Coevolution of the Major Histocompatibility Complex and the *t*-Complex in the Mouse. I. Generation and Maintenance of High Complementarity Associations

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ABSTRACT

A quantitative model is developed to explore the effects of prezygotic and postzygotic incompatibility on the origin and maintenance of associations between the major histocompatibility complex (MHC) and the *t*-complex in the mouse. Incompatibility is represented by a reduction in the rate of conception or gestation of offspring derived from sperm bearing MHC antigens in common with the mother. Incompatibility encourages the evolution of associations from a state of complete independence between the two complexes by promoting the invasion of all novel antigens, including those that exhibit associations with the *t*-complex. Incompatibility can modify the relative numbers of antigens associated with each haplotype by actively promoting the exclusion or invasion of recombinants that bear formerly +-specific or *t*-specific antigens on the alternative haplotype. The results of the analysis indicate that the state of complete independence between the MHC and the *t*-complex is not preserved over evolutionary time in the presence of incompatibility. Further, the expression of incompatibility maintains fully associated states that include a single antigen associated with the *t*-haplotype and up to three to five antigens associated with the +-haplotype within a single population.

ANTIGENS of the major histocompatibility complex (MHC) exhibit strong associations with the *t*-complex in the mouse (HAMMERBERG and KLEIN 1975; LEVINSON and MCDEVITT 1976; STURM, FIGUEROA and KLEIN 1982; KLEIN, SIPOS and FIGUEROA 1984). A number of speculations concerning the adaptive significance of this phenomenon have been advanced. SNELL (1968) proposed that the function of the association is to preserve polymorphism at *H-2* through absolute linkage with the *t*-complex, within which viability of fertility selection favoring the +-haplotype and segregation distortion favoring the *t*-haplotype preclude monomorphism. HAMMERBERG and KLEIN (1975) suggested that the particular antigens that are associated with the *t*-haplotype interact in some fashion with the *t*-complex to produce physiologically superior sperm.

More recently, the consensus appears to eschew direct selective or physiological functions, and to interpret the restriction of certain antigens to *t*-haplotypes and the low sequence diversity within this set as evidence for the common origin of all known *t*-haplotypes (SHIN *et al.* 1982; SILVER 1982; NIZETIC, FIGUEROA and KLEIN 1984; FIGUEROA *et al.* 1985). Under this view, the association arose upon the appearance of the *t*-haplotype, and has been maintained by suppression of recombination between the complexes resulting from the inversion in gene order in *t*-haplotypes relative to +-haplotypes [see SILVER (1985) for a review of the genetic structure and transmission of *t*-haplotypes]. Derivation of new *t*-haplotypes from a single original mutation rather than by independent mutational events (SILVER *et al.* 1987) permitted diversification of antigens among *t*-haplotypes while maintaining the association. The association of the *t*-haplotype with the same set of *H-2* antigens in different semispecies of *Mus* indicates that the association antedated the speciation events that permitted divergence between *Mus musculus* and *Mus domesticus* over one million years ago (NIZETIC, FIGUEROA and KLEIN 1984; FIGUEROA *et al.* 1985). Comparisons of sequences within the *t*-complex region itself support this estimate for the age of the *t*-haplotype (FRISCHAUF 1985; WILLISON, DUDLEY and POTTER 1986). Analysis of *t*-complex sequences from more distantly related taxa within the genus suggest that the *t*-haplotype may have arisen more than three million years ago (DELARBRE *et al.* 1988).

The purpose of the present study is to explore the effects of prezygotic and postzygotic incompatibility in response to sharing of MHC antigens on the generation and maintenance of associations between the MHC and the *t*-complex. The apparent universality of nonrandom associations in natural populations and their persistence over considerable periods of time suggest the existence of some factor that actively maintains the associations in the face of rare recombination events between the complexes, which oc-

In celebration of Professor R. C. Lewontin's sixtieth birthday.

cur in approximately one in 10^3 gametes produced by $+/t$ individuals (ARTZT and BENNETT 1975). Incompatibility can serve to maintain such associations; further, in the presence of incompatibility, the state of complete independence between the MHC and the *t*-complex is susceptible to the invasion of associated antigens.

