

PRE-TRANSPLANT RECIPIENT-DONOR INTERACTION:

A PROGNOSTIC INDICATOR IN LIVING RELATED KIDNEY TRANSPLANTATION?

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Abstract Based on the hypothesis that not only genetically determined immune characteristics, but also psychosocial and especially interpersonal factors may influence the outcome in living related kidney transplantation, we investigated the type of relationship between recipient and donor, and its association with graft prognosis. The study group consisted of 154 kidney transplant candidates and their selected donors. Donor and recipient were assessed prospectively prior to transplantation using an interactional task (Usandivaras Marbles Test) and assigned to one of four groups, according to their pattern of contact. Kidney survival was calculated for each test group, and results compared by life table methods and logistic regression. The group that showed progression from initial contact avoidance or enmeshment to contact with boundaries had a significantly better outcome than the other groups (no change or loss of contact with boundaries). Differences could not be related to other variables such as age, sex, sex difference, relationship, HLA-matching, and treatment.

Resumen *Interacción dador-receptor previa al trasplante renal. ¿Es un indicador pronóstico en el trasplante con donante familiar?* Se ha avanzado mucho en el conocimiento de la interdependencia entre el sistema inmune, el sistema nervioso y la conducta. Sin embargo, no se ha estudiado hasta qué punto esa interdependencia juega un rol en el trasplante de órganos. A partir de la hipótesis que la evolución de un trasplante puede estar relacionada no sólo con características inmunológicas determinadas genéticamente, sino también con factores psicosociales y, en especial, interpersonales, investigamos el tipo de relación existente entre el familiar donante y el receptor, y la asociación entre esa relación y el pronóstico. La muestra consistió en 154 candidatos a trasplante renal con sus respectivos donantes. Dador y receptor fueron evaluados juntos y prospectivamente, poco antes del trasplante, usando un test interaccional, el Test de Usandivaras (Test de las Bolitas). Se definieron cuatro grupos, según el patrón de contacto entre donante y receptor. Se calculó luego el tiempo de sobrevida del trasplante en cada grupo y se compararon los resultados por tablas de sobrevida, regresión logística y método de Cox. El grupo en que donante y receptor, partiendo de patrones primitivos de contacto (indiscriminado o evitado), lograban contactarse discriminadamente, tuvo una sobrevida significativamente mejor que los otros, donde no había cambios o se perdía el contacto discriminado. Las diferencias en la sobrevida no se debieron a variables tales como edad, sexo, diferencia de sexo, parentesco, compatibilidad HLA o tratamiento. La aceptación de un órgano trasplantado es un proceso complejo que debe estudiarse en varios niveles. El modo en que el dador y el receptor interactúan poco antes del trasplante, parece ser un indicador pronóstico adicional en trasplante renal con dador vivo familiar.

Key words: renal transplantation, transplantation psychology, graft rejection psychology, recipient donor interaction

The immunological process through which a grafted organ is rejected is presently considered a function of differences in the genetic makeup of recipient and donor. While identical tissues or organs will not evoke an immune rejection reaction (histocompatibility), differences in the major histocompatibility complex genetic region (HLA) and in other histocompatibility systems will be responsible for tissue transplant rejection, when the

immune system recognizes tissues, from a different individual as genetically foreign¹. Strategies to improve graft survival are mainly based on this assumption. Careful tissue matching is done prior to transplantation and potent immunosuppressant drugs such as Cyclosporine are implemented to diminish the normal reaction to a foreign organ.

On the other hand, evidence for endocrine, neural, and behavioral modulation of immunological processes is increasing. Studies on the effect of stress on immunological competence, on the hypothalamic influences on the immune system, on the modification of immune responses through classical conditioning techniques, and on the immunological consequences of bereavement and depression²⁻¹¹, make the general hypothesis increasingly

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plausible, that not only inborn tissue characteristics but also psychosocial variables may play a role in modulating the immune response to a graft.

