

Presensitization and kidney transplant failures

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Summary

Over 1000 kidney transplant patients were tested for cytotoxic antibodies before transplantation.

It was found that patients with preformed antibodies had a significantly poorer outcome than those without antibodies in terms of clinical ranks and survival. This effect was over and above the instances of hyperacute failures previously shown to be associated with preformed cytotoxins.

Among patients who received second transplants from cadaver donors, an extremely high failure-rate was observed in patients who had developed antibodies following the first graft, whereas if antibodies were not present, the failure-rate was comparable with that of first transplants done in patients without antibodies.

By analysis of survival curves using logarithmic plots, it is postulated that pre-immunization has its greatest effect in the early 3-6 month high risk period and magnifies incompatibilities which occur with unrelated cadaver donors.

Introduction

The outcome of clinical renal transplantation appears to be improving (Transplant Registry Advisory Committee, 1970), although the sharp difference between the use of related and cadaver donors still persists in all series. The highly significant difference in survival rate is shown for a series of patients transplanted since 1965 (Fig. 1) and in the statistics of the Kidney Transplant Registry. The lower survival rate for patients receiving kidneys from unrelated donors is actually determined to a large measure in the first 6-month period. The magnitude of the early effect is shown by replotting the survival curves into 'high- and low-risk' phases (Fig. 2). The gradual failure-rates during the long-term low-risk phase was thought to be attributable to incompatibility for HL-A antigens (Terasaki, Vredevoe & Mickey, 1967b). Mortality during the early period was postulated to be the result of accelerated rejection among recipients who were

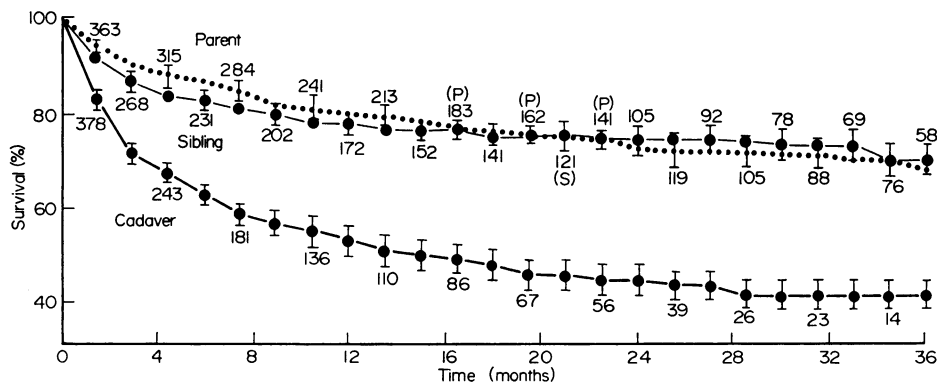


FIG. 1 Actuarial plot of survival of kidney transplants done since 1965, pooled from fifty-two transplant centres. The vertical bars indicate the standard errors. Numbers denote the number of recipients at risk at each time period.

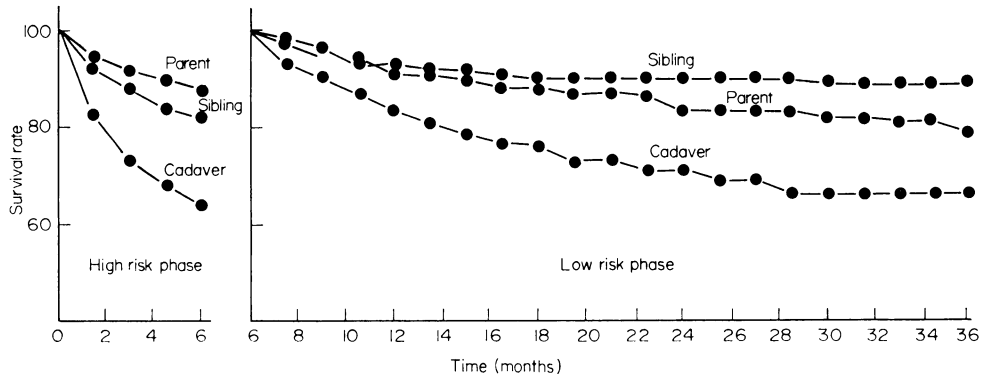


FIG. 2. A replot of the data from Fig. 1 by two periods: high- and low-risk. The first 6-month high-risk phase can be seen to be different from the low-risk phase, which was recalculated at 6 months as the fraction surviving.

presensitized (Terasaki, Thrasher & Hauber, 1968). It is the purpose of the present study to provide data gathered in support of this hypothesis. We will attempt to show that the largest fraction of early failures is accounted for by grafts into preimmunized recipients. The effect of mismatching for HL-A antigens is magnified by preimmunization, thus forcing survival curves to levels which are lower than might be expected on a proportional basis with the low-risk period. Presensitization has been identified by the presence of cytotoxic antibodies in the serum of patients before transplantation.

