HUMAN LEUCOCYTE TYPING IN CLINICAL TRANSPLANTATION*

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At the outset two firm statements can be made: firstly, there is now convincing proof that human leucocyte antigens are transplantation antigens which are capable of influencing the function and survival of kidney transplants; secondly, it is becoming almost universally accepted that matching of donor and recipient in terms of their leucocyte antigens is desirable. There is, however, uncertainty in many quarters as to just how desirable, or necessary, prospective leucocyte antigen typing is in clinical practice; and if it is done, to what extent it must be taken into consideration before embarking on a transplant.

The current value of leucocyte typing in transplantation practice is best assessed by reviewing the accumulated evidence which established a correlation between the degree of leucocyte antigen matching of donor-recipient pairs and the outcome of their renal transplants. When doing so, it is as well to bear in mind the many reservations expressed in these reports by the investigators themselves. Problems arose from the fact that neither of the two variables under examination, i.e. the degree of rejection and the degree of histocompatibility, was easy to measure. Clinical assessment of the success of transplantation was often unsatisfactory. Rejection was difficult to recognize in the presence of post-transplantation surgical and medical complications; there were differences in immunosuppressive treatment from patient to patient, and between groups of patients; and differing criteria could be and were applied to judge failure of a kidney transplant. On the other hand, the second variable, i.e. what constitutes a matched donor-recipient pair, was also difficult to define. Initially there was uncertainty because the antisera which were used were admittedly unsatisfactory as regards specificity and reproducibility of results; and it was recognized that current methods of typing were almost certainly not capable of distinguishing all the transplantation antigens. An important criticism of the earlier studies which were based on retrospective leucocyte typing of live donors and recipients was exclusion of those recipients who had died.

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LEUCOCYTE ANTIGEN MATCHING AND THE RESULTS OF KIDNEY TRANSPLANTS

Table I summarizes most of the experience of the past 5 years of leucocyte antigen matching and kidney transplants.[1-23] Studies dealing mainly with related donors should be regarded separately from those which are con-

TABLE I. SUMMARY OF KIDNEY TRANSPLANT RECIPIENTS AND THE CRITERIA FOR GRAFT SUCCESS WHICH WERE USED TO ESTABLISH THE VALUE OF LEUCOCYTE ANTIGEN TYPING

Year	*Reference*	*Recipients studies*	*Type of donor*	*Criteria of success*	*Correlation*
1964	Starzl *et al.*[1]	36 survivors	Mainly related, live	(1) Clinical status (2) Graft histology	Inconclusive
1965	Vredevoe *et al.*[2]	15 survivors 2 non-survivors	Mainly related, live	Clinical status	Some degree
1966	Terasaki *et al.*[3]	36 survivors	Mainly related, live	(1) Clinical status (2) Graft histology	Highly significant
1966	Terasaki *et al.*[4]	32 prospective	Related and unrelated, live	(1) Patient survival (2) Graft histology	Significant
1967	Lee *et al.*[5]	36 survivors	Mainly related, live	Clinical status	Significant
1967	Terasaki *et al.*[6]	196 recipients	Related and unrelated	Graft survival	Marginal
1967	Terasaki *et al.*[7]	209 recipients	Related and unrelated	Clinical status	Highly significant
1967	Payne *et al.*[8]	23 survivors	Related	Clinical status	Significant
1967	Stickel *et al.*[9]	7 prospective	Related	Clinical status	Significant
1967	Rapaport *et al.*[10]	59 survivors	Related	Clinical status	Significant
1968	Rapaport and Dausset[11]	59 survivors	Related	Clinical status	Significant
1968	Dausset and Rapaport[12]	61 survivors	Related	Clinical status	Significant
1968	Dausset *et al.*[13]	71 survivors	Related	Graft survival	Very highly significant
1969	Singal *et al.*[14]	107 recipients 147 recipients	Sibling Parent	Clinical status Clinical status	Highly significant Significant
1967	Van Rood *et al.*[15]	45 survivors	(1) Sib-to-sib (2) Parent-to-child	(1) Patient survival (2) Graft histology	Partly significant
1968	Van Rood *et al.*[16]	45 survivors	(1) Sib-to-sib (2) Parent-to-child	Patient survival	Borderline
1968	Van Rood and Eernisse[17]	45 survivors	(1) Sib-to-sib (2) Parent-to-child	Patient survival	Significant
1968	Van Rood *et al.*[18]	(1) 72 survivors (2) 37 prospective	(1) Related and unrelated (2) Unrelated cadaver	Patient survival Patient survival	(1) Highly significant (2) Significant
1968	Kissmeyer-Nielsen *et al.*[19]	66 prospective and retrospective	Separate genetic classes, and unrelated	Clinical status	Highly significant
1968	Hume *et al.*[20]	61	Related and unrelated	Clinical status	Highly significant
1968	Patel *et al.*[21]	104 prospective and retrospective	Unrelated, mainly cadaver	(1) Clinical status (2) Graft survival	Significant
1968	Morris *et al.*[22]	27 prospective and retrospective	Unrelated, all cadaver	(1) Clinical status (2) Graft histology	Significant
1969	Batchelor and Joysey[23]	52 recipients	Unrelated, all cadaver	Clinical status	Significant

cerned mainly with unrelated donors. Such distinction on the basis of the genetic class of the donor is of considerable importance in considering the immunogenetic theory of leucocyte antigen matching; and the greater degree of success which has been obtained in practice with related-donor transplants has long been recognized clinically.

In these studies several criteria have been used for assessing the results of kidney transplants. These have included survival of the patient, survival of the graft, the clinical condition of the surviving patient and the histology of the transplanted organ. Among these measures of success or failure, the clinical status of the surviving recipient has proved the most difficult. In order to achieve acceptable clinical comparison between recipients in a series, it has been necessary to base the clinical ranking on several parameters. Among the proposals for establishing several clinical ranks, the formula which was used by Lee *et al.*[5] from Richmond, Virginia, has been adopted in other centres. As an example of a clinical approach the outlines of this scheme are given in Table II. Renal function is judged on blood urea nitrogen levels, endogenous creatinine clearance and blood pressure; rejection is graded according to the onset, number and severity of separate episodes observed clinically. The clinical status of each patient is finally determined by a synthesis of renal function and rejection.

The function of a transplanted kidney may be affected by medical and surgical complications other than rejection; and it is commonly difficult to diagnose a rejection episode with certainty, particularly in the early postoperative period. Histological examination of the graft provides a more objective and certain means of determining the occurrence and severity of rejection. Furthermore, post-mortem material and biopsy specimens may be combined to provide an entire series. The histological grading of Porter *et al.*[24] has been widely adopted and has proved very useful. The main features which are taken into account are the following:

1. Fibrous thickening of the intima of interlobular arteries.
2. Hyalinization of the walls of the arterioles.
3. Thickening of the glomerular capillary basement membranes.
4. Generalized interstitial fibrosis.
5. Superficial subcapsular interstitial fibrosis.
6. Cellular fibrosis.
7. Tubular atrophy.

Each lesion is scored from 1 to 3 for severity and then scores are totalled for each kidney. Possible scores range from 0 to 21.

Differences in clinical results were analysed in terms of degrees of correspondence between the leucocyte antigens of donor and recipient. The degree of leucocyte antigen matching has also been expressed in several ways. Several terms have been used, quite often synonymously. 'Mismatched' is sometimes used to imply incompatibility, i.e. the donor possesses an antigen which is lacking in the recipient; at other times 'mismatched' implies lack of identity but compatibility, i.e. the donor is lacking an antigen which is present in the recipient; this latter situation is sometimes described by the term 'reverse mismatch'; 'matched' may be used to imply 'identity', i.e. donor and recipient agree in respect of every antiserum which is used; however, in some studies 'matched' means no more than that there is no direct incompatibility from donor to recipient, but still permits the recipient to react positively with certain antisera to which the donor is negative.

The confusion which may arise from untidy semantics is bad enough. Even more confusing has been the use of several different nomenclatures to designate leucocyte antigens; and the number of antigens which were detected by different serological techniques used in several centres varied considerably from centre to centre, and within one centre from time to time.

Less ambiguous definitions for classifying the degree of leucocyte antigen matching have been introduced recently. As examples, the terms used by Terasaki and by Van Rood respectively are given in Tables III and IV.