Organ transplantation with a living donor offers a unique opportunity to assess the interplay of psychosocial variables and immunological responses to a foreign organ. A foreign graft can be received as a gift but also as a threat to psychological individuality and identity, and a graft from a close relative will be loaded with specific meanings and expectations. Nevertheless, while the immunological workup previous to transplantation has reached a high level of refinement and detail, studies on organ transplantation have seldom or incompletely included psychosocial factors as an intervening variable, and no attention has been paid to psychological issues that are involved in the donor-recipient situation preceding the operation. Studies¹²⁻¹⁶ have focused on the recipient's state –anxiety and depression mainly– without taking into account the essentially relational nature of the procedure, namely that recipient and donor are simultaneously involved in the pretransplant situation, and that interaction occurs on several levels. In immunological terms, compatibility is not defined as an individual's condition, but as an individual's response to a specific 'other'. Assessing the behavioral interplay between the recipient and his particular donor might bring forth more relevant information with regard to the outcome of the operation, than assessing only the recipient's individual psychological state.

This study, which represents both a modification and an extension of a previous one¹⁹ reported in 1987, is based on the hypothesis that not only genetically determined immune characteristics, but also psychosocial factors may play a prognostic role in kidney transplantation and, specifically, that interpersonal phenomena related to identity preservation and to the recognition and acceptance of the donor, have to be studied when living related donors are involved.

Material and Methods

The study group consisted of 154 chronic renal patients, who were asked to participate in the study with their related kidney donor who had been chosen for transplantation following conventional medical criteria. For enrollment in this study, no selection criteria were applied other than the availability of one of us (MIM and SGA) to give the test shortly before the operation. Assessment was prospectively done from 1979 to 1993. Each of the 154 participating recipient (R) –donor (D) pairs was assessed in one session, mostly within the preceding two weeks before transplantation. The study was presented to the patients as an investigation on psychological aspects of transplantation, and consent was obtained. All assessed and transplanted pairs were included in the study. There were no refusals. One pair that could not complete the test, because the recipient felt ill, was not included in the sample. The evaluation

was done using Usandivaras Marbles Test, an interactional task described below.

There were 70 parent-to-child and 67 sibling R-D pairs. The remaining 17 were child-to-parent (6), spouse (9), aunt-niece (1), or in-law (1) pairs. These combinations are accepted by the Argentinean transplant law. Mean age was 30 years for the recipients and 41 years for the donors. No children were included. Fifty-three recipients and 97 donors were female. Sex was different in 86 R-D pairs. Eighteen pairs shared two haplotypes (HLA-identical pairs); the remaining pairs shared one haplotype, with exception of a few cases who shared less than one. In 40 cases, Azathioprine and Prednisone were used as immunosuppressants, while Cyclosporine (CsA) was also used in 114 cases. Assessment was performed between 1979 and 1985 in 39 cases, and between 1986 and 1993 in 115 cases. Longest follow up time was 165 months.

Test method

Usandivaras Marbles Test²⁰⁻²², an instrument designed to study qualitative and quantitative aspects of group, family, and couple interaction, was used to assess recipient-donor interaction. The test does not require any sophisticated cognitive, verbal, or fine motor abilities and is well accepted by patients from different socioeducational levels. Around half an hour is needed to complete the task. Each participant was given twenty marbles of a different color (red for the recipient, blue for the donor) and asked to work together putting the marbles on one common peg board at will. The only instruction was: "Please put your marbles on this board, trying to make something, working together". No further instructions, suggestions, or answers were given, other than "do as you wish". When they indicated that they had finished, the resulting design was recorded by the interviewer and the task was repeated twice immediately with the same instruction.

The three graphic designs, the names given to them by the participants, their behavior during the test, and the answers given to the standard questions (what did you make?, what do you think your partner made?, what did you make together?), were recorded.

Classification criteria

a) Design patterns

For the present study we focused on the resulting design patterns. According to criteria given by Usandivaras²⁰, the designs were assigned to four pattern categories. When faced with the task of working together on the same peg board, R and D may decide to isolate themselves making individual designs, or to join in a common one. In the first case, the design is classified as non-contacted if there is no relationship between the two individually made designs, and as contacted if, although individually made, they are similar in shape (e.g. mirroring each other) or in subject (e.g. "a willow and a pinetree"). In Fig. 1, both (a) and (b) are examples of individually made patterns; (a) is classified as non contacted pattern, while (b) is classified as contacted.

When R and D, instead of working separately, make together one common design, it is classified as differentiated or non-differentiated, depending on the presence or absence of distinguishable parts that are made by each participant. In Fig. 1, (c) and (d) show one common design. While (c) shows an enmeshed pattern where marbles are intermingled without boundaries, with no attempt to differentiate the part made by each participant, Fig. 1 (d) clearly shows the parts of a house made by each participant while working together.