Methods

Data on 1715 patients who were evaluated *before* transplantation for the presence of cytotoxic antibodies are included in this study. Heparinized plasma was usually obtained 1–2 days after bleeding at dilutions between 1:2 and 1:3 since the blood had been sent to the laboratory from distant centres in mailing packets* containing McCoy's medium. Tests for cytotoxic antibodies were performed by the microlymphocyte cytotoxicity test (Mittal *et al.*, 1968) using lymphocytes from forty to 120 random donors. A positive reaction with lymphocytes from more than 5% of the random population was taken as evidence of the presence of antibodies. Cross-match tests with the lymphocytes of the donor were done with 0.003 and 0.001 ml of plasma. Follow-up data on the transplant recipients were kindly provided from fifty-two different transplant centres, without whose close collaboration in the past 5 years this work would not have been possible. Computation and data management were accomplished with the aid of the UCLA Health Sciences Computer Facility.

* Lymphocyte Transport Kits: Life Instrumentation, 2020 Ridge Avenue, Evanston, Illinois. Cat. No. T9199.

Results

Incidence of cytotoxins

The incidence of antibodies among kidney recipients varies considerably depending on their status (Table 1). The overall figure of 16.7% is derived from 1715 prospective kidney transplant recipients tested in the past 16 months. This incidence compares with the 19.2% incidence found in a separate earlier series of 681 prospective recipients (Terasaki *et al.*, 1968). Additionally, the two-fold greater incidence among females (24.2%) as compared with males (13.5%) was confirmed in this series. Presumably this difference is produced by preimmunization with pregnancies and restimulation by transfusions. The increasing frequency of cytotoxins with prolonged periods of waiting for cadaver donors and the accumulation of recipients with cytotoxic antibodies is reflected in the higher incidence of 25.5% among recipients in the national pool. Among fifty-one patients who have rejected first or second transplants, the incidence of cytotoxins is as high as 54.8%.

It is noteworthy that once antibodies develop, they may persist for long periods at relatively stable levels, particularly if the antibodies are strong and react with a large fraction of the population (Fig. 3). However, some notable instances of loss of antibodies and decrease in reactivity have been seen. Thus, the specificity of antibodies present at different times may vary considerably by including more or at times fewer HL-A specificities.

Development of cytotoxins

In the course of this work several patients were found who did not have antibodies initially, but who subsequently developed them prior to transplantation. In order to develop quantitative information about the likelihood of development of cytotoxic

TABLE 1. Incidence of cytotoxins

	No. tested	No. with antibodies	Percent with antibodies
Prospective kidney recipients	1715	286	16.7
Males	980	130	13.5
Females	633	153	24.2
Prospective recipients waiting in the national pool for cadaver donors	534	136	25.5
Waiting for first transplant	483	108	22.8
Waiting for second or third transplant	51	28	54.8

antibodies in patients awaiting transplantation, test results were examined for a series of 432 patients who did not have antibodies at initial test and whose sera were subsequently tested for antibodies. By considering the dates of initial test, last negative test before any positive tests and date of first positive test one can obtain partial information on the elapsed time before formation of antibodies. An extension of the life table analysis computation to include the case in which the time of the event being considered is not known but is bracketed enables evaluation of the time-course of development of antibodies. Such calculations were made and are summarized by a constant risk rate of $0.89 \pm 0.42\%$ per month. The chances of a patient developing antibodies within a month of an initial negative test are thus estimated as slightly less than 1%; the chances of developing antibodies within a year are approximately $10 \pm 5\%$.

To some extent the result may represent the uncertainties in detecting weak antibodies or those cytotoxic to a small fraction of the normal population. In several cases, however, the antibodies developed were strong enough (Fig. 3) to rule out these considerations as a major factor. It is perhaps surprising that some patients can be maintained for long periods without their developing antibodies. Of the twelve patients whose tests spanned a 2-year period, none had developed antibodies. A selection factor against patients who develop antibodies could exist in long-term dialysis patients.

Cytotoxins and hyperacute rejection

Relatively few transplants have been done in the face of a positive cross-match since the publication of the earlier statistics (Patel & Terasaki, 1969). Of the ten new cases not published by us earlier, seven resulted in immediate failure. The most striking new

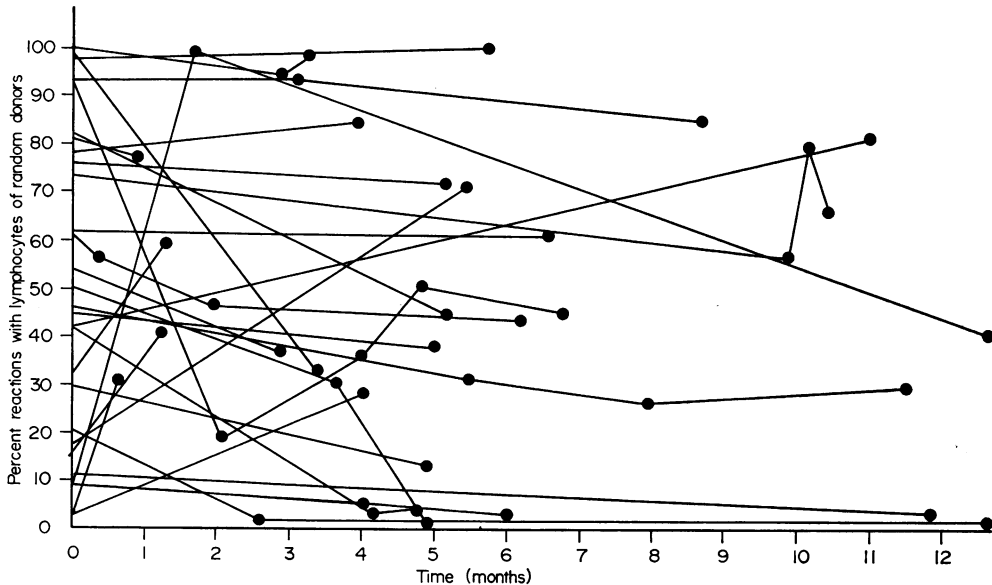


FIG. 3. Fluctuation in strength of cytotoxins present in prospective recipients. The percent of random donors whose lymphocytes reacted with sera from recipients is shown. Some sera can be seen to lose activity with time.