Leucocyte serology made a very significant advance when it was shown at the 1967 Workshop in Turin[25] that many independent workers using a variety of serological methods were recognizing equivalent or closely related antigens (Table V). Furthermore, penetrating family studies such as those performed by Kissmeyer-Nielsen *et al.*[19,26] and Dausset and Rapaport[27] have revealed the distribution of antigens of narrow specificity at either of two sub-loci of the HL-A system[28] of leucocyte groups (Table VI). In these terms, an individual could possess a

TABLE II. THE CLINICAL RANKING OF KIDNEY TRANSPLANT RECIPIENTS (AFTER LEE *et al.*)[5]

1.	*Renal Function**	
	Grade A	BUN less than 20 mg./100 ml. ECC over 70 ml./min. BP normal
	Grade B	BUN 20–40 mg./100 ml. ECC 70–40 ml./min. BP diastolic(over 110 mm.Hg)controlled without medication
	Grade C	BUN 40–100 mg./100 ml. ECC 40–20 ml./min. BP hypertension (over 110 mm.Hg) controlled with medication
	Grade D	BUN over 100 mg./100 ml. ECC less than 20 ml./min. BP hypertension difficult to control
2.	*Rejection*	
	Type A	No rejection in first 4 months No significant protein loss in urine
	Type B	One rejection episode in first 4 months
	Type C	Multiple rejection episodes in first 4 months Any rejection episode after first 4 months
	Type D	(1) Rejection in the first week (2) Rejection lasting longer than 30 days (3) Rejection episode requiring nephrectomy
3.	*Clinical Ranks*	
	Rank A	Minimum rejection crisis Normal renal function Excellent general condition
	Rank B	Moderate rejection crisis Subnormal but good renal function Good general health
	Rank C	Moderate rejection crisis Poor renal function Fair to poor general health
	Rank D	Kidney has rejected

*BUN = blood urea nitrogen; ECC = endogenous creatinine clearance; BP = blood pressure.

maximum of 4 antigens in the HL-A system. It is to be noted, however, that evidence for the possibility of a third sub-locus has been presented;[29] this would raise the possible maximum to 6 antigens per individual. As the immunogenetics of the leucocyte antigens are becoming increasingly clear, the possibility of accurately analysing the degree of correspondence between a donor and recipient also increases.

TABLE III. TERMS USED BY TERASAKI *et al.*[4]

Symbol	*Meaning*
A	Identical A+ = sib-to-sib A = parent-to-child A− = unrelated
B	Matched D to R (mismatched R to D) B+ = R–D mismatched in 1 group B = R–D mismatched in 2 groups B− = R–D mismatched in 3 or more groups
C	Mismatched D to R in 1 group C = R to D further mismatched in 0–2 groups C− = R to D further mismatched in 3 or more groups
D	Mismatched D to R in 2 groups D = R to D further mismatched in 0–2 groups D− = R to D further mismatched in 3 or more groups
F	Positive crossmatch: R serum reacts positively in cytotoxic test with D lymphocytes

TABLE IV. TERMS USED BY VAN ROOD

Term	*Meaning*
Identity	Leucocyte groups of donor and recipient are identical for the HL–A antigens
Near identity	Leucocyte groups of donor and recipient are identical for the HL–A antigens, except for one antigen
Not identical 2–3	Leucocyte groups of donor and recipient are different for 2 to 3 of the HL–A antigens
Not identical 4 or more	Leucocyte groups of donor and recipient are different for 4 or more of the HL–A antigens

REPRESENTATIVE EXAMPLES OF CORRELATION STUDIES

Although some uncertainty has admittedly existed in measuring clinical success as well as in defining leucocyte antigen matching, the majority of studies concluded that the closer the degree of matching the better the outcome of the kidney transplant. The statistical correlation has become progressively stronger in more recent analyses; this is undoubtedly due to a combination of more successful management of clinical complications other than rejection, and increasing accuracy of leucocyte typing methods.

Several important points which must be considered in determining the importance of leucocyte antigen matching in human organ transplantation emerged from the reports listed in Table I. For the purpose of discussion, a number of illustrative tables have been reproduced or prepared from those reports.

The pioneer studies of Terasaki *et al.*[3,6] showed that a closer degree of matching was correlated with improved results in several directions; recipients who had been better matched with their donors had less evident rejection, were in better clinical condition and had a greater chance of survival (Tables VII - IX). Payne *et al.*,[5] using a different technique of determining leucocyte antigens, confirmed the observation that recipients with matched correlated donors were in better clinical condition than those patients whose related donors were not well matched; the recipients were assessed clinically according to Lee *et al.*[5] (Table II). Using the same clinical classification, but yet another serological technique, Dausset and Rapaport[31] found a strong statistical correlation between compatibility and a reduced evidence of rejection and longer survival of the recipient (Table X). Whereas the conclusion had

TABLE V. HL-A NOMENCLATURE AND PREVIOUS DESIGNATIONS[25, 28]

New HL-A nomenclature	*Amos*	*Batchelor*	*Ceppellini*	*Dausset*	*Kissmeyer-Nielsen*	*Payne/ Bodmer*	*Van Rood*	*Shulman*	*Terasaki*	*Walford*
HL-A1	19	1	To-8	11	LA1	LA1			1	Lc-1
HL-A2	1	5	To-9	1 or Mac	LA2]Ba	LA2	8a	PIGrLyB[1]	2	Lc-2
HL-A3	4		To-10	12	LA3]ILN	LA3		Hill	8	Lc-3
HL-A4							[4a]			
HL-A5	45	25	To-5	5	MH				6	
HL-A6							[4b]			
HL-A7	2		To-20	10	KN4B	4d	7c		5	Lc-8
HL-A8	41	2	To-7	8		7d	7d		11	Lc-7

HL-A4 will be reserved for one of the higher frequency 4a factors, and HL-A6 for 4^b.

TABLE VI. ANTIGENS ALLOCATED TO THE TWO MAIN SUB-LOCI OF THE HL-A SYSTEM ACCORDING TO DAUSSET AND KISSMEYER-NIELSEN RESPECTIVELY

Kissmeyer-Nielsen	*Two alleles controlling the HL-A system of leucocyte antigens*	*Dausset*
LA1, LA2, LA3, LA4, (NIH), Ba, ILN	First sub-locus	LA1 (= 11), LA2 (= 1), LA3 (= 12), 15, 16, 17,
T12, MH, 7c, 7d, 4c(Payne), HN, BB	Second sub-locus	4, 5, 10, 8

been made in some of the earlier studies that the beneficial effect of leucocyte matching only became evident among long-term survivors, Dausset's study revealed that proved leucocyte compatibility also had an effect in reducing the number and severity of early rejection episodes (Table XI).

Among the criticisms levelled at these earlier studies was that of Van Rood *et al.*[15-17] who pointed out that although the donor-recipient pairs were exclusively or mainly related, the clinical material under analysis was not genetically homogenous. It was known from the earlier days of kidney transplantation that the genetic relationship between donor and recipient had in itself a significant effect in survival. Fig. 1, which is redrawn from the presentation of the Boston Kidney Transplantation Registry data by Ceppellini *et al.*,[30] illustrates the post-transplant course of recipients divided according to the genetic relationship of their donor. The genetic explanation for this variation was published by Van Rood *et al.*[16] and in Table XII we have extended his argument.

TABLE VII. CORRELATION BETWEEN NUMBER OF MISMATCHED LEUCOCYTE GROUPS AND CLINICAL GRADES OF 36 KIDNEY RECIPIENTS SURVIVING 2 YEARS (AFTER TERASAKI *et al.*)[3]

Clinical grade	*Number of mismatched groups*		
	Nil	*One*	*Two*
1	10	3	1
2	5	5	1
3	0	4	4
4	0	2	1
	15	14	7

$p' = \cdot 004$

TABLE VIII. CORRELATION BETWEEN MISMATCHED LEUCOCYTE GROUPS AND HISTOLOGICAL EVIDENCE OF REJECTION IN KIDNEYS SURVIVING 2 YEARS AFTER TRANSPLANT (AFTER TERASAKI *et al.*)[3]

Group	*Rejection*	
	Evident	*Not evident*
Incompatible	18	2
Compatible	7	8

TABLE IX. CORRELATION BETWEEN LEUCOCYTE GROUP MATCHING AND SURVIVAL OF PATIENTS WITH RENAL ALLOGRAFTS (AFTER TERASAKI *et al.*)[6]

Patients and donors	*Patients*	
	Alive	*Died*
Matched	69	17
Mismatched	63	43

$x = 8 \cdot 6$
$P = \cdot 005$

TABLE X. LEUCOCYTE GROUP COMPATIBILITY CORRELATED WITH REJECTION OR SURVIVAL OF RENAL TRANSPLANTS (RELATED DONORS) AT 28 MONTHS (AFTER RAPAPORT AND DAUSSET)[11]

Patients	*Incompatibles*	*Compatibles*
Total patients	13	24
Rejection evident	69·2%	8·3%
Surviving transplant	30·7%	91·6%

$P < 0 \cdot 001$

TABLE XI. LEUCOCYTE GROUP COMPATIBILITY CORRELATED WITH SEVERITY OF EARLY REJECTION CRISES IN 14 SIBLING TRANSPLANTS (HUME'S SERIES) (AFTER RAPAPORT AND DAUSSET)[11]

Degree of compatibility	*Severity of early rejection*	
	Milder	*Severe*
Compatible	8	1
Incompatible	0	5

$P < 0 \cdot 01$

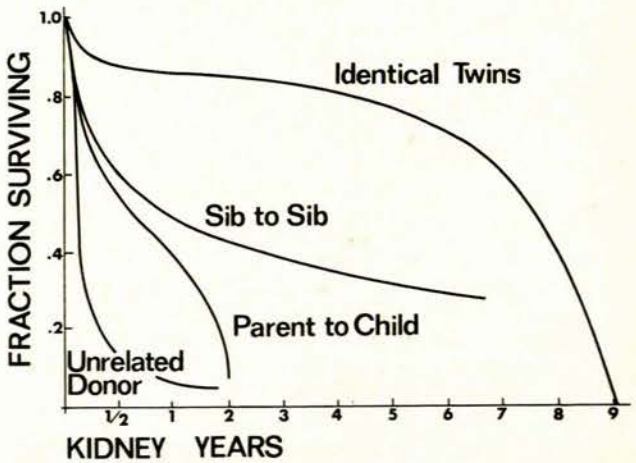


Fig. 1. Different survival curves for several classes of related donor kidney transplants and unrelated donor kidney transplants before 1966.