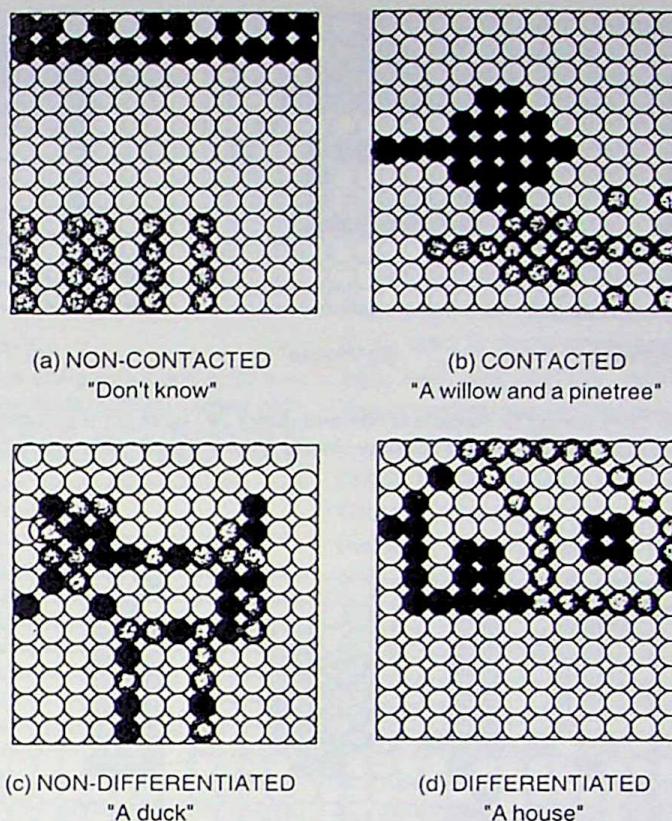


Fig. 1.- Examples of the basic patterns. Red (recipient's) and blue (donor's) marbles are represented here as \circ and \bullet respectively.

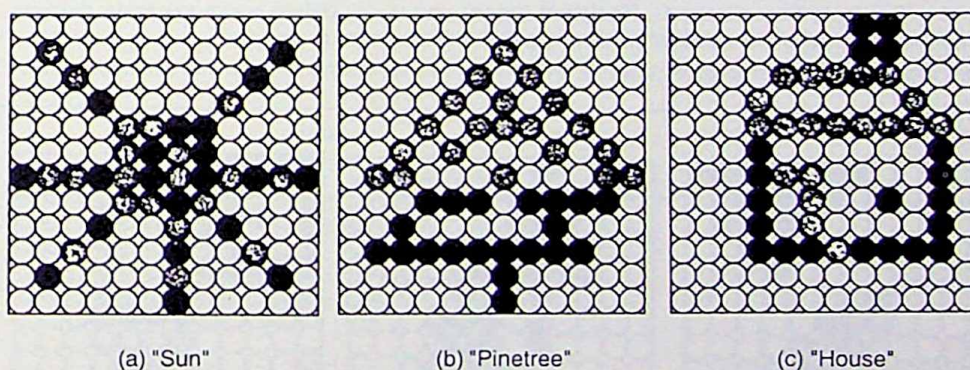


Fig. 2.- Example from Group A. Recipient (\circ) and donor (\bullet) work on a common design. At the beginning (a), recipient's and donor's marbles are randomly distributed in an enmeshed, non-differentiated pattern. As the test progresses (b and c), the designs show clearly differentiated parts, separately made by each participant.

b) Changes throughout the test

After classifying each design, the complete series of three consecutive designs made in one session has to be considered. The sequence may begin with contact avoidance (Fig. 1a) or with enmeshment (Fig. 1c), and then progress to contact (Fig. 1b) or to distinct boundaries (Fig. 1d); or it may change from contact or boundaries at the beginning, to avoidance or enmeshment at the end. It may also show stable contact or

boundaries throughout the test, as well as stable enmeshment and contact avoidance throughout.

Using these criteria, four patient populations were defined:

Group A: from a non contacted or a non differentiated pattern at the beginning, to a contacted or a differentiated one at the end (Fig. 2).