finding has been the relatively high rate of hyperacute failure in spite of a negative cross-match among patients with preformed antibodies (8%). Thus, the presence of antibodies as detected by activity against random cells is often more certain evidence of a possible humoral triggering of hyperacute failure than is the isolated negative cross-match test. In addition to a false-negative test produced by technical variations in the test conditions, it is quite possible that the limits of sensitivity of the particular test conditions must be increased to pick out this 8% of immediate failures not currently being identified by a positive cross-match test. Some of the false-negative effect could also be accounted for by the failure to recheck the cross-match tests immediately before operation, for many of the tests had been done as much as 6 months prior to the transplant.

The clear association between preformed cytotoxins and hyperacute rejection is shown by the thirteen-fold higher incidence of hyperacute failure among patients with preformed cytotoxins (12%) in contrast to patients without antibodies (0.9%) (Table 2). A negative cross-match is therefore not as significant for patients known to have antibodies as for recipients without antibodies.

Cytotoxins and outcome of transplantation

Excluding the effect of hyperacute failure, the trend of having greater numbers of failures among patients with preformed antibodies is present in transplants from cadaver donors (Table 3). The association, calculated at 6 months after transplantation, is significant for first transplants ($P=0.05$) and highly significant for second grafts ($P<0.001$). The presence of antibodies prior to second grafts results in an extremely high failure rate of fifteen out of twenty or 75% if hyperacute failures are also counted. Excluding the hyperacute rejections, the failure rate is still nine out of fourteen. If no antibodies are found, it is interesting that the failure rate after a second transplant may actually be slightly less (one out of fifteen) than after a first transplant.

Rather than taking the clinical ranks at one time, such as 6 months as done above, survival rates among patients with and without antibodies could be examined. All failures are included, including technical nonimmunologic and hyperacute to provide 'realistic' survival rates. As shown in Fig. 4, a statistically significant difference develops for transplants done from cadaver donors at 6 months.

TABLE 2. Incidence of hyperacute failures

	Hyperacute failure	No hyperacute failure	Total	Hyperacute failure (%)
<i>Preformed antibodies active against random cells</i>				
Positive cross-match	5	3	8	63
Negative cross-match	7	86	93	8
No cross-match	14	108	122	11
Total	26	197	223	12
<i>No preformed antibodies active against random cells</i>				
Positive cross-match	0	0	0	0
Negative cross-match	2	308	310	0.6
No cross-match	4	359	363	1.1
Total	6	667	673	0.9

TABLE 3. Cytotoxins and outcome of transplantation

	Clinical ranks at 6 months*							Total	P value excluding H, N, T	Rank sum test excluding N, T
	A	B	C	D	F	H	N, T			
<i>First transplant cadaver</i>										
No antibodies	52	27	25	10	49	2	28	193	0.05	0.001
With antibodies	12	8	6	3	20	6	10	65		
<i>First transplant parent</i>										
No antibodies	58	46	31	5	20	2	11	173	0.59	0.49
With antibodies	18	13	5	2	6	3	1	48		
<i>First transplant sibling</i>										
No antibodies	67	22	15	3	14	3	11	135	0.84	0.49
With antibodies	23	7	5	1	6	3	5	50		
<i>Second transplant cadaver</i>										
No antibodies	12	1	1	0	1	0	5	20	<0.001	<0.001
With antibodies	0	4	1	0	9	6	2	22		

* Clinical Ranks: A=Excellent, B=Good, C=Mediocre, D=Poor, F=Failure, H=Hyperacute failure, N=Nonimmunologic failure, T=Technical failure.