TABLE XII. RELATIONSHIP BETWEEN GENOTYPES OF PARENTS AND THE DIFFERENCE IN DEGREE OF HISTOCOMPATIBILITY FOR THE TWO DONOR-RECIPIENT RELATIONSHIPS (AFTER VAN ROOD *et al*)[16]

Type of mating	*Genotypes of:*		*Donor-recipient relationship*	*Random donor-recipient matches*	
	Parents	*Children*		*Identical*	*Compatible*
Both heterozygous;	1, 2 ×	1, 3; 1, 4;	Sib-to-Sib	25%	0
no common allele	3, 4	2, 3; 2, 4.	Parent-to-Child	0	0
Both heterozygous;	1, 2 ×	1, 1; 1, 3;	Sib-to-Sib	25%	12½%
one common allele	1, 3	1, 2; 2, 3.	Parent-to-Child	25%	0
One homozygous;	1, 1 ×	1, 2; 1, 3;	Sib-to-Sib	50%	0
no common allele	2, 3		Parent-to-Child	0	50%
One homozygous;	1, 1 ×	1, 1; 1, 2;	Sib-to-Sib	50%	50%
one common allele	1, 2		Parent-to-Child	50%	75%

In order to allow for the influence of this variable in their analysis, Van Rood *et al.*[15-17] separated sibling-to-sibling transplants from parent-to-child transplants, and in both genetic classes compared matching with the 2-year survival of the recipients (Tables XIII and XIV). It appeared from this study that identity or near identity (no more than one antigen differing between donor and recipient), for the 9 antigens of Van Rood's group 4 system, was the only situation which improved the survival. Compatibility

alone, i.e. a situation where the donor lacked antigens which were present in the recipient, was not associated with better results than were incompatibilities. Identical matching was statistically associated with survival in the sibling-to-sibling transplants; the correlation was not statistically significant in the parent-child combinations in this series. These observations persuaded Van Rood and Eernisse[17] to classify as well-matched only related donor-recipient pairs which were identical, or nearly so (Table XV). Kissmeyer-Nielsen *et al.*[19] provided clear confirmation of the importance of identity or near-identity in family donor transplants. In Table XVI it can be seen that such a degree of leucocyte antigen matching was consistently associated with recipients in better clinical ranks; whereas incompatibility for two of Kissmeyer-Nielsen's antigens was associated with an inferior clinical condition.

The difference in the degree of correlation between matching and clinical outcome as observed in sibling-to-sibling transplants compared with parent-to-child transplants has recently been further emphasized by Singal *et al.*[14] In a series of sibling transplants a very clear correlation between leucocyte antigen matching and the clinical outcome was observed. In contrast, very little difference was seen between matched and mismatched donor-recipient pairs in parent-to-child transplants (Figs. 2 and 3). In considering this discrepancy, it was suggested that different degrees of compatibility, which would be expected in the two genetic classes, may offer an explanation.

TABLE XIII. KIDNEY GRAFT SURVIVAL AND HL-A ANTIGENS (SIB-TO-SIB) (AFTER VAN ROOD *et al.*)[16]

Patients grafted	40		
Patients alive		18	
	Expected from random population studies	*Patients observed*	*% surviving*
Identical	10·4	10	96·2
Compatible	8·3	2	24·1
Incompatible	21·3	6	28·2
		$p < 0·01$	

TABLE XIV. KIDNEY GRAFT SURVIVAL AND HL-A ANTIGENS (PARENT-TO-CHILD) (AFTER VAN ROOD *et al.*)[16]

Patients grafted	54		
Patients alive		27	
	Expected from random population studies	*Patients observed*	*% surviving*
Identical	6·8	7	102·9
Compatible	11·8	3	25·4
Incompatible	35·3	17	48·2
	54	27	
		$p < 0·1$	

TABLE XV. CORRELATION BETWEEN IDENTITY FOR LEUCOCYTE ANTIGENS AND SURVIVAL OF SIB-TO-SIB KIDNEY GRAFT RECIPIENTS (AFTER VAN ROOD AND EERNISSE)[17]

Patients grafted	40		
Patients alive		18	
	Random patients expected	*Surviving patients expected*	*Surviving patients observed*
Identical	10·4	4·7	10
Not identical	29·6	13·3	8
	40	18	18
		$p = ·01$	

TABLE XVI. CORRELATION BETWEEN DEGREE OF LEUCOCYTE MATCHING AND CLINICAL STATUS, IN 17 RELATED DONOR-RECIPIENT PAIRS (AFTER KISSMEYER-NIELSEN *et al.*)[19]

	Sib to sib	*Parent to child*	*Clinical ranks*			
Matching grade			*I*	*II*	*III*	*IV*
Identical antigens	8	1	9			
One D to R incompatibility		4	2	2		
Two D to R incompatibilities	2	2			2	2
					$p = > ·002$	

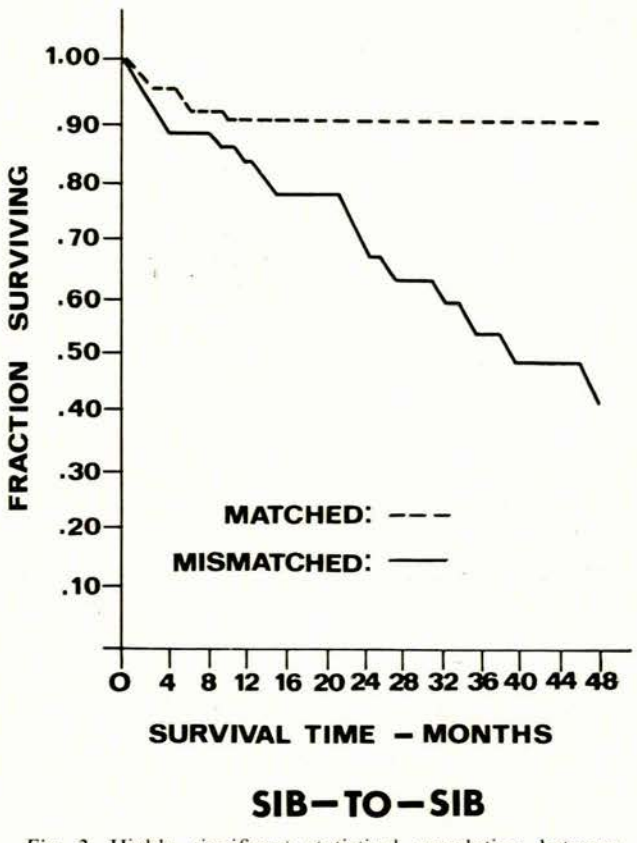


Fig. 2. Highly significant statistical correlation between leucocyte antigen matching and survival in sibling kidney transplants (adapted from Singal *et al.*).[14]

In our opinion the genetic basis for these observations can be easily illustrated; and the survival curves of sibling-to-sibling transplants can then be tentatively redrawn to provide a particularly good illustration of the role of leucocyte antigens in determining the success or otherwise of kidney transplants.

Because of the relatively large number of leucocyte antigens at each of two sub-loci, many different alleles are found in the general population. (In leucocyte immunogenetics, an allele at present represents a permanent coupling of two genes on one chromosome. Ceppellini has introduced the very useful term 'haplotype' to designate coupled antigens which segregate together in a family.) It is therefore common to find that both parents are heterozygous, i.e. each possesses two differing haplotypes or alleles. The varying probabilities of obtaining different degrees of histocompatibility in unselected parent-to-child and sibling-to-sibling transplants in this type of family is deduced from Fig. 4. In such a situation a transplant from either parent to any child must of necessity carry one different, or incompatible, allele. The distribution of these 4 parental alleles among the offspring determines that a random transplant between any two siblings will stand a 50% chance of being incompatible for one allele, i.e. the same degree of incompatibility which follows from parent-to-child transplants; however, every fourth random transplant from sibling-to-sibling will be identical, i.e. both the alleles will be matched; and by the same token every fourth transplant will be incompatible for two alleles.

With reference to Fig. 2, we should like to suggest that the upper survival curve for matched sibling-to-sibling transplants represents the sum of the identical transplants plus most of the transplants carrying the lesser incompatibilities which may be associated with a one-allele difference between donor and recipient; while the lower curve for mismatched sibling pairs represents the transplants of two-allele differences, plus that proportion of one-allele-differing transplants which carry the less favourable degrees of incompatibility which may be associated with one-allele differences. On theoretical grounds survival curves for the 50% of sibling transplants which are different for one allele would occupy more or less the same position as that occupied by the curve of parent-to-child transplants in Fig. 3; in theory the completely identical transplants, if analysed separately, may then follow an even higher curve than that plotted by Terasaki for matched sibling-to-sibling transplants, while the 25% of transplants involving differences for both alleles may show a much steeper decline in survival if regarded separately. This hypothesis is illustrated in Fig. 5.