Group B: contacted or differentiated patterns throughout the test (Fig. 3).

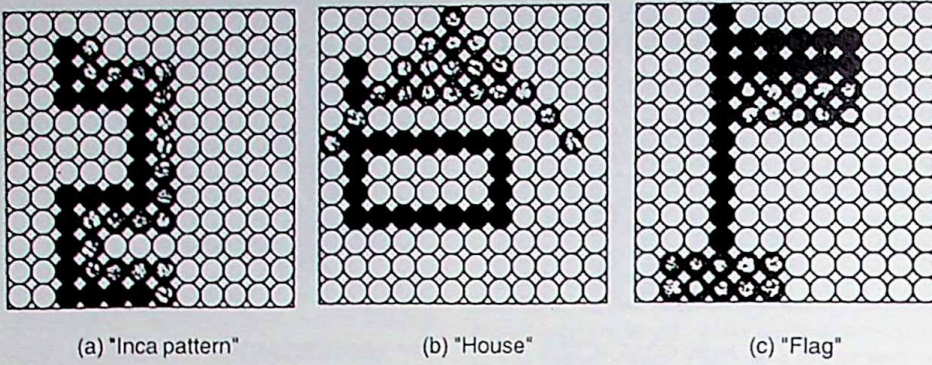


Fig. 3 – Example from Group B. Recipient (○) and donor (●) work on a common design. Patterns throughout the test (a, b, and c) show clearly differentiated parts made by each participant.

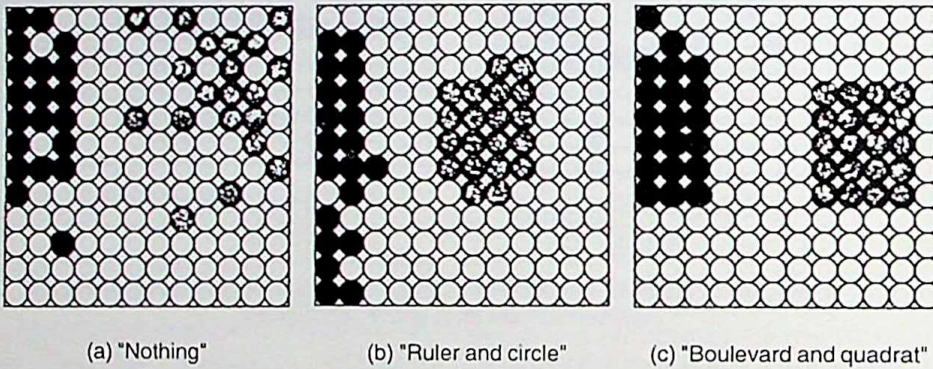


Fig. 4.– Example from Group C. Recipient (open) and donor (filled) make separate designs, and no connection is established at any point of the test (a, b, and c).

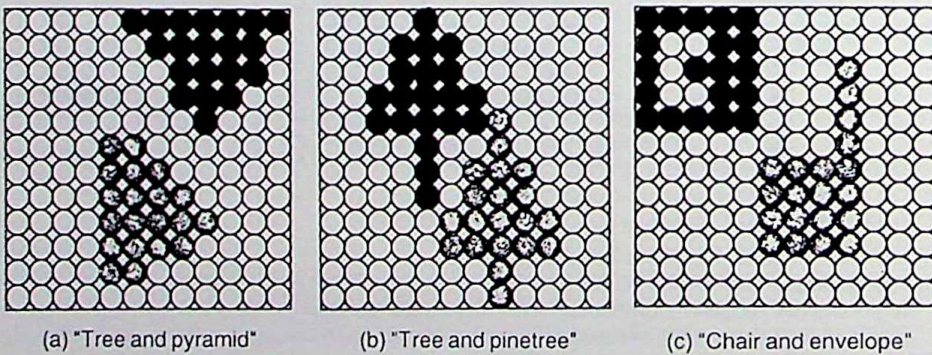


Fig. 5.– Example from Group D. The initial similarity or connection in shape (a) or subject (b) disappears in the last trial (c).

Group C: non contacted or non differentiated patterns throughout the test (Fig. 4).

Group D: from a contacted or a differentiated pattern at the beginning, to a non contacted or a non differentiated one at the end (Fig. 5).