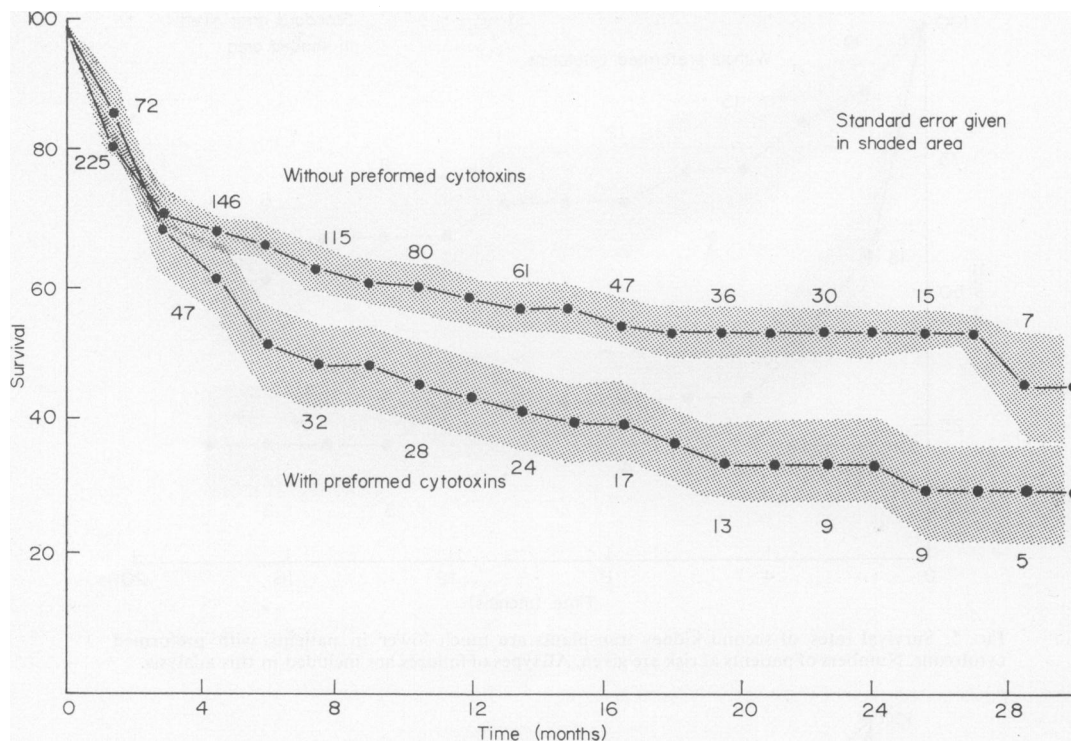


FIG. 4. Actuarial survival rates of first kidney transplants in patients with preformed cytotoxins can be seen to be less than in patients without cytotoxins. Numbers denote number of patients at risk. No exclusions on types of failures—such as hyperacute, nonimmunologic, and technical were made.

The pronounced higher failure rate among pre-sensitized recipients receiving second cadaver grafts is evident from Fig. 5. Early loss in survival up to 4 months accounts for most of the difference in overall survival rates. The biphasic nature of the loss can be more clearly appreciated from a logarithmic plot of the survival curve (Fig. 6). Overall survival of second grafts, when split into recipients with and without antibodies, can be postulated to be made up of two components in which the long-term rate of fall-off is similar. Initial mortality rates are, however, much steeper in recipients with preformed antibodies.

The higher early failure-rates are remarkably alike in all three genetic categories of donors if the recipients had cytotoxins (Fig. 7). The uniform high failure-rates are followed by almost no failures among the parental and sibling donors, as though all the incompatible transplants which were going to be eliminated were rejected in an accelerated fashion during the early high-risk period. With cadaver donors, the situation appears more complex. The initial loss rate during the high-risk period is similar but more prolonged than with related donors. Moreover, among recipients with preformed antibodies a

longer intermediate phase appears to exist even to 2 years during which accelerated loss takes place (Fig. 7).

These general observations are supported by the quantitative estimates of failure-rates given in Table 4. The rates were computed separately for the intervals: 10–100 days, 100 days–6 months, 6 months–1 year and greater than 1 year. The estimation formula used was: number of failures occurring during the interval divided by the total survival time within the interval, results are expressed in units of percent per month; standard errors were calculated as: rate divided by square root of the number of failures in the interval. In the case of parent and sibling donors to recipients with preformed antibodies the data were not sufficiently extensive to subdivide the intervals beyond 100 days and single rates are given for the combined periods. The main findings from Table 4 are that the initial failure rates are greater for sensitized recipients than for nonsensitized in each of the categories of donor-recipient genetic relation. Failure experience for transplants with parent and with sibling donors are essentially identical throughout the first year; thereafter the failure-rate for parental donated kidneys

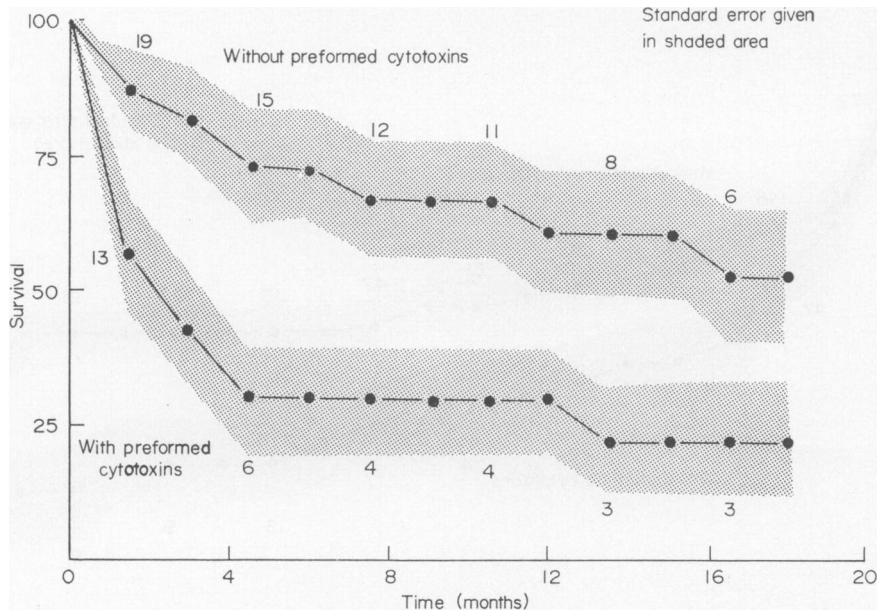


FIG. 5. Survival rates of second kidney transplants are much lower in patients with preformed cytotoxins. Numbers of patients at risk are given. All types of failures are included in this analysis.