Since it is postulated that parent-to-child transplants in a family with two heterozygous parents always involves incompatibility for one allele, the argument that this class of transplant may be either more favourable or less favourable needs to be considered further. This raises the question of the relative strength of different leucocyte

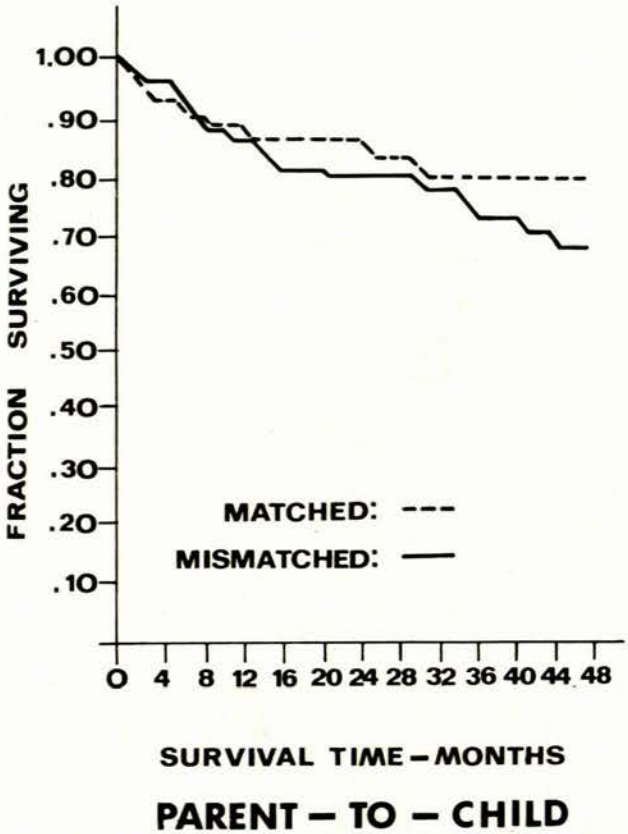
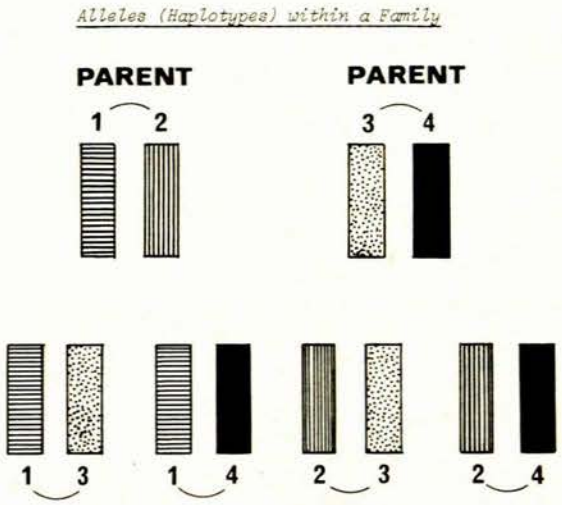


Fig. 3. Lack of high significant statistical correlation between leucocyte antigen matching and survival in parent-to-child kidney transplants (adapted from Singal *et al.*).[14]



POSSIBLE TRANSPLANTS WITHIN THE FAMILY

Genetic Class of Transplant	Compatible (identical)	Incompatible One Allele	Incompatible Two Alleles
Parent-to-child		100%	
Sib-to-sib	25%	50%	25%

Fig. 4. The probabilities of obtaining various degrees of histocompatibility in random transplants between members of a family in which the parents are heterozygous without an allele or antigen in common.

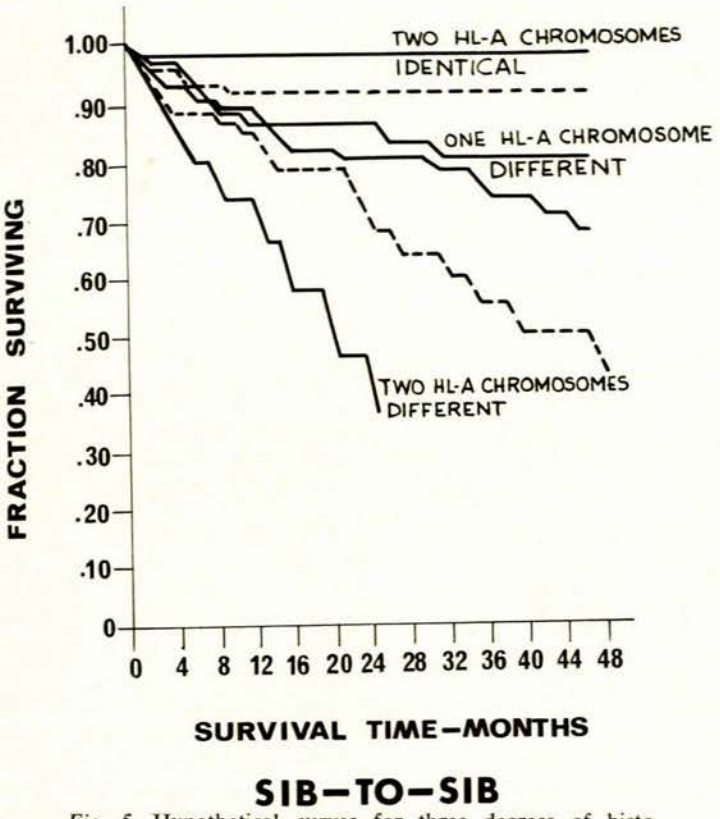


Fig. 5. Hypothetical curves for three degrees of histo-incompatibility which may be expected in sibling-to-sibling transplants in families where both parents are heterozygous for the HL-A antigens and do not possess an antigen in common; the curves in broken lines represent the observations in Fig. 2.

antigens. There is some serological, experimental and clinical evidence to suggest that certain antigens are stronger than others.[14,17,22,31-35] More important perhaps is the histocompatibility function of the total number of incompatible antigens.

Since the HL-A antigens are determined at two sub-loci at least, each individual must possess 2 - 4 differing antigens. If each parent possesses 4 different antigens and none are shared, then every parent-to-child transplant in the family will involve incompatibility for 2 antigens. Where the two parents have one antigen in common, a proportion of the parent-to-child transplants will involve only a single incompatible antigen (Fig. 6). Other variations on this theme will occur if the parents have more than one antigen, or even haplotypes in common. The different influence exerted by one-antigen incompatibility or two-antigen incompatibilities in parent-to-child transplants may explain the improved clinical results of the apparently better matched parent-to-child transplants in the series reported by Singal *et al.*[14] The fact that a high statistical correlation was not obtained is not surprising in view of the fact that antisera recognizing only 5 leucocyte groups (antigens) were used in this analysis; it is evident that such a limited range of antisera will, in a significant proportion of instances, fail to distinguish the subtle degrees of incompatibility which may occur in parent-to-child transplants.

This type of immunogenetic analysis makes it obvious also that subtle variations in the degree of incompatibility may occur in sibling-to-sibling transplants. While it remains true that incompatibility involves one allele in 25% and 2 alleles in 50% of sibling transplants, the number of incompatible antigens may vary from one to a maximum of 4. The degree of incompatibility which may occur in random sibling transplants, where the two parents have one antigen in common, is shown in Table XVII.

It becomes clear that unless an extensive range of antisera of sufficiently narrow specificity is used to type donor and recipients, it is not possible to determine with a high degree of accuracy the number of incompatible antigens, even in sibling-to-sibling transplants. In such inadequate circumstances it is not possible to obtain a clear correlation between leucocyte antigen matching and clinical results. On the other hand, when adequate serological investigation is possible, clear correlation becomes evident. This has been shown by Kissmeyer-Nielsen's experience that prospective typing of parents and children combined with genetic analysis makes it possible to obtain absolutely certain match grades for the HL-A system in certain families, without potential incompatibilities for undetermined antigens.[19] In 13 such instances where donors and recipients were pre-operatively classified as identical, or incompatible for one antigen only, the recipients were all in good clinical ranks; whereas 4 recipients whose donors were prospectively classed as incompatible for two antigens, were all in inferior clinical ranks (Table XVI).

Members of a family may be incompatible to a varying degree and the situation within a single family is determined by the degree to which the haplotypes of the two parents are similar. Indeed, if the father and mother have a haplotype in common, i.e. an identical chromosome with two genes occurs in both, it is possible to obtain

TABLE XVII. VARIOUS DEGREES OF LEUCOCYTE ANTIGEN MATCHING WHICH MAY BE FOUND IN RANDOM SIBLING TRANSPLANTS IN A FAMILY WHERE THE PARENTS HAVE ONE ANTIGEN IN COMMON OUT OF 8 ANTIGENS DETERMINED OR TWO SUB-LOCI

Proportion of possible sib-to-sib transplants	*No. of alleles which differ*	*No. of antigens which are incompatible*
4/16	0	0
2/16 } 50%	1	1
6/16 }	1	2
3/16 } 25%	2	3
1/16 }	2	4

identity even in parent-to-child transplants. The fact that such parent-child pairs have been found in a series of transplants[16] implies, in turn, that two genetically unrelated individuals, such as parents usually are, must have an allele in common. The important deduction which follows from this observation has been stressed by Van

TABLE XVIII. CORRELATION BETWEEN DEGREE OF LEUCOCYTE MATCHING AND CLINICAL STATUS, IN 64 RECIPIENTS OF 66 TRANSPLANTS WITH DIFFERENT GENETIC CLASSES OF DONORS (AFTER KISSMEYER-NIELSEN *et al.*)[19]