Prezygotic and postzygotic incompatibility in response to antigen-sharing: JAMES (1965, 1967) raised the intriguing possibility that maternal-fetal incompatibility may maintain antigenic diversity within the MHC. These studies indicated that preimmunization of female mice to paternal antigens improves fetal growth. Subsequent investigations using the same mouse strains failed to confirm the results and challenged the existence of such a system (CLARKE 1971; MCLAREN 1975). Recent explorations using more refined immunological techniques have resurrected the experimental study of maternal-fetal incompatibility, an issue which once again finds itself embroiled in controversy (reviewed by CHAOUAT *et al.* 1987; and by BOBE, STANISLAWSKI and KIGER 1987). CHAOUAT *et al.* (1985) reported that the elevated abortion rate observed in crosses between *CBA/J* females and *DBA/2J* males declined as immunological recognition by mothers of foreign antigens increased, and that this protection from abortion was transferred to nonimmunized mice through serum alone. In other studies, immunization failed to affect or even increased the rate of abortion (reviewed by TARTAKOVSKY 1987).

Behavioral tests conducted on trained laboratory mice have implicated *H-2* in prezygotic incompatibility (reviewed by BOYSE, BEAUCHAMP and YAMAZAKI 1987). In general, antigenic dissimilarity promoted mate formation, although some individuals expressed consistent preferences for antigenically similar mates. Mice can detect differences in *H-2* antigens from urine alone (YAMAGUCHI *et al.* 1981). Regulation of recognition and response to antigen similarity appears to be encoded by a number of loci within the *H-2* region (YAMAGUCHI, YAMAZAKI and BOYSE 1978; ANDREWS and BOYSE 1978).

The available evidence concerning prezygotic and postzygotic incompatibility appears to support the existence of a genetic system which promotes dissimilarity with respect to MHC antigens between mother and offspring, a phenomenon that is functionally distinct from inbreeding depression in offspring. While conflicting results obtained from the immunization experiments illustrate the complexity of maternal-fetal interactions of this kind, the controversy for the most part appears to concern the magnitude of the effect more than its existence. The model to be described assumes weak incompatibility, in which the production of offspring derived from incompatible sperm is only slightly inhibited.

Overview of the evolutionary questions to be investigated: I have proposed that the primary evolutionary function of incompatibility systems in both plants and animals is to serve as a eugenic mechanism that improves offspring quality by eliminating or preventing the conception of certain zygotes at a stage that is sufficiently early to permit their replacement (UYENOYAMA 1988a). Because variation in offspring viability or fertility is often not expressed during the period of parental expenditure, this hypothesis requires that cues expressed by offspring before or soon after conception afford a means by which parents can assess offspring quality. Incompatibility systems that promote antigenic dissimilarity between mates or between parent and offspring can reduce the expression of deleterious recessive alleles at correlated loci. I developed a two-locus model involving a modifier locus that influences the intensity of expression of incompatibility in response to sharing of antigens encoded by a distinct locus (UYENOYAMA 1988b). I showed that the increased expression of incompatibility is favored if the magnitude of the association between the antigen locus and a locus influencing viability exceeds a threshold that is determined by the level of inbreeding, the number of antigens, and the frequency of deleterious alleles.

The MHC and the *t*-complex in the mouse together represent a prime candidate for an incompatibility system of the proposed kind by virtue of three properties: clear effects on viability or fertility of the recessive *t*-haplotype, implication of the MHC in prezygotic and postzygotic incompatibility, and well-documented associations between the *t*-haplotype and specific MHC antigens. In the present study, I explore the effect of the expression of incompatibility on the generation and maintenance of associations between the MHC and the *t*-complex. In the companion study (UYENOYAMA 1989), I consider the effect of those associations on the evolution of incompatibility.

MODEL CONSTRUCTION

Following CHRISTIANSEN and FELDMAN (1975), I recognize three classes of antigen alleles: antigens that occur with only the wild-type (+) allele (class A), with only the recessive *t*-allele (class B), and with both alleles (class C). Homozygotes for the wild-type allele (+/+) occur in frequencies of the form u_{ij}, in which indices i and j represent particular antigens belonging to class A or class C. Among these individuals, the fraction that carry only one antigen is

$$u(Hom) = \sum_{i \in A,C} u_{ii}, \qquad (1a)$$

and the fraction that are heterozygous at the antigen locus is

$$u(Het) = \sum_{i,j \in A,C} u_{ij}/2 \qquad (i \neq j). \qquad (1b)$$

The variable v_{lm} represents the frequency of individuals formed by the fusion of a haplotype carrying the wild-type allele and antigen l ($+A_l$) and a haplotype carrying the t-allele and antigen m (tA_m). The frequency of the alternative linkage relationship ($+A_m/t\,A_l$) corresponds to v_{ml}. Among $+/t$ individuals, antigen homozygotes occur with frequency

$$v(Hom) = \sum_{i \in C} v_{ii}, \tag{2a}$$

and antigen heterozygotes with frequency

$$v(Het) = \sum_{i \in A,C} \sum_{j \in B,C} v_{ij} \qquad (i \neq j). \tag{2b}$$