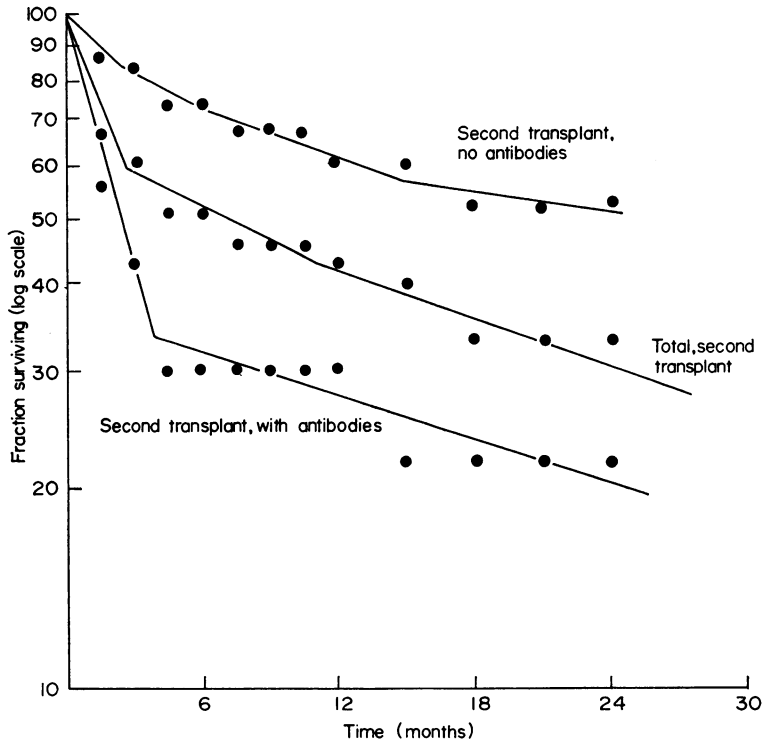


FIG. 6. Logarithmic plot of second transplant survivals from Fig. 5 shows the marked difference in early failure rate for patients with cytotoxins.

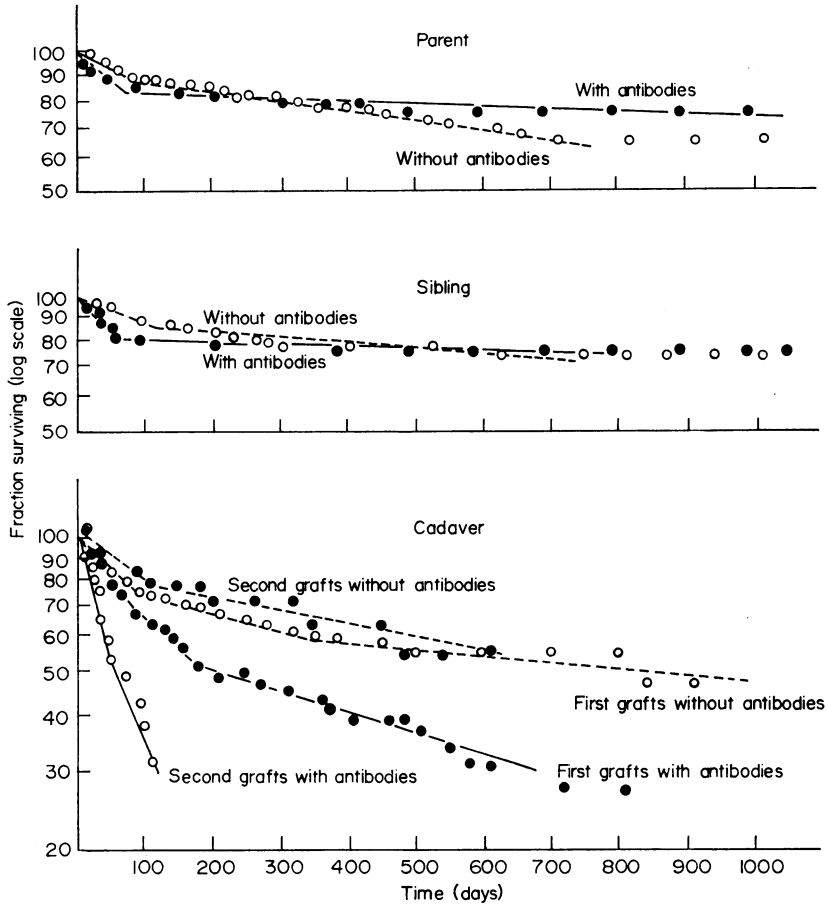


FIG. 7. Logarithmic plots of transplants from three different genetic classes of donors illustrate the sharp break in slopes in the early and late periods. Patients with preformed antibodies have a higher initial slope. Hyperacute failures before 10 days were excluded in this analysis.