Interrater reliability

Assignment to one of the four groups was performed prior to transplantation by two of the authors (SGA and MIM) working jointly. To assess interrater reliability, fifty-one consecutive

tests were classified by an independent scorer (Dr. E. Dykens, Yale CSC), following the criteria described above. When her classification was compared with the classification of the authors, interrater reliability was high (Kappa = .81).

Patient characteristics

Table 1 shows patient characteristics in the four groups. Thirty-three patients fell into Group A, 33 into Group B, 53 into Group C, and 35 into Group D.

Statistical methods

The overall association of group assignment and graft survival was compared by life table methods. Kaplan - Meier estimates²³ were calculated for each group, using reentrance in chronic dialysis as the end point (graft failure). Patient death was always considered graft failure. Graft survival in the four groups was compared by the log-rank test²⁴.

Univariate and multivariate analyses were performed²⁵. Univariate analysis correlated interactional pattern (group assignment) with R and D sex, sex difference, relationship, HLA-identity, immunosuppression, and graft failure. Graft failure was also correlated with those variables through univariate analysis. We then categorized patients according to whether they belonged to Group A or to non-A (Groups B, C, and D) and used a logistic regression analysis with graft failure as the outcome variable, examining the following covariates: interactional pattern (Group A / Group non-A), immunosuppression (Azathioprine and Prednisone vs Azathioprine, Prednisone and CsA), R and D sex, age, sex identity, relationship, and HLA-identity (HLA-identical vs HLA-non identical). The same covariates were examined using Cox' proportional hazards regression method²⁶.

Final results were considered significant for $p < 0.05$. Data were analyzed using the statistical software package CSS/Statistica 3.1, in IBM PS/2 35-SX. DeltaGraph Professional 2.0.1 was used for graphs in McIntosh Ilci.

Results

No significant differences in patient characteristics were found among the four groups (Table 1). Groups A, B, C, and D were comparable with regard to R and D age, sex, sex identity, relationship, HLA-identity, and immunosuppressive treatment received.

As shown in Fig. 6, kidney graft survival was significantly better for Group A than for any other group, with Group D having the worst transplantation results. For instance 72 months after transplantation, Group A had 80% of functioning grafts, while Group D had only 29%. The difference in survival between Group A and the other groups increased with time. Differences between Groups B, C, and D were not significant.

Causes of graft failure for each group are shown in Table 2. Rejection, both acute and chronic, and infections secondary to immunosuppression, were considered immunological causes. Non immunological causes included cardiac arrest, accidents and suicide. Ninety percent of graft failure or deaths were due to immunological causes.

TABLE 1.— Recipient and Donor Characteristics in Four Test Groups According to Interactional Pattern

		Group A N: 33	Group B N: 33	Group C N: 53	Group D N: 35	P Value
Age	Mean/SD					
	R	31.7 ± 10.8	31.3 ± 9.9	31.4 ± 9.7	29.5 ± 9.6	NS
	D	40.8 ± 13.5	43.2 ± 10.7	39.7 ± 11.4	44.1 ± 12.1	NS
Sex	Male/Female					
	R	20/13	26/7	36/17	19/16	NS
	D	16/17	11/22	20/33	10/25	NS
Sex identity	Identical	19	10	23	16	
	Different	14	23	30	19	NS
Relationship	Parent to child	13	17	21	19	
	Siblings	17	13	24	13	NS
	Other	3	3	8	3	
HLA - Identity	Non-identical	27	30	46	33	
	Identical	6	3	7	2	NS
Immunosuppression	Aza + Pred	13	8	9	10	
	CsA added	20	25	44	25	NS