The variables $w(Hom)$ and $w(Het)$, defined in a fashion similar to (1), represent the frequencies of t/t individuals. The frequencies of the genotypes sum to unity:

$$u(Hom) + u(Het) + v(Hom) + v(Het) + w(Hom) + w(Het) = 1. \tag{3}$$

Segregation distortion causes the haplotype frequencies in sperm to depart from those computed from the genotypic frequencies among males. Haplotypes bearing the wild-type allele at the t-complex occur with frequency x_i, in which the subscript denotes the allele carried at the antigen locus, and haplotypes bearing the t-allele with frequency y_j. These variables are determined by the genotypic frequencies and the segregation rate k ($k > 1/2$), which represents the proportion of sperm produced by $+/t$ males that bear the t-allele. The frequency of haplotype $+A_i$ in sperm is

$$x_i = u_{ii} + \sum_{j \neq i} u_{ij}/2 + (1-k)\left[v_{ii} + (1-r)\sum_{j \neq i} v_{ij} + r\sum_{j \neq i} v_{ji}\right], \tag{4a}$$

in which r represents the rate of recombination between the antigen locus and the t-complex. The frequency of haplotype $t\,A_i$ is

$$y_i = k\left[v_{ii} + r\sum_{j \neq i} v_{ij} + (1-r)\sum_{j \neq i} v_{ji}\right] + w_{ii} + \sum_{j \neq i} w_{ij}/2. \tag{4b}$$

Equations 4a and 4b include recombination only for the purpose of elucidating the transmission process; the analysis to be described incorporates the assumption of complete suppression of recombination in $+/t$ individuals.

Incompatibility is represented by a reduction in the rate at which sperm sharing antigens in common with the mother result in offspring that complete gestation. Sperm bearing antigens held by the mother effect fertilization and generate offspring that survive maternal-fetal incompatibility at the rate g ($1 \geq g \geq 0$) relative to incompatible sperm. This component of selection includes both premating and postmating incompatibility. No depression of brood size is assumed to result from incompatibility. For example, the fraction of the offspring produced by A_i/A_i mothers that result from fertilization by $+A_i$ sperm is

$$x_i g/N_1(ii), \tag{5}$$

in which $N_1(ii)$, the average rate at which offspring derived from sperm received by this female complete gestation, is

$$N_1(ii) = g(x_i + y_i) + 1 - (x_i + y_i). \tag{6}$$

Similarly, the average gestation rate among sperm received by mothers of genotype A_i/A_j ($i \neq j$) is

$$N_2(ij) = g(x_i + y_i + x_j + y_j) + 1 - (x_i + y_i + x_j + y_j). \tag{7}$$

Viability selection occurs after the completion of gestation, the phase to which maternal-fetal incompatibility is restricted. Offspring that are homozygous for the recessive t-allele survive at the rate σ ($1 \geq \sigma \geq 0$) relative to individuals carrying the wild-type allele. For most of the analysis to be described, the t-allele will be assumed to be lethal ($\sigma = 0$). Variation in brood size arises at this point in the generation cycle, reflecting the assumption that females are incapable of replacing offspring lost to viability selection. This representation of incompatibility differs from other models (HULL 1964; CLARKE and KIRBY 1966; HEDRICK and THOMSON 1988) in that complete reproductive compensation is assumed to replace all zygotes terminated by incompatibility. In the absence of reproductive compensation, the effect of incompatibility is indistinguishable from viability selection.

The assumptions enumerated in this section determine the recursion equations, a subset of which appears in APPENDIX 1.

RESULTS

Absence of incompatibility

BRUCK (1957) derived expressions for the equilibrium frequency of a completely recessive t-allele with lethal expression in both sexes that is maintained by segregation distortion in males. In the notation used in the present study, he obtained:

$$u = 1 - v = \sqrt{(1-k)/k} \tag{8a}$$

$$y = 1 - x = kv \tag{8b}$$

$$T = 1 - vy/2 = 1/2 + ku, \tag{8c}$$

in which u represents the frequency of $+/+$ individuals, v $+/t$ individuals, y t-bearing sperm, x $+$-bearing sperm, and T the mean fitness of the population. Under partial viability of t/t individuals ($1 \geq \sigma > 0$),

the cubic equation in APPENDIX 2 determines the equilibrium frequencies.

