HLA-Sharing, Recurrent Spontaneous Abortion, and the Genetic Hypothesis

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ABSTRACT

A number of studies indicates that there is a high sharing of HLA antigens in couples having recurrent spontaneous abortions. The genetic hypothesis to explain this phenomenon suggests that this fetal loss results from homozygosity of recessive lethal or deleterious alleles in gametic disequilibrium with HLA antigens. Theory predicting the lethality rate is derived when antigens are shared at one, two or three loci, given that the disequilibrium is absolute. In addition, the effects of partial disequilibrium, inbreeding, and segregation distortion on the lethal proportion are examined.

APPROXIMATELY 30% of the couples having two or more spontaneous abortions do not have a demonstrable basis, such as a chromosomal or anatomical abnormality, for the fetal loss (THOMAS *et al.* 1985). A number of studies indicate that such couples often share antigens for HLA loci (see Table 1 for a summary of 14 studies from THOMAS *et al.* 1985). The frequency of shared antigens in Table 1 is higher for aborting couples in all comparisons but when two or three loci are examined simultaneously, it is much higher for couples with a history of recurrent spontaneous abortion than for control couples. There are, however, some reports not consistent with this trend (*e.g.*, OKSENBERG *et al.* 1984). In addition, there may be some bias in the reported data sets with some negative results being unpublished.

Two main hypotheses have been suggested to explain the association between HLA antigen-sharing in couples and recurrent spontaneous abortion. First, the immunological hypothesis suggests that the presence of an immune response occurring when the mother and fetus differ at the HLA loci is necessary for proper implantation and fetal growth [*e.g.*, GILL (1983) and references therein]. In other words, sharing of HLA antigens in a parental couple results in a fetus similar to the mother and consequently an immune response that is abnormal in some way by the mother to the fetus [see HEDRICK and THOMSON (1988) for a discussion of the theory of this model].

Second, the genetic hypothesis suggests that recurrent spontaneous abortions in couples that share HLA antigens are the result of homozygosity in the progeny of recessive lethal or deleterious alleles at linked loci that are statistically associated with HLA antigens [*e.g.*, SCHACTER, WEITKAMP and JOHNSON (1984) and references therein]. The *T/t* complex in the mouse is closely linked to the MHC region, making it possible that there is an analogous complex linked to the HLA region. Because mutant *t* alleles result in mice with abnormal neurological development, it has been proposed that an analogous human system could result in neural tube defects as well as early fetal loss (*e.g.*, BOBROW *et al.* 1975). Although initial surveys (*e.g.*, BOBROW *et al.* 1975) did not support this hypothesis, SCHACTER, WEITKAMP and JOHNSON (1984) found increased HLA-sharing in couples who had an anencephalic fetus when compared to couples with no fetal loss.

There has been considerable speculation concerning the significance of the genetic hypothesis in explaining the association of HLA antigen sharing and repeated spontaneous abortion without a basic theoretical examination. Therefore, in this paper, I will examine the genetic hypothesis and formulate the expected quantitative relationship between the number of HLA antigens shared in couples and the proportion of fetal deaths. I will also examine the effects of inbreeding or segregation distortion on these expectations.

THEORETICAL PREDICTIONS

Absolute gametic disequilibrium: Let us begin by assuming the most extreme situation, *i.e.*, a different noncomplementary recessive lethal is in absolute gametic disequilibrium (*sensu* CLEGG *et al.* 1976) with each HLA antigen. (We will use the term gametic rather than linkage disequilibrium because such statistical associations may occur between unlinked loci (*e.g.*, HEDRICK, JAIN and HOLDEN 1978)). In other words, if we gave the complete gamete (or haplotype), then the only gametes present would be A_1l_1, A_2l_2 $\cdots$ A_il_i where A_i is an allele at a HLA locus and l_i is a recessive lethal at a linked locus. Therefore, all