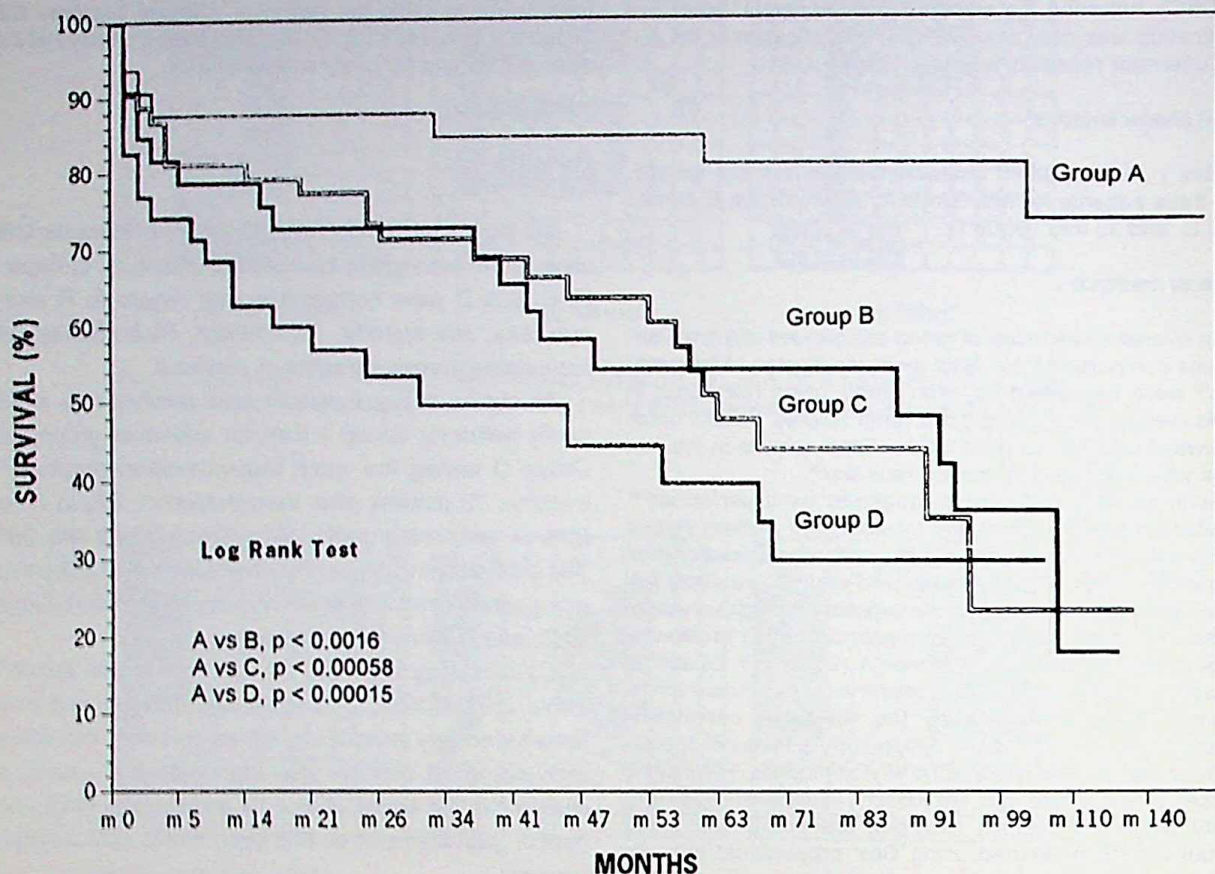


Fig. 6.- Kidney survival in 154 recipient-donor pairs according to interactional pattern. In Group A survival of the graft is significantly better than in any other group. Differences between Groups B, C, and D are not significant.

TABLE 2.- Causes of graft failure or death in 154 transplantations

	Group A N : 33	Group B N : 33	Group C N : 53	Group D N : 35
<i>Immunological</i> (N: 65)				
(Rejection or secondary to immunosuppression)	6	18	21	20
<i>Non immunological</i> (N:7)				
(Cardiac arrest, accident, suicide, etc)	1	0	5	1

Ninety percent of graft failure or deaths were due to immunological causes

Logistic regression analysis (Table 3) showed evidence for a relationship between failure of kidney graft and interactional pattern ($p < 0.0005$). Having a non-A interactional pattern significantly increased the probability of graft failure. Conventional immunosuppressive treatment (Azathioprine and Prednisone without Cyclosporine)

was also significantly associated with graft failure ($p < 0.004$). No other variable was prognostically significant.

