analysis for parasites must therefore be performed to reduce the risk of transmission of such diseases whenever the transplantation of organs from such high-risk donors is contemplated.

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CALCULATION OF A PREDICTIVE VALUE FOR TRANSPLANTATION

The highly sensitized patient has diminished opportunity for transplantation. To counterbalance this, many transplant centers establish a priority status for such patients and/or participate in regional organ exchange programs (*1*). The criterion commonly used for evaluating presensitization is percent reactive antibody (PRA),[1] determined by dividing the number of subjects whose lymphocytes give a positive cytotoxic reaction with serum from the recipient by the total number of subjects tested. PRA, however, may not provide an accurate measurement of the probability of finding a serologically compatible donor (i.e., a donor acceptable by serologic typing and crossmatch criteria), because the HLA antigen frequencies and phenotypes of the panel of cell donors may not be representative of that of the organ donor pool, and because PRA does not take into account other compatibility systems such as the ABO system.

An alternative approach is to use information about the array of antigens against which the recipient is sensitized to calculate the probability of finding a donor lacking unacceptable antigens. For a single genetic system, this probability (P_s) is given by the sum of the population frequencies of the various genotypes consisting of acceptable antigens. When donor compatibility involves multiple antigen systems, the overall probability of compatibility (P_c) for all systems is given by the product of the probabilities for each of the individual systems. The probability calculations, which are based on the Hardy-Weinberg Law, are straightforward. Depending on the nature of the antigen system (i.e., controlled by a single locus or by multiple, linked loci) and the level of presensitization, different approaches to the calculations may be used, as shown:

Probability of finding a compatible donor when the unacceptable antigens are controlled by a single genetic locus. Let the alleles determining unacceptable antigens be represented by A_i (where $i = 1 \rightarrow n$) with gene frequencies p_i. If A_x, with frequency p_x, represents all alleles which are not A_i, compatible donors are those with the genotype A_xA_x. The probability of finding a compatible donor is then the frequency of the A_xA_x homozygote:

$$P_s = p_x^2 = (1 - \sum_i p_i)^2$$

Example A. A recipient must not receive transplant bearing antigens HLA-A1 or HLA-A2. The gene frequencies of A1 and A2 are 0.138 and 0.264, respectively. The probability of compatibility for the HLA-A system is:

$$P_{HLA} = (1 - [.138 + .264])^2$$
$$= 0.3576$$

Example B. A blood type B recipient. Frequency of the A allele is 0.2630. Probability of compatibility for the ABO system is:

$$P_{ABO} = (1 - .2630)^2 = .5432$$

Probability of finding a compatible donor when the unacceptable antigens are controlled by two (or more) linked loci. Let A_i and B_i represent alleles, with frequencies p_i and q_i, respectively, of linked loci A and B, which determine unacceptable antigens. Let h_k be the frequency of the haplotype A_iB_j. If A_xB_x, with frequency h_x, represents all haplotypes lacking A_i and/or B_j, the genotype of the compatible donor is A_xB_x/A_xB_x. Then the probability of finding a compatible donor when there is no linkage disequilibrium is:

$$P_s = h_x^2 = ([1 - \sum p_i][1 - \sum q_j])^2$$
$$= ([1 - \sum p_i - \sum q_j + \sum_{ij} p_iq_j])^2$$

However, when there is linkage disequilibrium, as in the HLA system, this equation becomes:

$$P_s = h_x^2 = ([1 - \sum_i p_i - \sum_j q_j + \sum_k h_k])^2$$

where $h_k = p_iq_j + \Delta$, and Δ is the linkage disequilibrium value for the A_iB_j haplotype.