Grade of matching	*Sib to sib*	*Parent to child*	*Other related*	*Unrelated*	*Clinical ranks* I	II	III	IV	V
A: Identical antigens	11	2		1	14				
B: No antigens D + R −	4	1		1	1		1	4	
C: One antigen D + R −	3	14	1	3	10	7	2	3	
D: Two antigen D + R −	6	7		4	1	2	4	9	
F: R antibody to D lymphocytes ..		1	1	6				3	5

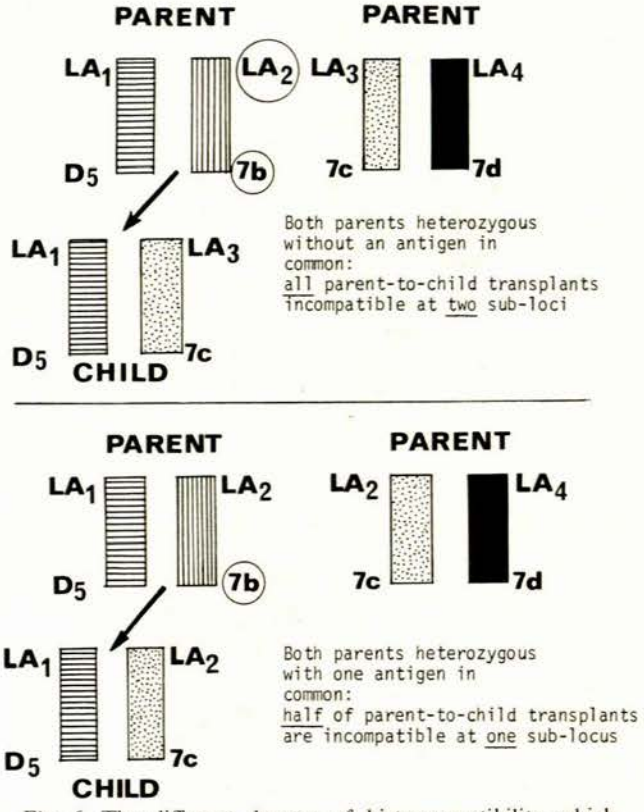


Fig. 6. The different degrees of histocompatibility which may be found in parent-to-child transplants depending on whether the parents have one antigen in common out of 8 antigens determined at two sub-loci. The ringed antigens will be incompatible in parent-child transplants indicated by an arrow.

Rood: that in the general population there must be unrelated individuals with the same two alleles. This means that identity could be obtained in unrelated donor (cadaver donor) transplants.

In none of the series of transplants reported to date have the leucocyte antigen determinations been penetrating enough to allow all the relevant antigens to be identified. If 3 antigens can be identified without question for any given individual, the question remains open as to whether the individual is homozygous for one of the 3 antigens (i.e. this antigen occurs twice at one of the sub-loci), or whether the individual possesses an antigen for which an antiserum is not yet available. It has frequently been pointed out that in related donor transplants identity for most of the detectable antigens would imply a strong probability of identity for any antigens not yet detectable. This argument does not apply to unrelated, cadaver transplants. It is therefore understandable that the correlation between leucocyte antigen typing and the clinical results of transplantation are not nearly as clear in the case of unrelated donor transplants as has been the case in the majority of reports on related donor transplants. It must be emphasized, however, that the smaller the number of antigens of narrow specificity which are identified, the bigger the 'grey area' of unpredictable or inexplicable clinical results becomes. This is well illustrated by comparing the data of Kissmeyer-Nielsen in Tables XVI and XVIII. Even related donor-recipient pairs have to be adequately typed and matched with the recipient on the basis of a formal genetic analysis in terms of the two sub-loci of the HL-A system, to ensure excellence of transplantation results.

During the past 2 years there have been several reports that the results obtained with cadaver kidney transplants are definitely influenced by leucocyte antigen matching. Van Rood *et al.*[18] found that the proportion of grafts surviving for one year is statistically correlated with the number of HL-A antigens differing between donor and recipient (Table XIX). Morris *et al.*[22] reported that the clinical status of the recipient as well as the early histology of the graft is statistically improved in compatible cadaver

TABLE XIX. CORRELATION BETWEEN LEUCOCYTE GROUP MATCHING (DIFFERENCE FROM D TO R AND R TO D ARE EQUAL) FOR 9 ANTIGENS, AND GRAFT SURVIVAL FOR ONE YEAR (UNRELATED DONOR–RECIPIENT PAIRS) (AFTER VAN ROOD *et al.*)[18]

Number of HL-A antigens differing	*% of grafts functioning*	*Total grafts performed*	*No. of grafts functioning*
0–1	75	8	6
2–3	60	12	7
4 or more	30	17	5

TABLE XX. CORRELATION BETWEEN LEUCOCYTE ANTIGEN MATCHING AND CLINICAL STATUS AS JUDGED BY REJECTION EPISODES (AFTER MORRIS *et al.*)[22]

Matching	*Clinical grades* A	B	C	D
Compatible	2	2	1	0
Incompatible	1	3	6	12
			$p > 0{\cdot}05$	

transplants (Table XX). Similar conclusions were reached in an analysis of a large series of unrelated donor transplants by Patel *et al.*[21] and for a further series of cadaver renal transplants by Batchelor and Joysey.[23] Our own ex-

perience with a small series of 10 unrelated donor transplants has been similar: there is a distinct trend for the fewer number of mismatched antigens to be associated with better clinical condition of the recipient, and vice versa. We have, however, also found evidence of a grey area in which apparently mismatched grafts are associated with a good clinical result (Table XXI).

TABLE XXI. CORRELATION BETWEEN LEUCOCYTE ANTIGEN MATCHING ACCORDING TO VAN ROOD AND CLINICAL CONDITION OF RECIPIENTS IN A SMALL SERIES OF CADAVER DONOR TRANSPLANTS (CAPE TOWN)

No. of antigens not identical	*Clinical grades*			
	I	*II*	*III*	*IV*
1		1		
2	1	2		
3				1
4	1	1	1	2

CLINICAL PROBLEMS

To place our current knowledge of tissue typing in its proper perspective within the field of present-day clinical transplantation, it is necessary to provide an answer to several recurring questions.

Why is Identity Important in Matching?

At an early stage of modern transplantation, Medawar[36] underlined the principle of avoiding transplantation of an antigen present in the donor but lacking in the recipient. This concept carries an immunological implication which is easily understood by most, and is therefore generally accepted in principle even if it is not equally generally applied in surgical practice. There are many, however, who have difficulty in understanding why it may be very undesirable in certain circumstances to transplant in the reverse situation, i.e. where the donor lacks an antigen which is present in the recipient. Too often this situation is ignored on the grounds that a missing antigen cannot possibly produce an antibody.

It has previously been stated by Walford[37] that while some significant antigens remain undetected, transplantation from a negative donor to a positive recipient is not permissible; and Dausset *et al.*[27,33] stated that whereas identity (where donor and recipient are both positive or are both negative) still permits incompatibility for one unknown antigen, lack of identity (this includes a negative donor and a positive recipient) permits incompatibility for two undetected antigens. We have found it useful on several occasions to illustrate the immunogenetic argument by reference to a theoretical antigen Xa for which no serologically detectable alleles have been found; but in our hypothetical situation two hitherto undetected alleles Xb and Xc are postulated. Table XXII shows the situation when donor and recipient are identical, either both positive for Xa, or both negative. Four out of 9 possible donor-recipient combinations will be incompatible for one of the undetected alleles. In contrast, where the donor is negative and the recipient positive for Xa, 7 of the 9 possible transplants will involve incompatibility for one of the two undetected alleles; and now incompatibilty for both of these antigens may occur in one instance. There is an additional theoretical objection to transplanting from negative to positive, which to our knowledge has not been considered previously. It is possible that a double dose of incompatible antigen has more serious implications for the survival of the graft than a single dose. As an example may be taken the difference of transplanting to an Xa Xc recipient from an Xb Xb donor or an Xb Xc donor. In both instances the incompatible antigen is Xb, but in the first transplant the recipient may receive twice the amount. We do not know of any evidence to suggest that leucocyte antigens have a double-dose effect in human organ transplantation; however, we have no evidence to the contrary. Perhaps it should be noted that the incompatibilities which may occur for undetected antigens in our theoretical model, where transplantation is from negative donor to positive recipient, will in the majority of instances be associated with a double dose of the incompatible antigens.