TABLE 4. Average risk rates (%/month) of renal transplant failure for first transplants surviving 10 or more days for patients for which an antibody determination was made prior to transplant

Relation of donor	Recipient antibodies	No. of transplants	No. of failures	Risk of failure rate (%/month)			
				10-100 days	100 days-6 months	6 months-1 year	1 year +
Sibling	No	152	32	3.5 ± 0.9*	1.9 ± 0.8	1.7 ± 0.6	0.2 ± 0.2
	Yes	47	12	6.5 ± 2.3		0.4 ± 0.2†	
Parent	No	193	48	3.9 ± 0.9	1.0 ± 0.5	1.8 ± 0.5	1.1 ± 0.4
	Yes	48	12	5.4 ± 2.0		0.5 ± 0.2†	
Cadaver	No	216	79	9.8 ± 1.4	2.3 ± 0.8	2.8 ± 0.7	1.0 ± 0.4
	Yes	68	41	12.0 ± 2.7	10.1 ± 3.2	3.1 ± 1.4	2.9 ± 1.2

* Value ± standard error.

† Average computed for 100 days; there were too few failures to meaningfully subdivide the range.

continues at about the same level whereas that for siblings becomes very low. Among the cadaver donor transplants to sensitized recipients the initial high rejection rate continues up to about 6 months; thereafter the rate is about the same as for unsensitized recipients from 100 days to 1 year, and after about a year the failure rate for unsensitized recipients of cadaveric organs is about the same as that for unsensitized recipients of parental organs.

Discussion

Kidney transplant survival curves (Barnes, 1965) have been extremely useful in analysing the factors which influence the fate of transplants. The use of survival rates for genetic inferences such as the

number of histocompatibility loci and alleles involved have been stimulating (Simonsen, 1965; Serra & O'Mathuna, 1966; Ceppellini, 1968). Most of these analyses have used the values at given points, e.g. survival at 1 or 2 years. Further analysis of these curves by plotting of survival on a logarithmic scale shows that two distinct phases exist: An initial steep decline in the early 6 months followed by a subsequent gradual loss (Figs. 6 and 7). The value of making this distinction is readily seen on examination of the Kidney Transplant Registry statistics where the overall improvement in survival rates on grafts done before and after 1967 is almost entirely attributable to improvement in survival at the early high-risk period (Fig. 8). The slope of the low-risk

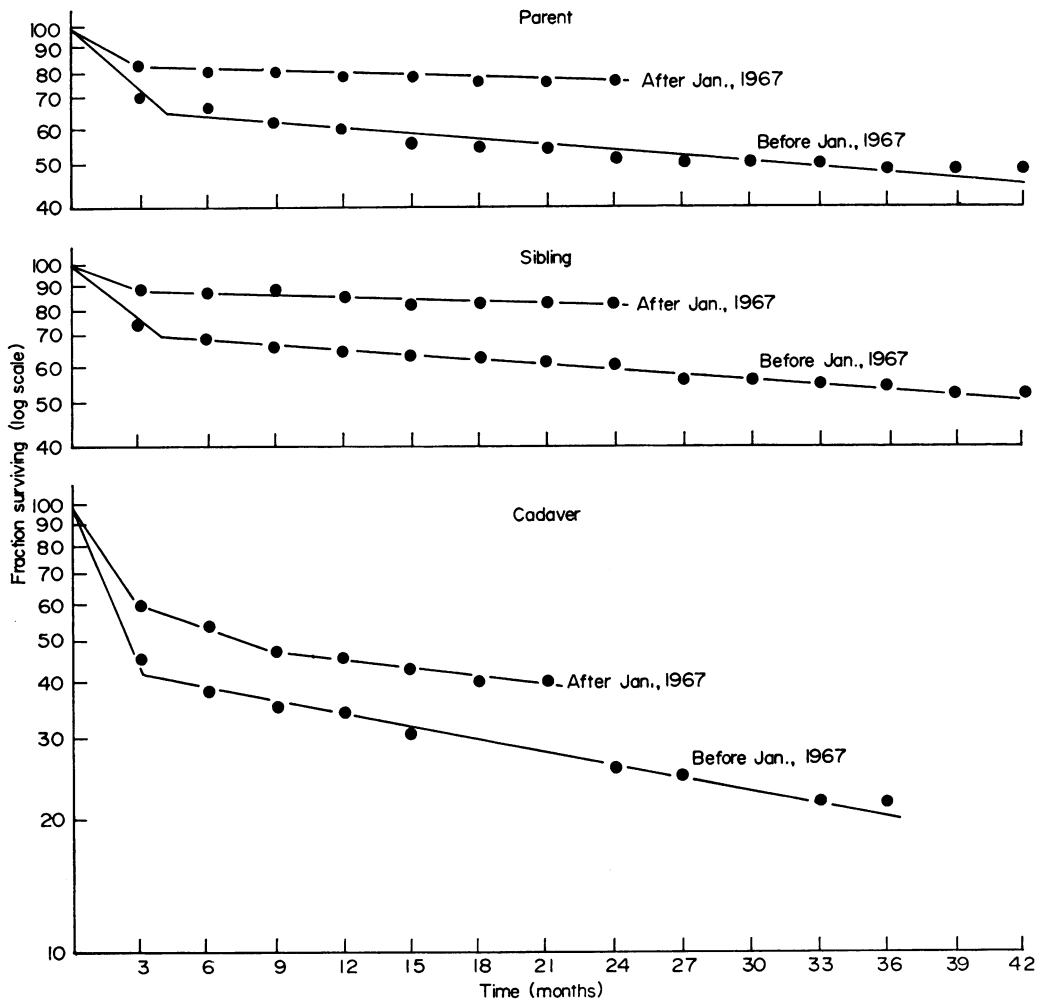


FIG. 8. A replot of the data from the Kidney Transplant Registry for the three genetic classes of donors shows that in this series also, a sharp division in the failure rate occurs at 3 months (adapted from the Transplant Registry Committee, 1970).

phase remains essentially the same. Overall survival had been improved therefore by reduction of early mortality, although this early mortality continued to be proportionally much higher in grafts from cadaver donors than related donors.