Introductions near high complementarity states

Characterization of the high complementarity equilibria: FRANKLIN and LEWONTIN (1970) described states of complete association, in which the multilocus haplotypes represented in the population bear complementary (disjoint) sets of alleles; such equilibria come into existence in the absence of recombination. CHRISTIANSEN and FELDMAN (1975) derived conditions for the existence and stability of equilibria in their model of viability selection controlled by two alleles segregating at one locus and m alleles at a linked locus. They denoted equilibria in which the alleles at the biallelic locus occur with complementary sets of alleles at the other locus as high complementarity states. In the present study, high complementarity states correspond to equilibria in which only +-specific and t-specific antigens segregate.

High-complementarity equilibria, which involve a class A antigens, b class B antigens, and no class C antigens, come into existence in the absence of recombination in $+/t$ individuals. Any two antigens within the same class are interchangeable. Under lethality of the recessive t-allele ($\sigma = 0$), this symmetry results in the reduction of the equations describing the equilibrium state or states to three variables, $u(Hom)$, $u(Het)$, and v:

$$\begin{aligned} u_{ii} &= u(Hom)/a, \qquad i \in A \\ u_{ij} &= 2u(Het)/[a(1-a)], \qquad i, j \in A, \quad i \neq j \\ v_{il} &= v/(ab), \qquad i \in A, \quad l \in B \\ x &= 1 - y = u(Hom) + u(Het) + (1-k)v \\ x_i &= x/a, \qquad i \in A \\ y_l &= y/b, \qquad l \in B. \end{aligned} \tag{9}$$

Simultaneous solution of three equations produces expressions for the genotypic frequencies:

$$Tu(Hom) = xg[u(Hom)/N_1 + u(Het)/N_2 + v/(2N_3)]/a \tag{10a}$$

$$Tu(Het) = x[(a-1)u(Hom)/N_1 + (a-2+g)u(Het)/N_2 + (a-1)v/(2N_3)]/a \tag{10b}$$

$$Tv = v/2 + y[u(Hom)/N_1 + u(Het)/N_2], \tag{10c}$$

in which

$$N_1 = (g-1)x/a + 1 \tag{11a}$$

$$N_2 = (g-1)2x/a + 1 \tag{11b}$$

$$N_3 = (g-1)(x/a + y/b) + 1, \tag{11c}$$

and T, the mean fitness of the population, ensures that $u(Hom) + u(Het) + v = 1$. Equation (10c) produces an expression for the mean fitness:

$$T = 1/2 + k[u(Hom)/N_1 + u(Het)/N_2], \tag{12}$$

which reduces to (8c) in the absence of incompatibility ($g = 1$). For general levels of expression of the incompatibility ($1 > g \geq 0$), the valid root or roots of a sixth degree polynomial determine the equilibrium genotypic frequencies. Under weak incompatibility, which corresponds to g approaching unity so that terms of the order $(1-g)^2$ or smaller are negligible, the equilibrium polynomial reduces to a cubic in v, the single root of which in the interval (0, 1) determines the equilibrium frequencies (see APPENDIX 3).

Substitution into this equilibrium cubic of the value of v expected in the absence of incompatibility (8) indicates that the expression of weak incompatibility increases the frequency of $+/t$ individuals and, as a consequence, decreases the mean fitness of the population. Near the high complementarity equilibrium, the expression of incompatibility by $+/t$ females improves the average viability among their offspring by reducing the rate of formation of the t/t genotype. Yet, the ultimate consequence of sheltering the lethal allele is to elevate its frequency, depressing the mean fitness of the population. Further, the expression of incompatibility can ensure the maintenance of a recessive lethal allele even if it is not favored by segregation distortion ($k = 1/2$). Incompatibility favors the t-haplotype by enhancing its success in fertilizing +/+ mothers and by sheltering its expression among the offspring of $+/t$ mothers.

Introduction of new antigens: The appearance of a rare, new class A antigen (A_R) in a population at a high complementarity equilibrium generates new genotypes that carry the new antigen and one resident antigen. Linearized recursions governing this introduction involve two variables, which represent the frequencies of +/+ and $+/t$ individuals that carry A_R:

$$u_{.R} = \sum_{i \in A} u_{iR} \tag{13a}$$

$$v_{R.} = \sum_{j \in B} v_{Rj} \tag{13b}$$

(see APPENDIX 4). In the absence of incompatibility ($g = 1$), the new antigen neither increases nor decreases, up to terms of the first order in the rare genotypes. The expression of weak incompatibility ($1 - g$ small) ensures the invasion of the new antigen.