Example C. A patient who must avoid HLA antigens A1, A2, B7, and B8:

Allele	Frequency	Haplotype	Frequency
A1	0.138	A1B7	0.0044
A2	0.264	A1B8	0.0609
B7	0.096	A2B7	0.0337
B8	0.090	A2B8	0.0142

$p_i = 0.138+0.264=0.402$

$q_j = 0.096+0.090=0.186$

$h_k = 0.0044+0.0609+0.0337+0.0142$
$= 0.1132$

$P_{HLA} = (1-.402-.186+.1132)^2 = .2758$

Probability of finding a compatible donor for a patient with polyspecific antibody and high PRA. It is often, if not usually, impossible to determine precisely the antibody specificities of a serum that yields a PRA of 90 or greater in tests against a selected panel of cell donors. In these cases it may be possible to use information from the recipient's phenotype and serum screening and crossmatch tests to construct a "safe" or acceptable antigen profile. The probability of finding a compatible donor is the sum of the frequencies of the genotypes that contain only the acceptable antigens. That is, if $h_i(_j)$ represents the frequency of a genotype that can be constructed from the safe antigen profile, the probability of a compatible donor is given by:

$$P_{HLA} = \sum_i \sum_j (h_i^2 + 2h_ih_j) \quad \text{where} \quad i<j$$

Example D. An individual with a safe antigen profile consisting of A1, A2, B7, B8 and Bw22:

Haplotype	Frequency
A1B7	h_1=.0044
A1B8	h_2=.0609
A1Bw22	h_3=.0011
A2B7	h_4=.0337
A2B8	h_5=.0142
A2Bw22	h_6=.0021

$$P_{HLA} = h_1^2 + h_2^2 + h_3^2 + h_4^2 + h_5^2 + h_6^2 + 2(h_1h_2 + h_1h_3 + h_1h_4 + h_1h_5 + h_1h_6 + h_2h_3 + h_2h_4 + h_2h_5 + h_2h_6 + h_3h_4 + h_3h_5 + h_3h_6 + h_4h_5 + h_4h_6 + h_5h_6)$$

$$= .0135$$

The cumulative probability (P_c) for multiple systems is the product of the probabilities for each of the individual systems. For example, for a blood type B patient with HLA antigens to avoid A1, A2, B7 and B8, the cumulative probability is:

$$P_c = P_{ABO} \times P_{HLA}$$

$$= (.5432)(.2758) \quad \text{(from examples B and C)}$$

$$= .1498$$

The gene frequencies used in the calculations should approximate those of the donor pool as closely as possible. Published gene frequencies may be applicable for a donor pool consisting of a single race—however, when more than one racial group is involved, the gene frequencies should be adjusted to account for the racial composition of the donor pool.

We compared PRA and P_c values for 76 patients with PRA ≥30, who were awaiting transplantation in the Northeast Ohio Transplant Programs, to determine whether Pc could be predicted from PRA. Serum samples from all patients were evaluated at the Cleveland Clinic Foundation using a cell panel of 50–60 unrelated individuals. The panel members were selected, by HLA phenotype, to optimize HLA antibody detection and characterization—i.e., to represent all serologically defined HLA antigens except Aw43, B46, and Bw54 in arrays that are sufficiently unique to distinguish the specificities of the various antibodies present.

The data for the 76 patients are shown in Table 1 and Figure 1. Although there is a correlation between Pc and PRA (r = −0.50), it can be seen from the outliers in Figure 1, and from the range of P_c values (0.000005–0.0029) among the 15 patients with a PRA of 100 that PRA cannot be used to predict Pc value accurately. This occurs whenever sera are tested against a cell panel that differs appreciably in its antigen composition from that of the donor pool. The effect of cell panel upon PRA can be seen by examining data from the Terasaki Cell and Serum Exchange (Table 2). Serum number 51 was tested in 85 laboratories with a reported reactivity ranging from 0 to 40%. It is likely that most of this variability is due to differences in panel

TABLE 1. Correspondence between P_c and PRA values for 76 patients in the Northeast Ohio Transplant Program[a]