Proportional hazards regression (Table 4) showed a significantly increased risk of graft failure for non-A interactional patterns (RR 4.92) and for patients treated

TABLE 3.— *The results of a logistic regression analysis relating graft failure to several variables*

Covariate	Coefficient	Standard error	P-Value	Adjusted O R	Confidence interval
Interactional pattern (B, C, and D vs. A)	- 1.813	0.509	< 0.0005	6.13	2.26-16.6
Immunosuppression (Aza+Pred vs. CsA added)	- 1.268	0.433	< 0.004	3.55	1.52-8.31
Recipient's sex	- 0.528	0.457	0.249		
Donor's sex	- 0.206	0.475	0.665		
Recipient's age	0.011	0.020	0.584		
Donor's age	- 0.022	0.0024	0.372		
Sex identity	- 0.369	0.461	0.424		
Relationship	- 0.747	0.482	0.123		
HLA - Identity	0.061	0.540	0.911		

TABLE 4.— *The results of a proportional hazards regression analysis of graft failure based on 154 transplanted patients*

Covariate	Coefficient	Standard error	P-Value	RR	95% Conf. interval
Interactional pattern (B, C, and D vs. A)	- 1.594	0.412	< 0.0001	4.92	2.19-11.1
Immunosuppression (Aza + Pred vs. CsA added)	- 0.606	0.260	< 0.022	1.83	1.10-3.05
Recipient's sex	- 0.014	0.304	NS		
Donor's sex	- 0.287	0.292	NS		
Recipient's age	0.014	0.015	NS		
Donor's age	- 0.006	0.016	NS		
Sex identity	- 0.012	0.312	NS		
Relationship	- 0.063	0.354	NS		
HLA-Identity	0.159	0.350	NS		

without Cyclosporine (RR 1.83). Patients with both conditions (non-A interactional patterns and no Cyclosporine) had a relative risk 9 times higher than patients with A-patterns and CsA-treatment.

Discussion

In this study we tried to answer the question whether assessing the behavioral interaction of recipient and donor would be useful in exploring prognostic aspects in organ transplantation. Our results clearly showed a correlation between the type of interaction immediately prior to transplantation and kidney graft survival.

The patient group with best survival chances was Group A. In this group, recipient and donor showed at the beginning of the test primitive patterns of interaction. Most pairs in this group (Fig. 2) began with an enmeshed, agglutinated graphic pattern with no boundaries between the two participants. As the test progressed, a pattern emerged where boundaries became clear while, at the same time, contact was not avoided. The other pairs in this group started with contact avoidance and were also increasingly able to contact each other while keeping some self-boundaries.

The group with the lowest survival chances, Group D, showed the exactly opposite sequence (Fig. 5): during the test, the initial contact with boundaries between re-