Introduction of a new class B antigen (A_R) generates a single group of rare genotypes:

$$v_{.R} = \sum_{i \in A} v_{iR} \tag{14}$$

(see APPENDIX 4). As expected, the frequency of the rare antigen fails to change at a geometric rate in the

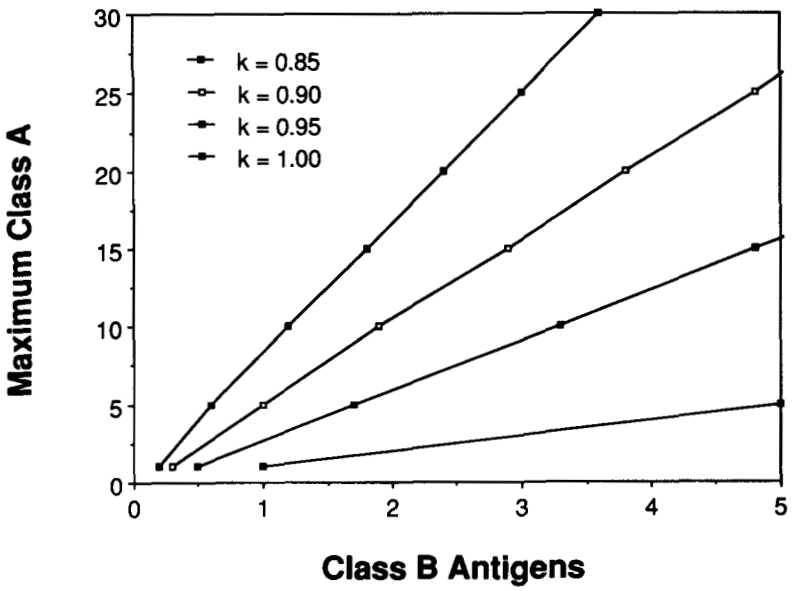

FIGURE 1.—Effect of the transmission rate (k) on the maximum number of resident class A antigens for which the weak expression of incompatibility excludes the conversion of a class A antigen to class C near high complementarity equilibria. Lower transmission rates and higher numbers of class B antigens permit greater numbers of class A antigens.

absence of incompatibility ($g = 1$), but increases under all levels of expression of incompatibility ($1 > g \geq 0$).

Changes in the frequencies of genotypes containing a new class C antigen are determined by recursions that include those governing the introductions of class A and class B antigens. Consequently, new class C antigens also increase when rare under all levels of expression of incompatibility ($1 > g \geq 0$).

Conversion of an existing class A antigen to class C: To explore the influence of incompatibility on the relative numbers of antigens associated with each t-complex haplotype, I studied the consequences of introducing a class A or class B antigen on the alternative t-complex haplotype. The population initially resides at a high-complementarity equilibrium. Antigen A_R now represents the single class C antigen that arises through the introduction, in low frequency, of the alternative t-complex allele on haplotypes containing this antigen. The disappearance or maintenance of the new genotypes generated by the conversion determines whether the initial state of high-complementarity resists invasion.

The introduction of the t-allele on haplotypes bearing an antigen formerly occurring only with + transfers the membership of that antigen from class A to class C. APPENDIX 4 includes the linearized recursions that describe changes in v_{RR} (the frequency of $+/t$ individuals that are homozygous for A_R) and $v_{.R}$ (the frequency of antigen heterozygotes that carry the tA_R haplotype; see (14)).

In the absence of incompatibility ($g = 1$), the frequency of the new haplotype neither increases nor decreases at a geometric rate. Under weak incompatibility (g approaching 1), the high complementarity equilibrium resists the conversion of A_R from class A to class C only if the original number of class A antigens is sufficiently small relative to the number of class B antigens:

$$[1 + u + u(1 - 1/a)(3/2 + k)]/(1 - 2ku) > a/b, \qquad (15a)$$

in which u is given by (8a). For all values of k between 1/2 and unity, the quantity on the left of (15a) exceeds unity, indicating that the number of class A antigens must exceed the number of class B antigens ($a > b$) in order to destabilize the high complementarity equilibrium. Figure 1 shows the maximum number of class A antigens for which the high complementarity equilibrium resists conversion.

Under the assumption of the maintenance of a single t-specific antigen in the population (as is observed in natural populations), the maximal number of class A antigens that permits preservation of the high complementarity equilibrium is determined as the larger root of the quadratic obtained from (15a) by setting b equal to unity and replacing the inequality with an equality. Figure 2 compares the actual bound to the approximate threshold value obtained by ignoring the $1/a$ term on the left of (15a). The close agreement between the curves in Figure 2 suggests that simpler bound, given by

$$[1 + u(5/2 + k)]/(1 - 2ku) > a, \qquad (15b)$$

provides an adequate approximation. For $k = 0.9$, the high complementarity equilibrium resists conversion for values of a up to about 5, and for $k = 0.95$, the maximal number is about 3. This result indicates that for values appropriate for the t-complex in the house mouse, high-complementarity equilibria are susceptible to conversions from class A to class C, if more than 3 to 5 class A antigens are maintained in single populations.

