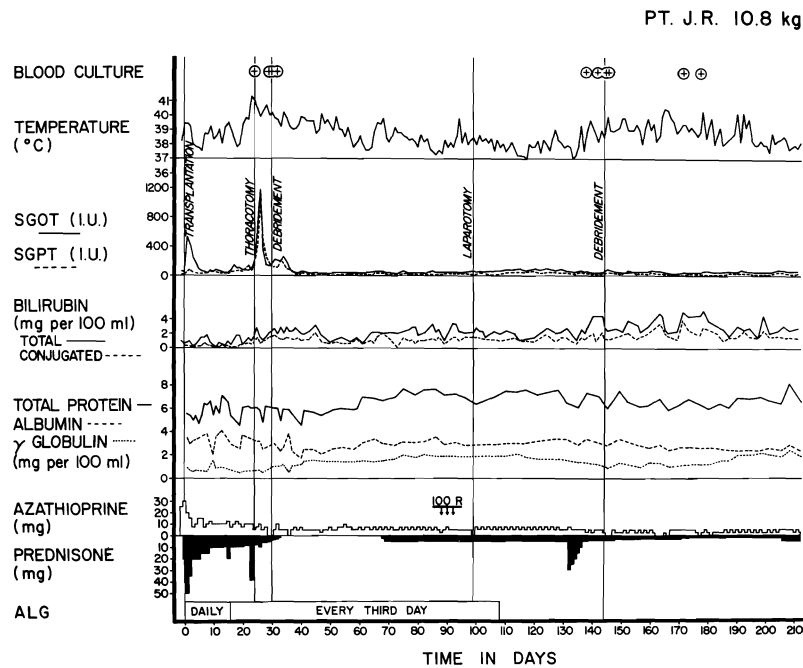


Figure 10. Course of a 1½-year-old girl who was treated with orthotopic hepatic homotransplantation. The indication for the operation was a hepatoma. Note the essentially stable liver function except at the times of septic liver infarctions which were treated with debridement. The septicemia, indicated by encircled crosses, was with various gram-negative rods or candida albicans. The thoracotomy was for an unexpanded right upper lobe. The laparotomy was for excision of a tumor recurrence.

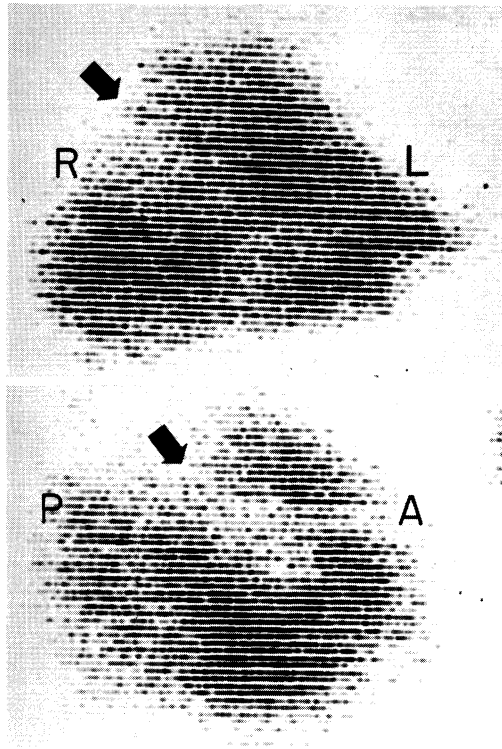


Figure 11. Liver scan performed 1 month after hepatic homotransplantation in the 1½-year-old patient whose course is depicted in Figure 10. Anteroposterior as well as lateral views show large defect (arrows). Exploration revealed a septic infarct in the homograft.

In all cases, a conservative attitude toward immunosuppression was taken during the early postoperative period, particularly in the dosages of azathioprine (Fig. 10). Large initial doses of prednisone were given but rapidly reduced. Finally, heterologous ALG was administered in a course similar to that described earlier after renal homotransplantation (Fig. 10).

The six recipients were all infants. The indication for operation was a hepatoma in the first patient and extrahepatic biliary atresia in the other five. In all but one case, the early convalescence was remarkably rapid. Pre-existing jaundice was quickly cleared. Eating was begun on the second to fourth postoperative days.

A specific life-threatening complication was encountered in all but the last two patients. From 2 days to 2 months postoperatively, septicemia with gram-negative microorganisms interrupted recovery. This was accompanied by large increases in SGOT and SGPT (Fig. 10), and eventually septic infarctions within the liver were found. Liver scans showed filling defects that were usually in the posterior-superior portions of the right lobe (Fig. 11).

In one case, the development of hepatic sepsis was not surprising inasmuch as a serious technical accident could be implicated. The homograft had a double arterial supply and the two vessels were anastomosed to the terminal right and left branches of the recipient hepatic

artery. The artery to the right lobe thrombosed on the second postoperative day, eventually necessitating a partial right lobectomy. In the three other children the complication occurred after a benign early postoperative course, and there was no obvious mechanical explanation.

The unusual susceptibility of the transplanted liver to invasion by enteric organisms is not surprising in view of its perfusion by splanchnic venous blood, as well as the necessity for connecting its biliary drainage system to the intestinal tract. The precise events of pathogenesis, however, can only be speculated upon in individual cases. In a recent analysis of the problem in dogs,³ any factor that caused liver necrosis, including the injury of rejection, was shown to predispose to liver abscess formation. It is thought that, in at least some clinical cases, the intensity of immunosuppression may have been inadequate, that the infarctions were a manifestation of rejection, and that the bacterial invasion was a secondary event.

Once established in the clinical cases, the infected liver infarcts required aggressive therapy. Debridement and drainage were carried out through lateral incisions in the right tenth intercostal space, taking care to enter neither the chest nor the abdomen. These local measures plus therapy with properly chosen antibiotics have tided two patients over the crisis, but two others with septic liver infarctions eventually died.

An alternative to orthotopic liver transplantation has also been given a clinical trial, namely transplantation of an auxiliary organ. Only five cases have been reported,^{1, 8, 14} but it is known that many more have been attempted. The longest survival after auxiliary liver transplantation has been 34 days.¹⁴ Analyses of the special physiologic and technical difficulties with this approach have been published,⁴² suggesting that it may be a less desirable procedure than the orthotopic operation.

SUMMARY

Several separate issues in organ transplantation have been reviewed, based upon our own experience with renal and liver transplantation. The topics surveyed include projections of survival after renal homotransplantation in the past and today, the role of histocompatibility typing, improvements in immunosuppression, an evaluation of thymectomy and the contribution of the Shwartzman reaction to hyperacute rejection. In addition, a specific problem of hepatic sepsis after liver transplantation has been described.

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