Evidence is provided here to support the hypothesis that the early steep slope is not only attributable to technical and nonimmunological causes, but also determined to a large extent by preimmunization of recipients which accentuates incompatibilities. Without this augmentation of incompatibility during the low-risk phase, only relatively small differences in rates of failure are found between the three genetic classes of donors: parents, siblings, and cadavers (Fig. 7). The difference in one-allele versus two-allele incompatibility (parents versus unrelated) is manifested by a difference of 83% versus 72% survival at 2 years (after eliminating the deaths up to 6 months) (Fig. 2). This is not as large a difference as might be expected if HL-A antigens were strong antigens. Thus, even the HL-A identical siblings have only about a 10% higher survival rate than one-allele incompatible parent-child transplants (Mickey *et al.*, 1970). In the late phase, therefore, only a spread of some 20% in 2-year survival rates separates the two extremes of zero- and two-allele incompatible transplants. The types of HL-A incompatibility which are fatal in the 20% and are acceptable in the remaining 80% are the subject of another study (Mickey *et al.*, 1970).

Returning to the early high-risk period which is the principal concern of this report, one might ask why the difference between the results obtained with unrelated and related donors is so much greater in this period than in the low-risk period. Although some of the difference is produced by the fact that variable ischemic damage is imposed on kidneys taken from cadaveric donors and operations are done under unscheduled, hurried conditions, these factors are not overriding, since *living* unrelated donors yield similar results (Starzl *et al.*, 1968). The incompatibilities which are encountered more often with unrelated donors are postulated to be magnified by a state of immunity in some recipients. This immunity is produced by blood transfusions in which leukocytes and platelets having HL-A antigens are the antigenic stimuli.

The ideal method of measuring immunity is by *in vitro* cellular immunity tests wherein the immunologic memory of the recipient's cells are tested. One such sensitive test has been recently described by Takasugi & Klein (1970). In the present study, we have taken the second-best measure, that of presence or absence of preformed antibodies as an index of presensitization. The presence of HL-A antibodies is a clear indication of preimmunization, for these antibodies have not been found in the sera of normal

persons. On the other hand the absence of antibodies cannot be assumed to indicate lack of preimmunization. Some patients could have lost their humoral antibodies (Fig. 3) or could be subliminally sensitized below the threshold of the routinely used cytotoxicity test. Loss of antibodies is commonly seen, for example, after pregnancy. That a state of preimmunization exists can be readily demonstrated by a small booster injection which within a few days results in high titres of antibodies. One solution to the problem of detection of presensitization may be to increase the sensitivity of the tests. Prolongation of incubation time (Mittal *et al.*, 1968), and pre-treatment of cells with enzymes (Mittal, Mickey & Terasaki, 1969), are two methods. Another possible method is testing for a prolonged period in the cold. This technique has been shown to detect lymphocytotoxins of IgM nature in the sera of patients immunized against a great variety of antigens (Mottironi & Terasaki, 1970). Although more sensitive than the conventional tests, a possible defect is that the cold cytotoxins appear after nonspecific stimuli and may not be a sufficiently selective index of preimmunization to HL-A antigens.

Use of the simple 1.5-hr incubation lymphocyte cytotoxicity test as the sole index of presensitization suffers from the possibility that not all the important transplantation antigens may be represented on lymphocytes. Certain practical difficulties of not being able to uniformly test patients just before transplantation have also been limiting. In this study only those patients who were tested for preformed cytotoxins more than 6 months prior to transplantation were considered. Yet these patients could have readily become immunized in that period. One common source of immunization was found to occur when diseased kidneys are removed before transplantation, at which time blood transfusions are often given. Thus, patients classified as not having preformed cytotoxins could have had them by the time of transplantation. Another practical problem imposed by the necessity of receiving blood in the mail has been the two- to three-fold dilutions of plasma in the mailing and flushing procedures.

In spite of these difficulties, the simple classification of patients into whether preformed lymphocyte cytotoxins were present or not before transplantation has yielded demonstrable differences in survival rates at the high-risk periods. Patients with cytotoxins receiving transplants from cadaver donors had a lower survival rate than those without cytotoxins (Table 3, Fig. 4). The initial high mortality is followed by another relatively rapid phase of loss, lasting for 2 years which could conceivably still be ascribed to the state of presensitization (Fig. 7). The proportion of related donors who suffer early rejection is not statistically significant, although the

higher attrition rate in the early phase is evident (Fig. 7). Most marked has been the difference after preimmunization with a kidney transplant. An extremely pronounced difference in survival rate (Figs. 5 and 6) and clinical ranks (Table 3) of second transplants into patients with and without antibodies could be demonstrated. Although based on somewhat low numbers, the presence of preformed cytotoxins is a more ominous sign prior to a second transplant than prior to a first graft. Interestingly, the absence of cytotoxins before a second transplant resulted in a slightly lower failure rate than before a first transplant. Possibly enhancing antibodies which were independent of the cytotoxins had aided in the higher survival rates, as has been shown for rat renal transplants (Ockner, Guttmar & Lindquist, 1970). Overall success rates with second grafts which parallel those with first transplants (Hume, 1968; Barnes, Murray & Atkinson, 1967), can perhaps be accounted for by the separation of recipients into those who have cytotoxins and who suffer accelerated rejection, and those without cytotoxins who have an unusually high survival rate.