Conversion of an existing class B antigen to class

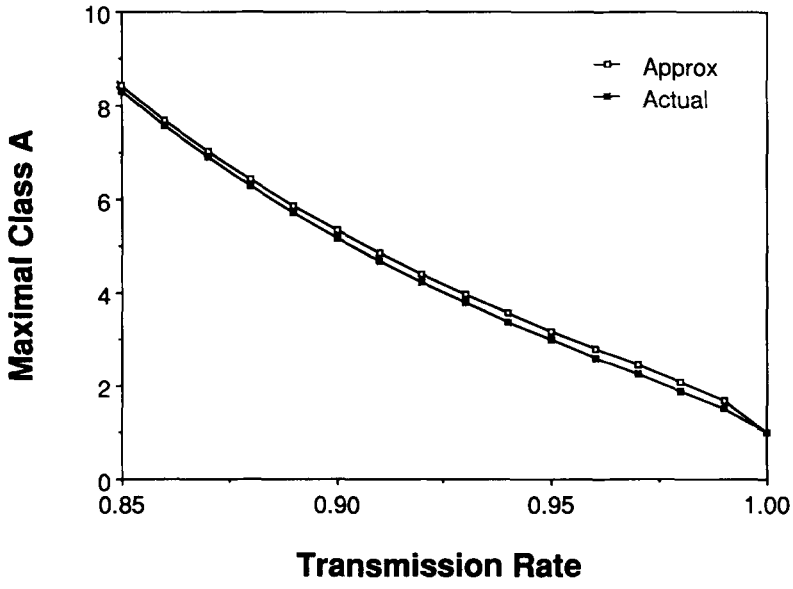

FIGURE 2.—The maximum number of class A antigens for which class A antigens resist conversion to class C in populations containing a single class B antigen. The actual value is obtained from (15a) and the approximation corresponds to the bound given in (15b).

C: Antigen A_R, now originally associated only with the t-haplotype, is introduced in low frequency on the +-haplotype. APPENDIX 4 includes linearized recursions in the three variables that govern the fate of the conversion near high-complementarity equilibria: $u_{.R}$ (corresponding to genotypes of the form $+A_i/+A_R$; see (13a)), $v_{R.}$ ($+A_R/t\ A_j$; [13b]), and v_{RR} ($+A_R/t\ A_R$).

As expected, the equilibrium is neutrally stable to the conversion, up to first-order terms in the frequencies of the rare genotypes, in the absence of incompatibility ($g = 1$). Under weak incompatibility (g approaching 1), the high complementarity equilibrium resists conversion if the quadratic that appears in APPENDIX 5 is positive when evaluated at the values of a and b in the original population. For the range in which the quadratic has two positive roots, local stability requires that the number of class B antigens lie outside of the range bounded by the roots. This result implies that t-specific antigens resist conversion if the number of t-specific antigens maintained in the population is either sufficiently high or sufficiently low.

Figure 3 shows the larger of the roots as a function of the transmission rate (k) for three choices for the number of class A antigens; the high complementarity equilibrium is locally stable if the number of class B antigens maintained in the resident population falls above this threshold. Increasing distortion of transmission rates requires increasing numbers of class B antigens. Any number of class B antigens is permissible for low numbers of class A antigens and moderate rates of transmission. However, for higher transmission rates the values plotted in Figure 3 appear to require more class B antigens in a single population than the total that have been observed in all samples studied. This result suggests that while states that include large numbers of t-specific antigens would resist conversion, high rates of segregation distortion preclude their establishment from an initial state that involves few t-specific antigens. Consequently, it is the lower range of values determined by the quadratic in APPENDIX 5 that addresses the maintenance of high complementarity equilibria in natural populations.

In order to determine whether even one class B antigen can resist conversion to class C, I determined the range of parameters for which this value ($b = 1$) satisfies the condition for local stability. Figure 4 indicates the maximal number of class A antigens for which the high complementarity equilibrium resists the conversion of its single class B antigen. This maximal value is highly sensitive to the transmission rate (k) within the range observed in laboratory studies. For values of the distortion rate sufficiently less than 0.95, the high complementarity equilibrium resists conversion for up to very large numbers of class A antigens. For values closer to 0.95, the threshold is too sensitive relative to structural error in the model and measurement error in the transmission rate to justify advancing a reliable quantitative conclusion. A qualitative conclusion, one that is more likely to be robust, emerges from the analysis: under very high rates of distortion, high-complementarity equilibria cannot be maintained over evolutionary time.