TABLE 1

Prevalence of shared antigens at different HLA loci for normally fertile couples or for couples having a history of recurrent spontaneous abortions with the sample size in parentheses (after THOMAS *et al.* 1985)

Locus (loci)	No. of antigens shared	Normal couples	Aborting couples
A	1 or 2	0.422 (408)	0.505 (325)
B	1 or 2	0.243 (408)	0.314 (325)
DR	1 or 2	0.219 (114)	0.504 (115)
A, B	2 or more	0.072 (83)	0.230 (152)
A, B, DR	2 or more	0.220 (150)	0.505 (109)

TABLE 2

Number of shared antigens, mating types and probability of inviable progeny for a single locus in absolute gametic disequilibrium

No. of antigens shared in parents	Mating types	Probability of inviable progeny
0	$AA \times AA$	0
1	$A_i^*A \times A_i^*A$	¼
2	$A_i^*A_j^* \times A_i^*A_j^*$	½

* Indicates shared antigens.

individuals homozygous at one or more HLA genotypes are inviable and all individuals heterozygous for all the HLA loci are equally viable.

First, assume that the parental couple shares either 0, 1, or 2 antigens at a single locus, say *A*. Of course, when they do not share any antigens, *e.g.*, the mating is $A_1A_2 \times A_3A_4$, all progeny are viable, resulting in no selection or $s_0 = 0$, where the subscript refers to the number of antigens shared in the parents. When the parents share one antigen, *e.g.*, $A_1A_2 \times A_1A_3$, ¾ of the progeny are viable so that $s_1 = ¼$. When the parents share two antigens, *e.g.*, $A_1A_2 \times A_1A_2$, ½ the progeny are viable so $s_2 = ½$. These results are summarized in Table 2 where the antigens shared are indicated by an asterisk (the subscripts indicating unshared alleles are not given).

Let us next consider two loci simultaneously, say *A* and *B*, a situation in which a couple could share either 0, 1, 2, 3, or 4 antigens. When the parents share 0 or 1 antigens, the probabilities are the same as for one locus. However, there are four basic ways in which two antigens can be shared, depending upon their gametic phase. The simplest case is like the single-locus example, *e.g.*, $A_1B_1/A_2B_2 \times A_1B_3/A_2B_4$. A second situation assumes that both loci are involved in sharing and that the shared antigens are all on different haplotypes, such as the example given in Table 3 where the couple $A_1B_1/A_2B_2 \times A_1B_3/A_3B_2$ is considered. If we assume that the rate of recombination between the two loci is *c*, the fitness

TABLE 3

Gametic types, their frequencies and the relative fitness of the progeny given the mating $A_1B_1/A_2B_2 \times A_1B_3/A_3B_2$ where *c* is the rate of recombination between loci *A* and *B* and w_A and w_B are the fitnesses of A_iA_i and B_jB_j, respectively

		Female gametes and frequencies			
Male gametes	Frequencies	A_1B_1 ½(1 − *c*)	A_2B_2 ½(1 − *c*)	A_1B_2 *c*/2	A_2B_1 *c*/2
A_1B_3	½(1 − *c*)	w_A	1	w_A	1
A_3B_2	½(1 − *c*)	1	w_B	w_B	1
A_1B_2	*c*/2	w_A	w_B	w_Aw_B	1
A_3B_3	*c*/2	1	1	1	1

TABLE 4

Number of shared antigens, mating types and probability of inviable progeny for two loci (when two values are given, the first is for an amount of recombination *c* between the loci and the second is for $c = 0$)