PRA	P_c	PRA	P_c	PRA	P_c	PRA	P_c	PRA	P_c
100	.000005	98	.00002	88	.0545	78	.1204	58	.2425
100	.000007	98	.0008	88	.0927	76	.0710	57	.1151
100	.00008	98	.0051	△88	.2603	76	.0815	□56	.0045
100	.0009	97	.0016	△88	.3252	76	.1648	□56	.0229
100	.0001	96	.00005	87	.0207	□75	.0344	55	.2666
100	.0002	96	.0008	86	.0707	74	.0824	54	.2911
100	.0002	96	.0025	△86	.2253	□70	.0198	52	.1313
100	.0003	96	.0029	□84	.0211	□68	.0426	52	.1593
100	.0003	96	.0115	□82	.0129	68	.1583	47	.3925
100	.0003	95	.0002	□82	.0254	68	.1900	□32	.0458
100	.0005	94	.0004	82	.0715	67	.1506	32	.1350
100	.0008	94	.0009	△82	.3185	60	.1578		
100	.0013	94	.0011	□80	.0195	60	.2520		
100	.0015	93	.0005	80	.0608				
100	.0029	93	.0005	80	.0869				
		93	.0008	80	.1325				
		92	.0033	80	.1524				
		90	.0009						
		90	.0013						
		90	.0044						

[a] P_c calculations are for ABO and HLA compatibility. The gene frequencies used for the P_c calculation were for a population composed of 85% American whites and 15% American blacks. PRA values were obtained from tests of recipients' sera against selected panels of 50–60 subjects.

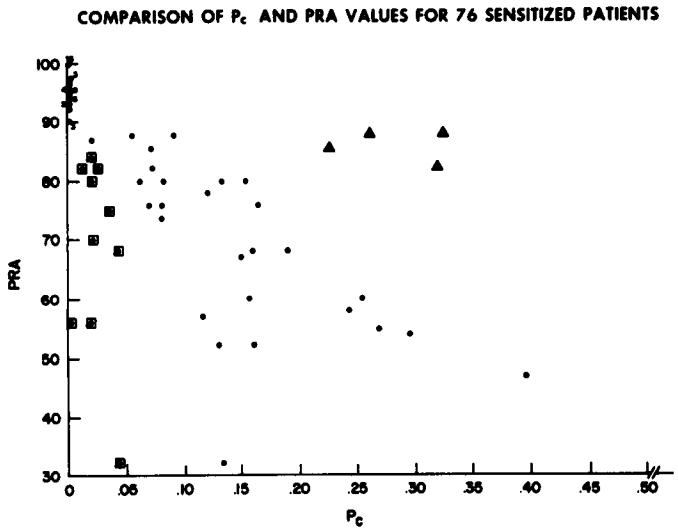

FIGURE 1. Associations between PRA and Pc values. For all data: r = −0.50; for data excluding outliers: r = −0.87 (See Table 1 and text for numerical values and panel composition). Outliers: (△) and (□).

TABLE 2. Reactivity of a serum specimen tested in 85 laboratories

LAB	PRA	r*	LAB	PRA	r*	LAB	PRA	r*
1	0	—	30	14	.90	58	23	1.00
2	0	—	31	14	.90	59	23	.93
3	0	—	32	14	.77	60	23	.91
4	1	1.00	33	15	1.00	61	23	.86
5	1	.89	34	15	1.00	62	23	.73
6	2	1.00	35	16	1.00	63	23	—
7	3	1.00	36	17	1.00	64	24	.95
8	4	1.00	37	17	1.00	65	25	.92
9	4	—	38	17	.93	66	25	—
10	5	1.00	39	17	.93	67	25	—
11	5	.92	40	17	.92	68	26	.96
12	6	1.00	41	17	.78	69	26	.92
13	7	1.00	42	17	.77	70	27	.94
14	7	.80	43	18	1.00	71	28	.90
15	8	1.00	44	18	.94	72	28	.78
16	8	.88	45	18	.89	73	29	.92
17	8	.63	46	18	.86	74	29	.82
18	10	1.00	47	19	1.00	75	29	.74
19	10	1.00	48	19	1.00	76	29	.67
20	11	.85	49	19	.90	77	30	.88
21	13	1.00	50	20	1.00	78	30	—
22	13	1.00	51	20	—	79	31	—
23	13	1.00	52	21	1.00	80	33	—
24	13	1.00	53	21	1.00	81	34	.96
25	14	1.00	54	21	.80	82	36	.78
26	14	1.00	55	21	.72	83	37	1.00
27	14	1.00	56	22	1.00	84	38	1.00
28	14	1.00	57	22	.94	85	40	.83
29	14	.90						