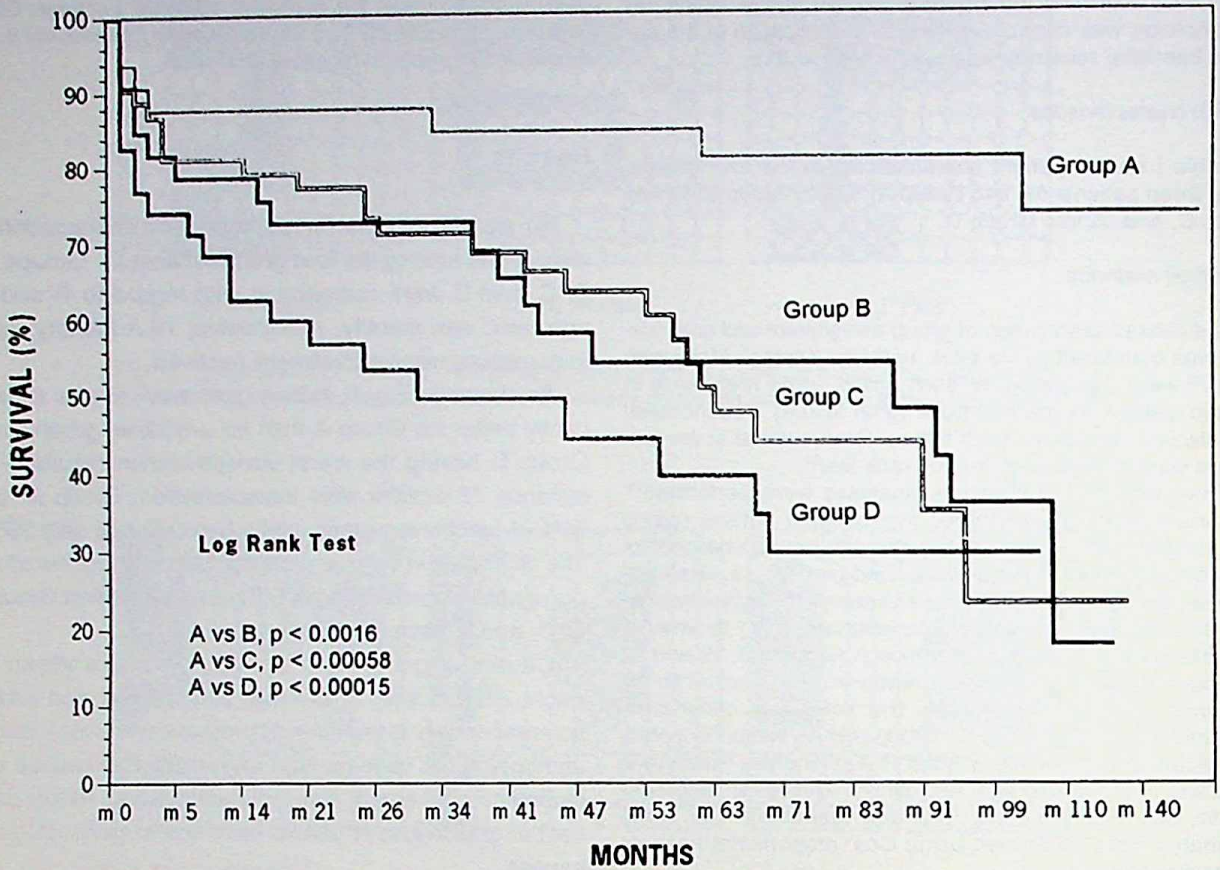


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The group with the lowest survival chances, Group D, showed the exactly opposite sequence (Fig. 5): during the test, the initial contact with boundaries between re-

recipient and donor was progressively lost and ended in isolation or enmeshment.

The population studied herein included patients who were transplanted at a time when major advances in treatment strategies, especially Cyclosporine, were not available, a fact that can account for the low overall survival figures. Treatment modality, however, was not different among groups: patients in Group A did not receive Cyclosporine more frequently than patients in the other groups.

The main cause of graft failure was immunological (rejection in most cases, and infections secondary to immunosuppression). Since immunologically determined graft failure appeared associated with test pattern, the question could be raised whether there are "behavioral markers" of the immune status, for which rejection is a good indicator. The present data are insufficient to answer such a question. It would also be inaccurate to postulate a unidirectional causal link between both levels, postulating for instance¹³ that psychological factors induce rejection. Although there is some evidence for the impact of anxiety, bereavement, depression, and poor coping strategies on immune system components^{4, 6, 7, 10, 11}, relationships between behavioral and biological dimensions of immune system functioning are more accurately represented as non-linear and complex²⁷. The mediating factors between primitive or rigid interaction patterns and graft failure still have to be identified, since these patterns could also be related to difficulties in managing the multiple problems involved in transplantation, and not primarily to the immune response to the graft.

In organ transplantation with a living donor, it seems fruitful to approach psychological variables from an interactional perspective. In a different context, studies of immune system functioning are beginning to include interpersonal factors^{28, 29}. We have not assessed the role of individual variables such as anxiety and depression on interaction and on transplant prognosis; the assessment of individual factors may help better understand interactive results such as blurred boundaries, avoidance behavior, or contacted patterns. However, the only systematic assessment of individual variables in relation to transplant outcome¹⁵ failed to show any significant correlation with prognosis.

In this study, we restricted our analysis of interaction to the sequence of graphic patterns in the selected test method. To ensure that differences are found, the relationship between recipient and donor has to be assessed by additional measures of interaction, and studies in other transplant centers with socioculturally different populations are also needed. In spite of these limitations, our study points to the possibility that a reproducible behavioral test contributes useful information for prognosis in kidney transplantation with a living donor, and that

prognosis can be related to the psychological ability to moderate the initial reaction of extreme affirmation or negation of self-identity and individuality in front of a specific donor. It underscores the necessity to include psychological and especially interactional questions in the investigation of factors involved in the human response to a grafted organ.

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Everywhere the old order changes and happy they who can change with it.

Por doquier, el viejo orden cambia y felices quienes, a su vez, pueden cambiar.

Sir William Osler (1849-1919)
The Principles and Practice of Medicine, 1895