No. of antigens shared in parents	Mating types	Probability of inviable progeny
0	$AB/AB \times AB/AB$	0
1	$A_i^*B/AB \times A_i^*B/AB$	¼
	$AB_k^*/AB \times AB_k^*/AB$	¼
2	$A_i^*B/A_j^*B \times A_i^*B/A_j^*B$	½
	$AB_k^*/AB_l^* \times AB_k^*/AB_l^*$	½
	$A_i^*B/AB_k^* \times A_i^*B/AB_k^*$	$½(1 - (c^2/2))$, ½
	$A_i^*B_k^*/AB \times A_i^*B/AB_k^*$	$½ - (c/4)(1 - c)$, ½
	$A_i^*B_k^*/AB \times A_i^*B_k^*/AB$	$¼(1 - c^2) + (c/2)$, ¼
3	$A_i^*B_k^*/A_j^*B \times A_i^*B_k^*/A_j^*B$	$½(1 + c - c^2)$, ½
	$A_i^*B_k^*/AB_l^* \times A_i^*B_k^*/AB_l^*$	$½(1 + c - c^2)$, ½
4	$A_i^*B_k^*/A_j^*B_l^* \times A_i^*B_k^*/A_j^*B_l^*$	$½(1 + 2c - c^2)$, ½

* Indicates shared antigens.

of $A_iA_i = w_A = 0$, and the fitness of $B_jB_j = w_B = 0$, then

$$s_2 = ½(1 - c^2/2). \tag{1a}$$

Third, if the shared antigens are on the same haplotype in both parents, *e.g.*, $A_1B_1/A_2B_2 \times A_1B_1/A_3B_3$, then

$$s_2 = ¼(1 - c^2) + c/2. \tag{1b}$$

Finally, two of the shared antigens may be on one haplotype in one parent and two haplotypes in the other, *e.g.*, $A_1B_1/A_2B_2 \times A_1B_3/A_3B_1$, so that

$$s_2 = ½ - (c/4)(1 - c). \tag{1c}$$

Notice that for all these cases when $c = 0$, $s_2 = ½$ except when the shared antigens are on the same haplotype in both parents. When the shared antigens

TABLE 5

Gametic types, their frequencies and the relative fitnesses of the progeny given the mating $A_1B_1C_1/A_2B_2C_2 \times A_1B_1C_1/A_3B_3C_3$ where c_1 and c_2 are the rates of recombination between loci A and B and between and B and C, respectively, and w_A, w_B, and w_C are the fitnesses of genotypes A_iA_i, B_jB_j, and C_kC_k, respectively

Male gametes	Frequencies	Female gametes and frequencies							
		$A_1B_1C_1$ $\frac{1}{2}(1-c_1-c_2)$	$A_2B_2C_2$ $\frac{1}{2}(1-c_1-c_2)$	$A_1B_2C_2$ $\frac{1}{2}c_1(1-c_2)$	$A_2B_1C_1$ $\frac{1}{2}c_1(1-c_2)$	$A_1B_1C_2$ $\frac{1}{2}(1-c_1)c_2$	$A_2B_2C_1$ $\frac{1}{2}(1-c_1)c_2$	$A_1B_2C_1$ $\frac{1}{2}c_1c_2$	$A_2B_1C_2$ $\frac{1}{2}c_1c_2$
$A_1B_1C_1$	$\frac{1}{2}(1-c_1-c_2)$	$w_Aw_Bw_C$	1	w_A	w_Bw_C	w_Aw_B	w_C	w_Aw_C	w_B
$A_3B_3C_3$	$\frac{1}{2}(1-c_1-c_2)$	1	1	1	1	1	1	1	1
$A_1B_3C_3$	$\frac{1}{2}c_1(1-c_2)$	w_A	1	w_A	1	w_A	1	w_A	1
$A_3B_1C_1$	$\frac{1}{2}c_1(1-c_2)$	w_Bw_C	1	1	w_Bw_C	w_B	w_C	w_C	w_B
$A_1B_1C_3$	$\frac{1}{2}(1-c_1)c_2$	w_Aw_B	1	w_A	w_B	w_Aw_B	1	w_A	w_B
$A_3B_3C_1$	$\frac{1}{2}(1-c_1)c_2$	w_C	1	1	w_C	1	w_C	w_C	1
$A_1B_3C_1$	$\frac{1}{2}c_1c_2$	w_Aw_C	1	w_A	w_C	w_A	w_C	w_Aw_C	1
$A_3B_1C_3$	$\frac{1}{2}c_1c_2$	w_B	1	1	w_B	w_B	1	1	w_B