Absence of association between loci

Characterization of the central equilibrium: The central equilibrium, which corresponds to complete independence between the antigen locus and the t-complex, is characterized by membership of all antigens in class C, none of which show an association with t-complex alleles. The complete symmetry among antigens permits a substantial reduction in the number

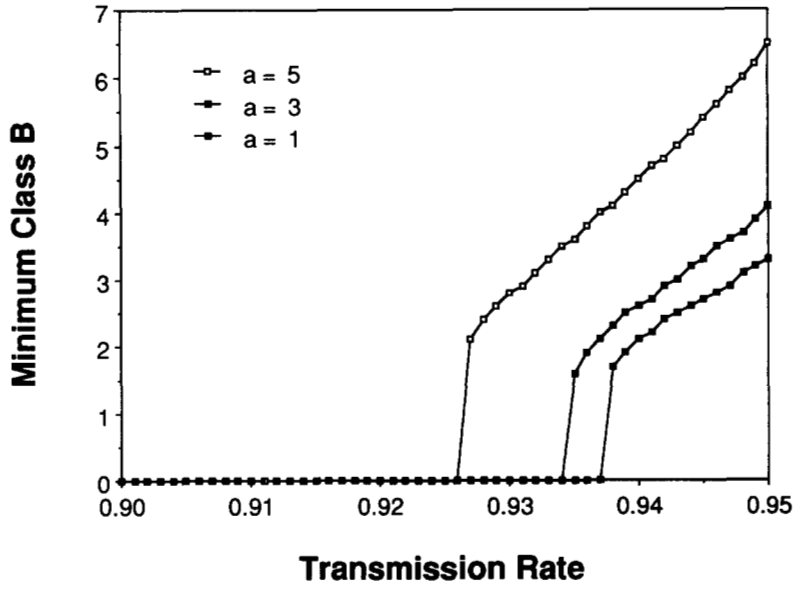

FIGURE 3.—Effect of the number of class A antigens (a) on a sufficient condition for the exclusion of conversions of class B antigens to class C. Numbers of class B antigens exceeding the values plotted permit the maintenance of high complementarity equilibria. More class A antigens require more class B antigens.

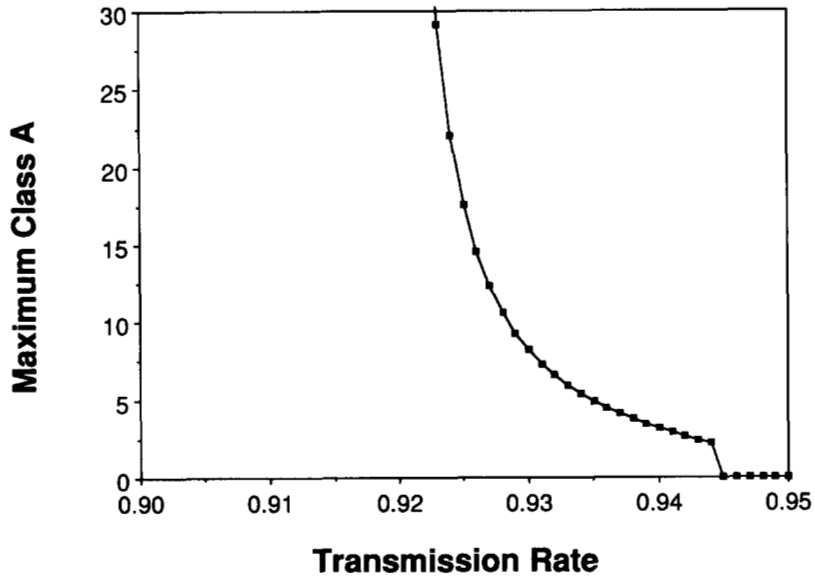

FIGURE 4.—Effect of the transmission rate on the maximum number of class A antigens that permits the stability to conversions from class B to class C of high-complementarity equilibria involving a single class B antigen. While a great many class A antigens can be tolerated for moderate rates of transmission, the curve declines sharply as the transmission rate approaches 0.95.