In an excellent example of sophisticated immunogenetic reasoning, Walford[37] used the LA series of antigens of Payne *et al.*[38] to illustrate his argument that it is undesirable to transplant from negative to positive. At the time, 3 alleles of this series were detectable, i.e. LA1, LA2 and LA3. It was known from population studies that at least one additional allele had to exist, and the antigen LA4 was postulated. From the population statistics at his disposal, Walford could calculate how often the postulated antigen LA4 would occur as an incompatibility when the donor was compatible (i.e. lacked the antigen) but not identical for the known antigens LA1, LA2, LA3. In the case of 3 phenotypes the probability of apparently compatible types being incompatible was over 50%. Walford's example has the particular merit in that the theoretical antigen LA4 has subsequently been proved to exist (Bodmer and Payne).[25]

TABLE XXII. THE POSSIBLE SIGNIFICANCE OF IDENTITY AND NON-IDENTICAL COMPATIBILITY FOR A THEORETICAL ANTIGEN Xa WITHOUT DETECTABLE ALLELES, BUT WITH POSTULATED ALLELES Xb AND Xc

Detected phenotypes			*Possible genotypes*	*Potential incompatibilities*	*Incompatible combinations*	*Maximum incompatibilities*
Donor	*Recipient*					
Xa+	Xa+		(i) Xa Xa (ii) Xa Xb (iii) Xa Xc	(ii) to (i), (iii) (iii) to (i), (ii)	4/9	One antigen
Xa−	Xa−		(iv) Xb Xb (v) Xc Xc (vi) Xb Xc	(iv) to (v) (v) to (iv) (vi) to (iv), (v)	4/9	One antigen
Xa−	Xa+	Donor Recipient	(iv), (v) or (vi) (i), (ii) or (iii)	(iv) to (i), (iii) (v) to (i), (ii) (vi) to (i), (ii), (iii)	7/9	Two antigens (vi) to (i)

The LA series of antigens have provided us with an actual example of the dangers inherent in transplanting negative to positive. With the exception of LA2, the antigens of the LA series are detectable only by leuco-agglutination methods using defibrinated blood, or by lymphocytotoxic techniques. This is so because the LA antibodies, with the exception of anti-LA2, require complement for their action; the EDTA which is incorporated in Van Rood's leuco-agglutination method renders complement ineffective, so that only the equivalent of LA2, i.e. the antigen 8a, is detected in Van Rood's system.[39,40] In one of our transplants the donor was negative and the recipient positive for 8a. The transplant operation was undertaken on the basis of the leuco-agglutination results. Subsequently the results of lymphocytotoxic testing, which included antisera for all 4 antigens of the LA series, showed that the donor possessed LA3 and LA4, whereas the recipient lacked both of these antigens. Therefore, compatibility but lack of identity for the 8a antigen in a leuco-agglutination system was demonstrably associated with incompatibility for two undetected antigens (Table XXIII).

TABLE XXIII. LEUCOCYTE ANTIGEN MATCHING IN A CASE OF HUMAN HEART TRANSPLANTATION

Leuco-agglutination antigen (*Van Rood*)		*8a*		
Donor		—		
Recipient		+		
Lymphocytotoxic antigens (*Payne et al.*)	*LA1*	*LA2*	*LA3*	*LA4*
Donor	—	—	+	+
Recipient	—	+	—	—

Why do Some Well-Matched Recipients have Poor Clinical Results?

A small proportion of recipients who exhibit this discrepancy has been noted from the earliest studies listed in Table I. Vredevoe *et al.*[2] ascribed this to the use of typing sera which were not sufficiently specific and therefore unable to detect certain antigens. Payne *et al.*,[3] Terasaki *et al.*[5-7] and others have recorded similar observations and conclusions. In general, the statistical correlation between closer matching and better clinical results has become progressively stronger, the more recent the study. This may mean that the proportion of recipients who would be regarded as well-matched but who exhibit rejection, is decreasing. This, in turn, is probably due to improvement in leucocyte serology.

The increasing refinement of leucocyte antigen detection is well illustrated by recent experience with one of our heart transplants. By the leuco-agglutination method of Van Rood the antigen 7b is a well-defined antigen.[37] We have obtained locally in Cape Town a leuco-agglutinating serum which gives virtually identical results with a reference anti-7b serum obtained from Van Rood. We have also lymphocytotoxic antisera which are specific for leucocytes from people who are 7b positive by leuco-agglutination tests; one serum gives a pattern of positives and negatives among random people which is almost identical with that obtained with the reference anti-7b, while another type of serum reacts positively only with people who are 7b positive but with a minority of them. Very recently Van Rood stated that the antigen 5 of Dausset is included in antigen 7b.[41] This would mean that leucocytes which are Dausset-5 positive will nearly always be 7b positive, whereas some leucocytes which are 7b positive may be Dausset-5 negative. The Dausset-5 antigen is identical with the official antigen HL-A5.[28] We have compared our lymphocytotoxic 'short anti-7b' with an anti-HL-A5 serum provided through the courtesy of the National Institutes of Health, USA, and obtained almost identical results. Retrospective analysis of our transplants revealed an occasion where a donor and recipient had both been positive with the standard leuco-agglutinating anti-7b serum and its local agglutinating and cytotoxic equivalents, but the recipient had been negative with the so-called 'short anti-7b' (Fig. 7).

It can be seen that antisera of broad specificity, when used by themselves, may fail to detect incompatibility for an antigenic component which is either included in a larger complex or which forms one of a series of frequently associated antigens. This would then explain why it is possible for donor-recipient combinations which are apparently well-matched, or even identical, in terms of typing sera of broad specificity to follow an unexpectedly poor clinical course.

Why do Some Poorly-Matched Recipients do Well Clinically?

In the absence of other complications, the outcome of renal transplantation depends on the balance between immunosuppression and rejection. Many factors other than good leucocyte antigen matching between donor and recipient may produce a favourable balance. Patients who are or have recently been uraemic have a reduced capacity for immunological response.[42] Individual variation in compensatory immunological phenomena such as acquired tolerance or adaptation may enable a proportion of recipients to carry a relatively greater load of histo-incompatibility. Apart from these reasons, the inadequacy of

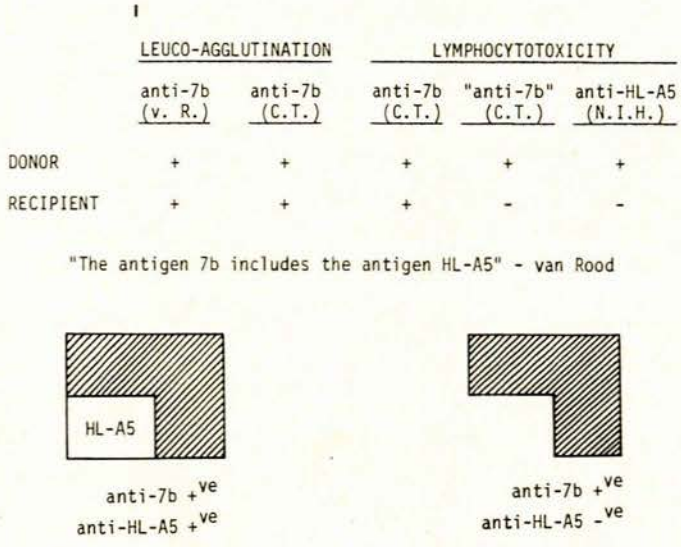


Fig. 7. Leucocyte typing sera of broad specificity, such as leuco-agglutinating anti-7b sera, may fail to demonstrate incompatibility for an included or frequently associated antigen, such as HL-A5.

tissue-typing reagents probably played a major part to date in the failure to recognize some suitable donor-recipient combinations. Again, this is failure attributable to the use of antisera which are not sufficiently specific.

The antigen 4a of Van Rood is a relatively strong transplantation antigen. It is well known, however, that this is an antigen of broad specificity which probably consists of a series of frequently associated component antigens.[17,19,27,34,43] Many anti-4a sera can be split up into 4 or 5 lymphocytotoxic components by appropriate absorption with leucocytes from selected 4a-positive individuals. We have also found 'short' agglutinating anti-4a antibodies in the sera of pregnant women. Table XXIV shows the results obtained with leuco-agglutination tests on random samples of 41 people from the Cape Town population; 27 of these people were positive with standard anti-4a sera supplied by Van Rood. Also shown are the results of one of the locally obtained sera which are identical with the standard serum. In addition there are two Cape Town sera (CT17 and CT51) which are specific in so far as they agglutinate only 4a-positive leucocytes, but they are 'short' in so far as they react only with a proportion of such persons. The last two sera represent reagents of narrower specificity.

TABLE XXIV. ANTI-4a SERA (CT = CAPE TOWN)

Leucocyte samples	*Van Rood 4a*	*CT 49*	*CT 17*	*CT 68*	*CT 51*
1	+	+	+	+	+
2	+	+	+	+	+
3	+	+	+	+	+
4	+	+	+	+	+
5	+	+	+	+	+
6	+	+	+	+	+
7	+	+	+	+	+
8	+	+	+	+	+
9	+	+	+	+	+
10	+	+	+	+	+
11	+	+	+	+	+
12	+	+	+	+	+
13	+	+	+	+	+
14	+	+	+	+	+
15	+	+	+	+	+
16	+	+	+	+	−
17	+	+	+	+	−
18	+	+	+	+	−
19	+	+	+	+	−
20	+	+	+	+	−
21	+	+	+	+	−
22	+	+	+	+	−
23	+	+	+	+	−
24	+	+	+	+	−
25	+	+	−	+	−
26	+	+	−	+	−
27	+	+	−	+	−
28	−	−	−	+	−
29	−	−	−	−	−
30	−	−	−	−	−
31	−	−	−	−	−
32	−	−	−	−	−
33	−	−	−	−	−
34	−	−	−	−	−
35	−	−	−	−	−
36	−	−	−	−	−
37	−	−	−	−	−
38	−	−	−	−	−
39	−	−	−	−	−
40	−	−	−	−	−
41	−	−	−	−	−

Table XXV illustrates how the use of a single serum for a particular antigenic specificity may provide misleading results. If the anti-4a serum CT17 had been used alone to type leucocytes from 1 to 24 in Table XXIV as prospective donors and the leucocyte samples 25 - 27 as prospective recipients, a transplant from any one of the 24 prospective donors would have been labelled as 4a incompatible with all three prospective recipients. Serum CT17 may be a somewhat weak reagent, or it may be that there is indeed incompatibility from donor to recipient for a more or less minor component of the 4a antigen; however, it would be quite incorrect to classify such a transplant as one involving incompatibility for the major antigen.