TABLE 6

Four basic mating types of the probability of inviable progeny with absolute disequilibrium and no recombination when antigens are shared at three loci where c_1 and c_2 are rates of recombination between loci A and B and between B and C, respectively

	Mating type	Probabilities of inviable progeny when $c_1 = c_2 = 0$
(a)	$A^*B^*C^*/ABC \times A^*B^*C^*/ABC$	$\frac{1}{4}$
(b)	$A^*B^*C^*/ABC \times A^*B^*C/ABC^*$	$\frac{1}{2}$
	$A^*B^*C^*/ABC \times A^*BC^*/AB^*C$	$\frac{1}{2}$
	$A^*B^*C^*/ABC \times AB^*C^*/A^*BC$	$\frac{1}{2}$
(c)	$A^*B^*C/ABC^* \times A^*B^*C/ABC^*$	$\frac{1}{2}$
	$A^*BC^*/AB^*C \times A^*BC^*/AB^*C$	$\frac{1}{2}$
	$AB^*C^*/A^*BC \times AB^*C^*/A^*BC$	$\frac{1}{2}$
(d)	$A^*B^*C/ABC^* \times A^*BC^*/AB^*C$	$\frac{3}{4}$
	$A^*B^*C/ABC^* \times AB^*C^*/A^*BC$	$\frac{3}{4}$
	$A^*BC^*/AB^*C \times AB^*C^*/A^*BC$	$\frac{3}{4}$

* Indicates shared antigens.

are at different loci and $c = \frac{1}{2}$, then $s_2 = \frac{7}{16}$ for the cases involving two loci as expected.

Using the same approach for three shared antigens, *e.g.*, $A_1B_1/A_2B_2 \times A_1B_1/A_2B_3$,

$$s_3 = \frac{1}{2}(1 + c - c^2) \quad (2)$$

and for four shared antigens

$$s_4 = \frac{1}{2}(1 + 2c - 2c^2). \quad (3)$$

For sharing of either three or four antigens when $c = 0$, then $s_3 = s_4 = \frac{1}{2}$. The results for sharing at two loci are summarized in Table 4.

Finally, let us examine three loci. The probabilities are the same as calculated above until three antigens are shared and they are at three different loci. As an example of this case, let us examine the mating $A_1B_1C_1/A_2B_2C_2 \times A_1B_1C_1/A_3B_3C_3$, where all shared antigens are on the same haplotype in both parents, and assume that c_1 is the recombination rate between loci A and B and c_2 is the recombination rate between loci B and C. The different gametic types and the fitnesses are given in Table 5. Using these segregation values and assuming that $w_A = w_B = w_C = 0$, then

$$s_3 = \frac{1}{2} - \frac{1}{4}(1 - c_1 - c_2)^2 + \frac{1}{2}c_1c_2(1 - c_1c_2). \quad (4a)$$

When $c_1 = c_2 = 0$, then $s_3 = \frac{1}{4}$. Another possibility occurs when three antigens are shared with two on one haplotype and one on the other in both parents, *e.g.*, $A_1B_2C_1/A_2B_1C_2 \times A_1B_3C_1/A_3B_1C_3$. In this case

$$s_3 = \frac{1}{2} + \frac{1}{2}(c_1 + c_2 - c_1^2 - c_2^2 - \frac{1}{2}c_1^2c_2^2). \quad (4b)$$

When $c_1 = c_2 = 0$ in this case, then $s_3 = \frac{1}{2}$. One way to summarize these possibilities is to categorize them by the probabilities of inviable progency when $c_1 = c_2 = 0$. Table 6 gives the four basic situations when three antigens are shared involving three loci. Notice that the values range from $\frac{1}{4}$ when all shared antigens are on one haplotype in both parents to $\frac{3}{4}$ as in the bottom type of Table 6. Using the same approach, the expected proportion of inviable progeny can be calculated for sharing of 4, 5, or 6 antigens when three loci are involved.