Hyperacute failure which occurs within minutes probably is at one extreme end of the accelerated rejection in presensitized recipients. Many presensitized recipients have negative cross-match tests with their donors, but have rapid hyperacute reaction and have a much higher risk of hyperacute failure than patients without antibodies (Table 2). Difficulties in diagnosis of hyperacute failure could account for the low incidence (0.9%) of such failures in patients without demonstrable cytotoxins. Presence of cytotoxins could be a necessary criterion by which hyperacute failure is diagnosed, for without them hyperacute reactions rarely occur. If preformed antibodies are not present, perhaps an entirely different mechanism of immediate failure is responsible. Starzl *et al.* (1968) have postulated that an antibody reaction against antigens other than HL-A antigens could trigger a Schwarzman reaction resulting in intravascular coagulation.

The hypothesis that the early high mortality of kidney transplants is the result of amplification of incompatibilities in presensitized recipients is also substantiated by the experience from skin grafting. Dausset *et al.* (1965) showed that the antigenicity of red cell A and B antigens, platelets and leukocytes could be more clearly shown if the recipients were preimmunized. Similar data on leukocyte antigens were obtained at the same time by van Rood *et al.* (1965). The cross-reactivity of guinea-pig transplantation antigens with group A Streptococci (Rapaport & Chase, 1964) and HL-A antigens with M1 proteins of type 1 Streptococci (Hirata & Terasaki, 1970), introduces the interesting possibility that transplant rejections are secondary

responses. Immunization by micro-organisms may lead to presensitization to transplantation antigens of certain donors.

If it is accepted that presensitization is detrimental to transplants, what can be done?

First, the rate at which immunization occurs can be reduced. The effectiveness of methods for obtaining buffy coat-poor blood or frozen blood in reducing immunogenicity is still incompletely evaluated. Utilization of HL-A compatible blood for transfusion is more remote, though perhaps not impossible. Nationally or internationally computerized blood banks are certainly not beyond the realm of possibility as more sophisticated advances become incorporated into the practice of medicine. The rate at which patients are immunized indicates that the risk increases constantly as a patient waits on dialysis, though interestingly a large fraction appear not to form antibodies even after long periods. Some patients undoubtedly do not make antibodies because of the immunodepression of uremia (Kirkpatrick, Wilson & Talmage, 1964; Kasakura & Lowenstein, 1967). Some probably do not make antibodies for unknown inherent reasons, just as some normal volunteers who are deliberately immunized in attempts to produce typing serum do not form antibodies (Hammond, Mattiuz & Curtoni, 1967; Walford, 1969). Slightly over half of women who are repeatedly immunized by multiple pregnancies also do not ever appear to form cytotoxins (Terasaki *et al.*, 1970).

We then come to the problem of how to prevent accelerated rejection and hyperacute failures in patients who are already sensitized. It is now apparent that ordinary cross-matching is often inadequate, partly because of the fluctuating strength of antibodies at any given moment. Thus, a patient's serum which reacts with lymphocytes of 10% of the random population and does not react with a given donor may have had antibodies only a few months previously to cells from 80% of the random population and to that donor (Fig. 3). This means that the patients had been sensitized earlier to a broader spectrum of antigens. Antibodies, unfortunately, are only an indicator of the level of sensitization at the moment the sample is drawn. A routine monitoring of all prospective recipients at frequent intervals is therefore invaluable. Test of cellular immunity may also be an important index of presensitization in patients whose antibody levels have dropped off. Mixed culture tests (Bach, Solliday & Stambuk, 1970) and cellular destruction tests (Takasugi & Klein, 1970) may be particularly useful.

The data presented here point to the principal means by which the challenge of how to transplant presensitized recipients can be met. A significantly higher survival rate was shown if presensitized

recipients were transplanted with kidneys from related rather than unrelated donors. The obvious conclusion is that if an immunized recipient is given a compatible transplant, his preimmunized state will have nothing foreign to react upon. One of the most striking examples of this is a patient of Dr Dossetor's who had cytotoxic antibodies to lymphocytes of 96% of the population, who had rejected hyperacutely a first graft, and who was successfully transplanted with an HL-A identical sibling with excellent results 2.5 years later. Tissue typing must advance to the point where such compatible donors who are exactly like the recipient can be identified from the unrelated donor population. Although the field of HL-A typing has not quite advanced to this stage, as is evident from the Fourth International Histocompatibility Testing Conference (Terasaki, 1970), progress from numerous laboratories is rapidly closing the gap.

Acknowledgments

We wish to acknowledge the aid in analysis provided by Miss Joyce Yuge, Miss Susan Maples and Mr Jay Langston.

This investigation was supported in part by Research Grants AM 02375 and AI 04444, from the National Institutes of Health, Contract PH 43 65 994 from the National Institute of Allergy and Infectious Diseases and Contracts HSM 110 69 253 and HSM 110 69 393 from the Health Science and Mental Health Administration. Computing assistance was obtained from the Health Sciences Computing Facility, UCLA, sponsored by National Institutes of Health Grant RR-3.

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