TABLE XXV. LEUCOCYTE TYPING RESULTS WHERE THE DONOR MAY BE POSITIVE AND THE RECIPIENT NEGATIVE, WITHOUT IMPLICATION OF INCOMPATIBILITY FOR A COMPLETE MAJOR ANTIGEN

	Anti-4a sera					*Anti-4a sera*		
	Van Rood	*CT 49*	*CT 17*	*CT 68*		*Van Rood*	*CT 49*	*CT 17*
1 to 24	+	+	+	+	No. 1–24 Donors	+	+	+
25	+	+	−	+	No. 25–27 Recipients	+	+	−
26	+	+	−	+				
27	+	+	−	+				
28	−	−	−	+				
29	−	−	−	−				
					No. 1–24 Donors			
					No. 25–27 Recipients			

Table XXV presents the same argument which we have advanced previously.[44] Unless antisera are capable of detecting such minor antigenic differences and placing them in their proper perspective in relation to major components, the matching and selection of donors and recipients will not lead to clinical results which are fully predictable. With reference to the schematic representation (Table XXV) of donors who possess an antigenic component which is lacking in the recipients, one may summarize as follows: if the incompatible antigenic determinant is sufficiently immunogenic to represent a transplantation antigen, then the failure to detect the incompatibility may lead to an unexpected immunological complication after transplantation; if the additional antigenic determinant is detected serologically, but does not represent a transplantation antigen, then an apparent incompatibility between donor and recipient may yet be associated with transplantation which is not followed by immunological complications.

The question may justifiably be asked, at this stage, what the prospects are of obtaining leucocyte typing reagents of sufficient specificity to avoid ambiguity. In our opinion some optimism is quite justified. Many workers, among them Kissmeyer-Nielsen, have now refined their antisera to a stage where the majority of antigens at the two subloci of the HL-A system can be accurately defined (Table XXVI). (For this very recent information we are greatly indebted to Dr Kissmeyer-Nielsen who kindly permitted one of his senior assistants to spend some time with us

for the purpose of testing our reference panel of leucocyte donors with his latest sera.)

TABLE XXVI. THE HLA SYSTEM OF HUMAN LYMPHOCYTE GROUPS ACCORDING TO KISSMEYER-NIELSEN

Two sub-loci	
First	HLA-1, HLA-2, HLA-3, HLA-4, Ba, ILN, D-17, LI
Second	HLA-5, HLA-7, HLA-8, R*, T12, HN, BB, FJH, LND, MH

We are not suggesting that the last of the missing leucocyte antigens will be discovered within the next months or even years. Red blood cell serology has been pursued for nearly 70 years, and new antigens, or new variants of old antigens, are still being discovered with great regularity. However, the major red blood cell antigens which are important in clinical blood transfusion were all discovered at a relatively early stage. By the same token, it will probably take a considerable time to unravel all the immunogenetic intricacies of leucocyte serology, but there is hope that the clinically more important antigens are being recognized for what they are with increasing regularity in the better-equipped typing laboratories.

The next question may well be: what are the chances of the more selective antisera becoming generally available for clinical application? Again, we think there is room for optimism. Many centres are pursuing active programmes for selection or production of excellent typing sera. With the micro-droplet methods which are now becoming standard practice, even a few millilitres of serum will sustain a very active transplantation programme for several years.

Our own experience has been encouraging. Over a period of approximately 6 months the sera from 10,000 pregnant women have been screened for leucocyte antibodies. Sera initially selected for leuco-agglutinating activity were recently re-examined in terms of the lymphocytotoxic antigens shown in Table XXVI. Preliminary results obtained from our computer programme indicate that 7 of these antigens can be identified adequately. Furthermore, it seems as if we have antisera for several of the remaining antigens, but that these antisera possess also some weak additional antibodies which will have to be eliminated. This can be done either by absorption or, possibly, by using the antiserum at a suitable dilution. Since we have at least 100 millilitres of most of these sera on hand, the needs for several very active transplantation centres for 1 or 2 years could be met with such a supply.

Why are Well-Matched Organs Not Transplanted?

It is now accepted that two histocompatibility criteria must be satisfied: the donor must be ABO compatible with the recipient,[45,46] and the recipient must be free of antibodies which react with donor leucocytes in direct cross-matching tests.[47-53] As yet there is no justification for a dogmatic statement about the particular leucocyte antigens, or the number of such antigens which preclude organ transplantation. Experience to date indicates that donors and recipients who are identical, or identical for all but one of the HL-A antigens, may be regarded as well-matched in terms of leucocyte antigens. While clinical transplantation is in its present form, this degree of match will be difficult to achieve for many patients; even compatibility for the major antigens may not be attained in every case. This applies particularly to transplantation other than that of the kidney. The small likelihood of achieving well-matched unrelated donors has been well documented both on theoretical and on practical grounds. The alternative to an identical match is best considered separately for related and unrelated donors.

CHOICE OF BEST DONOR

Family Donors

Whereas many leucocyte phenotypes have been observed in terms of defined antigens (over 100 phenotypes with the 16 antigens detected by Dausset and Rapaport),[32] a maximum of 6 genotypes (ab × cd → ac, ad bc and bd) exists within a family, and among siblings only 4, so that the chance of identity is much increased among family members.

When the leucocyte phenotypes of both parents and the siblings are available, genetic analysis may identify the segregation of chromosomes (i.e. clusters of antigens) in the family. This permits one to consider the possible existence of identity or semi-identity, and compatibility or incompatibility for postulated allelic genes not yet detected serologically.[17,27,33,54]

Dausset and Rapaport[32] have suggested that in the absence of a monozygous twin, the best donor is an identical sibling; next best is a donor, either sibling or parent, who carries only one chromosome (a combination of antigens) which is absent in the recipient, i.e. donor and recipient are semi-identical. The decision which of the two chromosomes that differ is less disadvantageous must be based on antigen number, strength and association. With equal degree of incompatibility, siblings are preferred to parents, since they are more likely to be identical for postulated but as yet undetectable antigen in the HL-A and other histocompatibility systems. If there are no semi-identical siblings, the parent with the better allele should be the third choice. Fourthly, siblings who are not semi-identical will be better than a non-related donor who presents an equal degree of incompatibility—again in view of the greater likelihood of identity for undetected antigens.

Unrelated Donors

Dausset *et al.*[35] have calculated the chance of a prospective donor, or an available donor organ, being identically matched for the 5 major histocompatibility antigens (i.e. blood groups A and B, and leucocyte antigens 1, 3 and 7) in their population. The chances of a recipient varied from 1·1 to 100% and for an organ from 0·6 to 71·3%. Taking into account 16 defined antigens, Dausset and Rapaport[32] observed more than 100 phenotypes in the population, which reduces the probability of identity in the random population to almost nil. Kissmeyer-Nielsen *et al.*[39] concluded that one must calculate with 7 and 8 genes on the two sub-loci respectively; this gives 1,008 possible phenotypes, without taking blood groups into account.

It has been pointed out, however, that different phenotypes will not be equally distributed in the general population. As with the rhesus system, certain phenotypes will be relatively common and offer a proportionately better

chance of being well matched.[30,32] Dausset has also pointed out that thousands of phenotypes exist for the red cell antigen, but that for the great majority of blood transfusions only 3 are considered, i.e. A, B and Rh positive (Rho and D). Van Rood has referred to the observation that certain rhesus alleles are less prone to provoke antibodies and suggests that this may be the case also with some leucocyte antigen haplotypes.[55]

Dausset and Rapaport[32] state that in the absence of an identical unrelated donor, it may be difficult to decide what is least incompatible. It is suggested that the least number of detectable incompatible antigens (D+ to R−) be selected, even if it is accepted that detectable reverse mismatches (D− to R+) may imply donor-to-recipient incompatibility. As a minimum, it should be the aim to achieve donor-recipient identity for the key antigens of each series of closely associated antigens (Dausset's 1, 3 and 7 which are equal or approximately equivalent to HL-A2, 4 and 6), on the assumption that this implies identity for known and unknown associated antigens.

Van Rood *et al.*[35] also suggested that for unrelated (cadaver) donor transplants one should concentrate on the main leucocyte antigens. In their leuco-agglutination system this implies 9 groups. With a reasonably large pool of recipients, their policy is: if an identical donor-recipient combination is not available, a combination mismatched for one or two antigens—and very exceptionally for 3 antigens—is accepted. It was previously shown that these 9 antigens, as distributed among 333 randomly selected persons, would produce 2 incompatibilities (donor positive and recipient negative) as the commonest situation in random matches; and that 3 incompatibilities with mismatches must be expected in nearly 17% of transplants. The average number of total mismatches (incompatibilities + reverse mismatches) would be between 3 and 4 in a large series of random selections.[16]

Summarizing their more recent experience, Terasaki *et al.*[56] reported that from a pool of 30 recipients on dialysis, the effective pool for a given cadaver organ was often reduced to between 4 and 8 by ABO incompatibility and clinical unsuitability at the given time. In spite of prospective typing, the policy of using all cadaver kidneys resulted in a large proportion of mismatched transplants. Furthermore, transplantation to those recipients in the pool who had phenotypes which were easier to match, created a collection of long-waiting recipients with phenotypes which had a lesser probability of being matched. Consequently the proportion of mismatched transplants increased progressively.