Partial gametic disequilibrium: In the previous section, we assumed the most extreme case, that of absolute gametic disequilibrium between HLA and lethal alleles. Let us now assume that the gametic disequilibrium between the HLA antigens and the recessive detrimental alleles is not absolute, *e.g.*, not all A_1 alleles are on chromosomes with l_1 alleles. The usual measure of disequilibrium is

$$D_{11} = x_{11} - p_1q_1 \quad (5)$$

where x_{11} is the observed frequency of chromosome A_1l_1 and p_1 and q_1 are the frequencies of alleles A_1 and l_1. More appropriate in many cases is the nor-

malized measure from LEWONTIN (1964)

$$D'_{11} = D_{11}/D_{\max} \tag{6a}$$

where $D_{\max}$ is the min $[p_1q_1, (1 - p_1)(1 - q_1)]$ if $D_{11} < 0$ or min $[p_1(1 - q_1), (1 - p_1)q_1]$ if $D_{11} > 0$. Here we are interested in the situation in which $D_{11} > 0$, *i.e.*, where there are more A_1l_1 chromosomes than expected if there is no association between alleles at the two loci. If we assume $p_1 \geqq q_1$, *i.e.*, the frequency of antigen A_1 is greater than or equal to that of lethal l_1, then $D_{\max} = (1 - p_1)q_1$ and

$$D'_{11} = \frac{D_{11}}{(1 - p_1)q_1}. \tag{6b}$$

Let us define the proportion of A_1 chromosomes having the l_1 allele as

$$z = \frac{x_{11}}{p_1} \tag{7a}$$

then by substitution

$$z = \frac{D_{11} + p_1q_1}{p_1}$$

$$= \frac{D'_{11}(1 - p_1)q_1 + p_1q_1}{p_1}. \tag{7b}$$

Because the maximum value of D'_{11} is 1, we can calculate the maximum proportion z for given allelic frequencies using this expression. If $p_1 = q_1$ and $D'_{11} = 1$, then $z = 1$. However, it is more likely that the frequency of an associated lethal would be much lower than that for a typical HLA antigen. For example, if $p_1 = 0.1$, a typical frequency for alleles at HLA loci *A* or *B* and $q_1 = 0.01$, a typical frequency for a recessive lethal, then if $D'_{11} = 1$, $z = 0.1$.

How much will gametic disequilibrium that is not absolute lower the expected proportion of recessive lethal progeny? First, let us examine the single-locus HLA situation in which the parents share one antigen. Because there are two types of gametes with A_1, A_1l_1 and $A_1\bar{l}_1$ (where the overbar means "not"), there are three possible mating types where both parents have A_1 alleles (see Table 7). Using these mating-type frequencies and the expected segregation proportions, then

$$s_1 = \tfrac{1}{4}z^2. \tag{8}$$

(Note that it is assumed that the frequency of gamete $\bar{A}l_1$ is negligible.) In this case, if $z = 0.1$, then s_1 is only 0.0025, two orders of magnitude below that for absolute disequilibrium.

Now let us assume that the parents share both antigens for a given locus. If we let z_1 be the proportion of A_1 gametes with l_1 and z_2 the proportion of A_2 gametes with l_2, then the ten possible mating types, their frequencies and segregation proportions

TABLE 7

Mating types, their frequencies and the proportion of lethal progeny assuming that allele A_1 is shared and there is association with lethal allele l_1 where z is the proportion of A_1 chromosomes having the l_1 allele

Mating type	Frequency	Proportion progeny l_1l_1
$A_1l_1/\bar{A}_1\bar{l}_1 \times A_1l_1/\bar{A}_1\bar{l}_1$	z^2	¼
$A_1l_1/\bar{A}_1\bar{l}_1 \times A_1\bar{l}_1/\bar{A}_1\bar{l}_1$	$2z(1 - z)$	0
$A_1\bar{l}_1/\bar{A}_1\bar{l}_1 \times A_1\bar{l}_1/\bar{A}_1\bar{l}_1$	$(1 - z)^2$	0