* Correlation coefficient reported for the association between the serum reactivity and HLA-A3. Data from the 26th serum exchange used with the permission of Dr. Paul I. Terasaki.

composition, because the range of reactivity reported by investigators who found a perfect correlation between the antibody and the HLA-A3 antigen was 1% to 38%.

It is interesting to note from Table 1 that 13 (20%) of 65 patients with a PRA ≥60, the cut-off value for priority status in many programs (*2*), have a greater than one-in-ten chance of finding an acceptable donor. Conversely, one patient with a PRA <60, has a lower Pc value—i.e., less chance of finding an acceptable donor—than half the patients who would have priority status by the PRA 60 criterion.

TABLE 3. Average expected waiting time (in years) for various probability values (P_c) and donor recovery rates

P_c	Recovery rate (No. of donors per year)				
	50	100	150	200	250
.000005	4000	2000	1333.3	1000	800
.00001	2000	1000	666.7	500	400
.00005	400	200	133.3	100	80
.0001	200	100	66.7	50	40
.0005	40	20	13.3	10	8
.0010	20	10	6.7	5	4
.0050	4	2	1.3	1	0.8
.0100	2	1	0.7	0.5	0.4

One can use the P_c value and donor recovery rate to estimate the average expected waiting time for patients to receive a cadaveric transplant. Expected waiting time for a variety of P_c and recovery rate values are shown in Table 3. This information could be useful in establishing criteria for high-priority status—and, possibly, in decisions about pretransplant and posttransplant treatment of the patient.

In summary, based on a patient's phenotype and sensitization, the probability of finding an acceptable cadaveric donor can be calculated. This value is more meaningful than PRA for estimating the opportunity of transplantation and for establishing high priority status because it takes into account all relevant antigen systems; it is unaffected by the cell panel used to screen recipient's sera; and it can be used to estimate the expected waiting time for transplantation.

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LYMPHOCYTE SENSITIVITY TO GLUCOCORTICOIDS BEFORE AND AFTER CADAVER KIDNEY TRANSPLANTATION[1]

Cadaver kidney graft survival has been related to a low donor-specific mixed lymphocyte culture (MLC)[2] response, which indicates the importance of the T lymphocyte response for graft rejections (*1, 2*). A predictive value of DR matching for kidney graft survival has also been demonstrated (*3, 4*). However, graft rejections occur despite low MLC response and DR compatibility—and, furthermore, a significant number of grafts survive despite DR incompatibility and high MLC response. Therefore, the sensitivity to steroids of lymphocytes from an individual patient could contribute to the heterogeneity of the immune response and be an additional determining factor for the outcome of kidney graft survival. Previous reports from our laboratory have demonstrated great interindividual differences of the in vitro immunosuppressive effects of glucocorticoids (*5*). Thus the discrepancy between patient immune response—i.e., graft rejections—and donor specific MLC response may be related to differences in patient sensitivity to the immunosuppressive effect of glucocorticoids. The present study, therefore, examined the individual in vivo as well as in vitro lymphocyte response to the immunosuppressive effect of methylprednisolone (MP) in relation to graft survival.

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[2] Abbreviations used in this article: ADCC, antibody-dependent cellular cytotoxicity; HPLC, high-performance liquid chromatography; MLC, mixed lymphocyte culture; MP, methylprednisolone; PHA, phytohemagglutinin; PHA SI, PHA suppressive index.