The experience which has been reviewed here, and considerations and arguments arising therefrom, have been largely concerned with kidney transplantation and experimental skin grafts. Other organs require a somewhat different approach as regards prospective typing and selection of the donor.

SELECTION OF DONORS FOR TRANSPLANTATION OF SINGLE ORGANS

In contrast to the prospective kidney recipient, patients requiring heart, liver or other visceral transplants are often too ill to wait an indefinite period and cannot be sustained by treatment equivalent to dialysis. Furthermore, this relatively urgent transplantation is entirely dependent on unrelated (cadaver) transplants. Altogether, the opportunity of finding a well-matched organ is less than in the case of a kidney.

The Cape Town experience with 5 heart transplants offers an illustration of the problems which are encountered in clinical practice. Table XXVII shows the ABO compatibility and the leucocyte antigen matching according to Van Rood; also shown are the matching grade symbols used by Terasaki. The tissue typing methods of Van Rood and of Terasaki are not strictly comparable, since each technique detects certain antigens not recognized by the other.[17,29] Nevertheless, it was considered worth while to convert the data obtained from Van Rood's method to the nomenclature of Terasaki, in order to compare our results with a larger series of heart transplants from Houston. For this purpose, the comparison contained in Table XXVIII was used. In determining the match grade according to Terasaki, the leuco-agglutination antigens 6a, 6b and 7a were ignored when these were present as incompatibilities. Van Rood has stated that the antigen 6a is a weak one, and has expressed some doubt whether 6b is a very distinct antigen; it is said that the recognition of the 7a antigen has never been quite satisfactory. On the other hand, the 3 antigens of Terasaki which do not have equivalents in Van Rood's system, i.e. 1, 8 and 4, are considered to be transplantation antigens. To accommodate these 3 antigens in arriving at a matching

TABLE XXVII. DEGREE OF LEUCOCYTE ANTIGEN MATCHING IN 5 HEART TRANSPLANT OPERATIONS (CAPE TOWN)

			4		6		7				8		*Incompatible antigens: donor +ve recipient −ve*	*Reverse mismatches: donor −ve recipient +ve*	*Tentative grading after Terasaki*	*Survival in days*
		ABO	*a*	*b*	*a*	*b*	*a*	*b*	*c*	*d*	*a*	*No. of non-identical antigens*				
1.	Donor	O	+	+	+	+	−	−	+	+	+					
	Recipient	A	+	+	−	+	+	−	+	+	+	2	6a	7a	B	18 (died)
2.	Donor	O	+	+	+	+	+	+	−	−	−					
	Recipient	B	−	+	+	−	+	+	−	−	−	2	4a, 6b		C	>582
3.	Donor	O	+	−	+	−	−	+	−	−	−					
	Recipient	A	−	+	+	+	−	+	−	−	−	3	4a	4b, 6b	C	>333
4.	Donor	O	−	+	+	+	+	+	+	−	−					
	Recipient	O	+	+	+	−	+	+	−	+	−	4	6b, 7c	4a, 7d	C	64 (died)
5.	Donor	O	+	+	+	+	−	+	−	−	−					
	Recipient	B	+	+	−	+	−	+	+	−	+	3	6a	7c, 8a	D	>111

grade according to the scheme of Terasaki, we have used the results which we obtained with antisera of the specificity LA1, LA3 and LA4. The last 3 antigens as described originally by Payne *et al.*[35] are the equivalents to Terasaki's 1, 8 and 4 (Table XXVIII), and are regarded as histocompatibility antigens.[8,22,33] The fifth transplant was allocated a grade D match on the two additional incompatibilities detected by lymphocytotoxic tests (Table XXIII).

TABLE XXVIII. COMPARISON MATCHING NOMENCLATURE

	Van Rood and Eernisse[17]								
	4a	4b	6a	6b	7a	7b	7c	7d	8a
Terasaki *et al.*[34]	3	7				(6)	5	11	2 – 8 4
									LA2 LA1 LA3 LA4
									Payne *et al.*[35]

'Antigen 6a is apparently a weak one . . . It is, however, also possible that the 6a antigen is almost always present and the 6b antigen is super-imposed on it. The antigen 6b is significantly associated with the antigen 7c. The recognition of the 7a antigen has never been quite satisfactory.' (Van Rood)

It is clear that our predetermined level of desirability,[57] i.e. identity or near identity for Van Rood's leucocyte antigens, was not obtained in any of the 5 transplants. This was due mainly to clinical considerations, because all these patients were at or near terminal stages of myocardial failure. As each of these patients was accepted as a prospective recipient on clinical grounds, the leucocyte antigen patterns were determined for the purposes of donor matching. In each instance it was realized that the individual leucocyte phenotype of the prospective recipients did not provide a reasonable probability of obtaining an identical or near-identical donor.

The probability of finding an acceptable match for these 5 recipient phenotypes could be calculated on the basis of the known ABO blood-group distribution among the several population groups of Cape Town, in conjunction with the distribution of leucocyte antigen phenotypes in a large series of randomly selected White and non-White persons in this area. The probabilities of achieving ABO compatibility and various grades of leucocyte antigen matching are shown in Table XXIX.

TABLE XXIX. APPROXIMATE PROBABILITIES OF ABO COMPATIBILITY AND DIFFERENT DEGREES OF LEUCOCYTE ANTIGEN MATCHING FOR 5 HEART TRANSPLANT RECIPIENTS (CAPE TOWN)*

Recipient	*ABO compatibility*	*Total number of leucocyte antigens mismatched in terms of Van Rood*				*ABO compatibility plus leucocyte identity or near*
		Nil	*One*	*Two*	*Three*	
1	·78	0	0	·04	·12	0·0
2	·56	·01	·07	·26	·5	0·04
3	·78	0	·03	·32	·73	0·02
4	·39	0	·05	·25	·53	0·02
5	·56	0	·11	·20	·41	0·06

*The probability of ABO compatibility further reduces the probability of the leucocyte matching.

The over-all probability of obtaining ABO compatibility plus identity or near identity for the 9 leucocyte antigens of Van Rood's system were, for the 5 prospective heart recipients respectively: nil, 4%, 2%, 2% and 6%. In view of these patients' deteriorating condition and the shortage of prospective donors, it was considered to be in the patients' best interests to accept a lesser degree of compatibility.

The degree of mismatch which was accepted must be judged on the function of the graft or on survival. Two of the recipients in this small series have died from the complications of immunosuppression; the number of non-identical antigens were 2 and 4 respectively. Two long-term survivors (582 and 333 days respectively) represent 2 and 3 non-identical antigens respectively; the third survivor who presents with less satisfactory graft function has survived for 111 days with 3 non-identical antigens. These observations may be compared with Van Rood's analysis of kidney graft survival for one year (Table XIX). Sixty per cent of donor-recipient pairs with 2 - 3 HL-A antigens differing survived this period, whereas 4 or more differing antigens were associated with only 30% survival.

In the terms used by Terasaki the two patients who died had grade B and C matches respectively; the two long-term survivors both have grade C matches, while the recipient with the shortest survival and who has presented some serious problems in clinical management represents a grade D match. These latter observations can be compared with those presented by Trenton[58] (Table XXX) in respect of 17 heart transplant recipients who had been typed retrospectively by Terasaki or prospectively according to Terasaki. On the basis of the Houston data we feel that grade C is the significant level of match in heart transplantation; lesser grades of match were associated with less than 50% survival at about 130 days.

TABLE XXX. CORRELATION BETWEEN GRADES OF LEUCOCYTE ANTIGEN MATCHING AND SURVIVAL OF HEART TRANSPLANT PATIENTS IN HOUSTON (AFTER TRENTON)[58]

Terasaki typing grades	*Living patients*	*Days of survival*	*Dead*	*Mean days of survival at death*
A	–	–	–	–
B	1	> 88	0	–
C+	1	> 172	0	–
C	4	> 110 (mean)	4	82
C–	1	> 130	4	57
D	1	> 53	5	53
F	–	–	–	–

From the combined but still limited observations available at present, it would appear that 2 - 3 non-identical antigens of Van Rood's group 4 system, or a grade C match, is acceptable in human heart transplantation, with the best of present-day methods of immunosuppression. This grade of match is better than would be obtained, on the average, in random unselected cadaver transplants. Therefore, even while the present shortage of prospective donors lasts, and heart transplantation is offered only to patients in the terminal stages of their disease, leucocyte typing has something to offer. It should be possible in the majority of instances to select better than the average achieved by chance, and to avoid altogether the gross mismatches which occur in a proportion of unselected transplants.

SUMMARY

Recent studies which established the correlation between leucocyte group matching of kidney donors and recipients, and the outcome of the transplantation, are reviewed. Some of the serological problems which are still inherent in leucocyte antigen typing are considered in detail. Experience with leuco-

cyte typing in heart transplantation is briefly recorded. It is concluded that even for prospective recipients of single organ transplants, who cannot wait indefinitely, leucocyte antigen matching offers a better than random chance of achieving a reasonable match and therefore the probability of an improved clinical result.

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