TABLE 8

Mating types, their frequencies, and the proportion of lethal progeny assuming that both alleles, A_1 and A_2, are shared and they are associated with lethals l_1 and l_2 where z_1 and z_2 are the proportion of A_1 chromosomes having l_1 alleles and the proportion A_2 chromosomes having l_2 alleles, respectively

Mating type	Frequency	Proportion l_1l_1 or l_2l_2 progeny
$A_1l_1/A_2l_2 \times A_1l_1/A_2l_2$	$z_1^2z_2^2$	½
$A_1l_1/A_2l_2 \times A_1l_1/A_2\bar{l}_2$	$2z_1^2z_2(1 - z_2)$	¼
$A_1l_1/A_2l_2 \times A_1\bar{l}_1/A_2l_2$	$2z_1z_2^2(1 - z_1)$	¼
$A_1l_1/A_2l_2 \times A_1\bar{l}_1/A_2\bar{l}_2$	$2z_1z_2(1 - z_1)(1 - z_2)$	0
$A_1l_1/A_2\bar{l}_2 \times A_1l_1/A_2\bar{l}_2$	$z_1^2(1 - z_2)^2$	¼
$A_1l_1/A_2\bar{l}_2 \times A_1\bar{l}_1/A_2l_2$	$2z_1z_2(1 - z_1)(1 - z_2)$	¼
$A_1l_1/A_2\bar{l}_2 \times A_1\bar{l}_1/A_2\bar{l}_2$	$2z_1(1 - z_1)^2(1 - z_2)$	0
$A_1\bar{l}_1/A_2l_2 \times A_1\bar{l}_1/A_2l_2$	$(1 - z_1)^2z_2^2$	¼
$A_1\bar{l}_1/A_2l_2 \times A_1\bar{l}_1/A_2\bar{l}_2$	$2z_2(1 - z_1)^2(1 - z_2)$	0
$A_1\bar{l}_1/A_2\bar{l}_2 \times A_1\bar{l}_1/A_2\bar{l}_2$	$(1 - z_1)^2(1 - z_2)^2$	0

are given in Table 8, making

$$s_2 = \tfrac{1}{2}z_1^2z_2^2 + \tfrac{1}{4}(z_1 + z_2) \times [z_1(1 - z_2) + z_2(1 - z_1)]. \tag{9}$$

If we let $z_1 = z_2 = 0.1$, then s_2 is only 0.00905, much lower than the value of ½ for absolute disequilibrium.

Inbreeding: When there is partial disequilibrium between the antigen and a lethal, the proportion of recessive lethal progeny may be higher when there is inbreeding. For example, let us assume that a mating pair share one allele and that it is a mating between first cousins. If we assume the grandparents are A_1A_2 and A_3A_4, then their progeny are expected to be $\tfrac{1}{4}A_1A_3$, $\tfrac{1}{4}A_1A_4$, $\tfrac{1}{4}A_2A_3$, and $\tfrac{1}{4}A_2A_4$. If one cousin, say the female, received an unrelated allele A_x and the male cousin received the unrelated allele A_y, then there are 16 equally frequent mating types expected (see Table 9). In four of these matings, with a total frequency of ¼, the first cousins share one allele that is identical by descent. Let us define the proportion of matings that share one allele due to inbreeding as f_1 and note that it is generally equal to $4f$ where f is the expected inbreeding coefficient

TABLE 9

Sixteen possible first cousin mating types indicating those that share one allele identical by descent (1) and those that share no alleles (0)

Male first cousin	Female first cousin			
	A_1A_x	A_2A_x	A_3A_x	A_4A_x
A_1A_y	1	0	0	0
A_2A_y	0	1	0	0
A_3A_y	0	0	1	0
A_4A_y	0	0	0	1

of an offspring from the consangineous mating. (For a full-sib mating, $f_1 = 2f$ because some full sibs share two alleles identical by descent.)

Incorporating the ¼ probability of a lethal offspring from a mating of individuals sharing one antigen, the proportion of ancestral alleles having a lethal z, and the probability of no recombination between locus A and the lethal allele in the lineages leading to the male and female parents, the proportion of lethal progeny from such a consanguineous mating is

$$s_{1f} = \tfrac{1}{4}f_1z(1 - c)^n \qquad (10)$$

where $(1 - c)^n$ is the probability of no recombination. For example, for a full first-cousin mating, $n = 4$.

The alleles shared may not be identical by descent with probability $1 - f_1$ so that the overall expected proportion of recessive lethal progeny is

$$\begin{aligned} s_1 &= \tfrac{1}{4}f_1z(1 - c)^n + \tfrac{1}{4}z^2(1 - f_1) \\ &= \tfrac{1}{4}z[f_1(1 - c)^n + z(1 - f_1)]. \end{aligned} \qquad (11)$$

If the parents are first cousins, then $f = \frac{1}{16}$, $f_1 = \frac{1}{4}$, and $n = 4$. As an example, assume that $z = 0.1$ and $c = 0.0$, making $s_1 = 0.0081$. Although this is over threefold that when $f = 0$, still less than 1% of the progeny would die resulting from homozygosity at lethals linked to the HLA gene. The impact would become even less if the consanguinity is more remote.

Segregation distortion: It has been suggested that alleles at a t-locus homolog linked to the HLA region can cause segregation distortion (*e.g.*, ALPER *et al.* 1985) although other studies (*e.g.*, KLITZ *et al.* 1987) do not support this claim. If there are such alleles then segregation distortion may influence the proportion of lethal offspring for couples sharing HLA alleles. As an example, let us assume that there is absolute disequilibrium between the A_1 alleles and an allele causing segregation distortion. As in mice, assume that segregation distortion takes place only in males so that the male heterozygote A_1A_2 produces a proportion m of A_1 sperm and $1 - m$ of A_2 sperm. In a mating $A_1A_2 \times A_1A_3$ with one shared antigen, then $s_1 = \frac{1}{2}m$, *i.e.*, this proportion of the progeny should be A_1A_1. If $m = 0.8$, then $s_1 = 0.4$, greater than the ¼ for no segregation distortion. However, for two shared antigens $s_2 = \frac{1}{2}m + \frac{1}{2}(1 - m) = \frac{1}{2}$ as it would be for no segregation distortion.

TABLE 10

Couples sharing two antigens when there is segregation distortion of the amount m in the males and the consequent probability of inviable progeny (when two values are given, the first is for an amount of recombination c between the loci and the second is for $c = 0$)

Male	Female	Probability of inviable progeny
A_i^*B/A_j^*B	A_i^*B/A_j^*B	½
AB_k^*/AB_l^*	AB_k^*/AB_l^*	½
A_i^*B/AB_k^*	A_i^*B/AB_k^*	$\frac{1}{2}[1 - c(1 - 2m + cm)]$, ½
A_i^*B/AB_k^*	$A_i^*B_k^*/AB$	$\frac{1}{2} - (c/2)(1 - m - cm)$, ½
$A_i^*B_k^*/AB$	A_i^*B/AB_k^*	$\frac{1}{2}c + m(1 - (3c/2) + (c^2/2))$, m
$A_i^*B_j^*/AB$	$A_i^*B_k^*/AB$	$\frac{1}{2}c + \frac{1}{2}m(1 - c^2)$, $\frac{1}{2}m$

* Indicates shared antigens.

If we examine the mating type given in Table 3 for two shared antigens at different loci (still with segregation distortion favoring A_1) but let the frequencies of male gametes A_1B_3, A_3B_2, A_1B_2, and A_3B_3 be $m(1 - c)$, $(1 - m)(1 - c)$, mc, and $(1 - m)c$, respectively, then

$$s_2 = \tfrac{1}{2}[1 - c(1 - 2m + cm)]. \qquad (12)$$

When $c = 0$, then $s_2 = \frac{1}{2}$, the same as when there is no segregation distortion. However, when $c \neq 0$, then the probability of inviable offspring is increased when $m > 1/(2 - c)$ and decreased when $m < 1/(2 - c)$. For example, when $c = 0.5$ and $m = 0.8$, then $s_2 = 0.55$ as compared to $s_2 = \frac{7}{16}$ when there is normal segregation ($m = 0.5$). This and the other possible gamete arrays when two antigens are shared at two loci are given in Table 10. For the last two mating types, segregation distortion increases the probability of inviable offspring for all recombination values including $c = 0$. For the mating type in row four, the probability is increased when $m > 1/(1 + c)$ and decreased when $m < 1/(1 + c)$.

DISCUSSION

Although there has been extensive discussion in the literature both supporting and rejecting a genetic explanation for the high rate of spontaneous abortion in couples that share HLA antigens, there has been no theoretical evaluation of this model. The development of the model here with the related predictions make it possible to suggest what situations or factors may result in high fetal mortality under the genetic hypothesis.

The probability that a fetus would be inviable given

that its parents share HLA antigens which are in absolute disequilibrium with a recessive lethal is given in Tables 2, 4, for one and two loci, respectively, and in Table 6 for three loci when there are up to three shared antigens. For one or two loci, these probabilities are either ¼ or ½ assuming no recombination for the two-locus case. When two antigens are shared at two loci without recombination, the probability of inviable progeny is ½ (with one exception) compared to probabilities of 0 and ¼ for no or one shared antigens. This difference is consistent with the observations of a higher frequency of shared antigens in aborting couples when two or more loci are considered as given in Table 1. For some haplotypes, when three antigens are shared at three loci, the probability of an inviable offspring is ¾. However, the overall impression is that the probability of an inviable offspring is generally ¼ to ½. Of course, when the disequilibrium between HLA alleles and lethal alleles is not absolute, these values are much lower. In addition, if the associated alleles are not lethals but only reduce viability, then the probabilities would also be lower.

It appears unlikely that there is a high association of given lethals with particular antigens, *i.e.*, high z values, from examination of population data. If z were high, then there should be a deficiency of HLA homozygotes. However, in large population surveys, data are generally close to Hardy-Weinberg expectations (*e.g.*, BAUR *et al.* 1984). Furthermore, segregation patterns for HLA-A and B antigens in Hutterites were consistent with multinomial distribution expectations, suggesting that lethal alleles linked to HLA are not common in this population (MORGAN *et al.* 1986).

There are two factors that may increase the expected proportion of lethal offspring in couples that share HLA haplotypes. First, when the disequilibrium is not absolute, inbreeding may increase the probability of lethal offspring somewhat. Second, segregation distortion may in some cases increase the probability of lethal offspring although in other cases it has no effect.

A major problem in comparing the genetic hypothesis to observed data is that couples are ascertained based on the occurrence of repeated spontaneous abortion. How to correct for this bias is not clear. For example, the often used model of single ascertainment (*e.g.*, LI 1961) is probably not appropriate because the likelihood of ascertainment for a couple with recurrent spontaneous abortion may increase faster than the weighting given in single ascertainment (see EWENS and SHUTE 1986). Therefore, without some empirical estimate of the ascertainment bias, it appears difficult to conclusively determine the likelihood of the genetic hypothesis from the available data.

However, one possible means to determine the importance of the genetic model could be to use couples with shared HLA antigens and a history of repeated spontaneous abortion to predict future fetal wastage. For example, when one HLA antigen is shared, then the probability of spontaneous abortion in the next conception would be only ¼ while for the immunological hypothesis, it presumably would be higher. Such an approach should obviate any ascertainment bias.

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