of variables: for all i and j ($i \neq j$),

$$\begin{aligned} x_i &= x/c \\ y_i &= y/c \\ u_{ii} &= u(1 - H_A)/c \\ v_{ii} &= v(1 - H_A)/c \\ w_{ii} &= w(1 - H_A)/c \\ u_{ij} &= 2uH_A/[c(1 - c)] \\ v_{ij} &= vH_A/[c(1 - c)] \\ v_{ij} &= v_{ji} \\ w_{ij} &= 2wH_A/[c(1 - c)], \end{aligned} \tag{16}$$

in which u, v, y, and x are obtained from (8) for lethal expression of the t-allele ($\sigma = 0$, with $w = 0$), or from APPENDIX 2 for partial viability ($1 \geq \sigma > 0$); c is the number of antigens; and H_A represents the frequency of antigen heterozygotes:

$$H_A = (c - 1)(c - 2 + 2g)/[(c - 1 + g)^2 - (1 - g)(c - 1)]. \tag{17}$$

No genetic associations occur between the loci. Gametic phase disequilibrium is absent. Identity disequilibrium (see COCKERHAM and WEIR 1968), a measure of association based on the difference between the frequency of double heterozygotes and the frequency expected on the basis of the levels of heterozygosity at each of the two loci separately, is zero:

$$v(Het) = vH_A. \tag{18}$$

Just as the alleles at the t-complex occur in the frequencies expected in the absence of incompatibility ((8) or APPENDIX 2), the antigen locus is independent of viability selection generated by the t-complex (see

(17)). The central equilibrium represents the outcome of the independent evolution of each component one-locus system (compare LEACH, MAYO and MORRIS 1986).

Introduction of a new antigen near the central equilibrium: In order to explore whether the state of complete independence is maintained over evolutionary time, I obtained conditions under which a novel antigen belonging to class A, B or C increases when rare. The introduction of the new antigen (A_R) generates up to four classes of rare genotypes: $+A_i/+A_R$ (with frequency u_{iR}), $+A_i/t\ A_R$ (v_{iR}), $+A_R/t\ A_i$ (v_{iR}), and tA_i/tA_R (w_{iR}), in which A_i represents a resident antigen. Symmetries among the frequencies of the resident antigens permit reduction of the local stability analysis to four variables:

$$\begin{aligned} p_R &= \sum_i (u_{iR} + v_{Ri}) \\ x_R &= \sum_i [u_{iR} + (1 - r)v_{iR} + rv_{Ri}]/2 \\ q_R &= \sum_i (w_{iR} + v_{iR}) \\ y_R &= \sum_i [w_{iR} + rv_{iR} + (1 - r)v_{Ri}]/2. \end{aligned} \tag{19}$$

The local stability matrix further resolves into two two-dimensional blocks. Linearized recursions in p_R and x_R determine the elements of the block that governs changes in the frequency of the new antigen when it occurs on the +-haplotype, and recursions in q_R and y_R generate the second block, which governs the fate of the new antigen when it occurs on the t-haplotype (see APPENDIX 4). Introduction of class A antigens depends on the former block, class B on the latter block, and class C on both blocks.

The leading eigenvalue of each submatrix exceeds unity under any level of expression of incompatibility ($1 > g \geq 0$), and equals unity in the absence of incompatibility ($g = 1$). This result indicates that near the central equilibrium, the expression of incompatibility actively promotes the invasion of all novel antigens, irrespective of their associations with the t-complex. Numerical iterations of the recursion system, reduced to three resident class C antigens and one novel antigen that belongs to either class A or class B, indicated that the invasion of a new antigen exhibiting an association with one t-complex haplotype induces all resident class C antigens to develop an association with the alternative t-complex haplotype.

DISCUSSION

This analysis supports the view that natural selection can actively maintain associations between the MHC and the t-complex in the mouse. The evolutionary process involves neither physiological interactions between specific antigens and t-haplotypes (HAMMERBERG and KLEIN 1975) nor group selection to preserve a device for the maintenance of heterozygosity at the MHC (SNELL 1968). Rather, by inhibiting the conception or gestation of zygotes that are inbred at the MHC, incompatibility promotes heterozygosity at the t-complex. This reduction in the rate of formation of the t/t genotype improves the average viability of offspring produced by mothers that express incompatibility.

Effect of incompatibility on selection within the t-complex

The sheltering of lethals: FISHER (1935) explored an hypothesis advanced by H. J. MULLER for the heterochromatinization of the Y chromosome. MULLER (1914) suggested that an association between the Y chromosome and a recessive lethal that is maintained by a balance between mutation and selection may evolve as a result of the reduction in the rate of expression of the lethal. FISHER's analysis failed to support this proposition, demonstrating that in large, randomly mating populations, the associations evolve from a state of independence only if the mutation rate on the Y chromosome exceeds that on the X chromosome by a factor of nearly three. NEI's (1970) analysis of the effects of genetic drift and incomplete linkage between the viability locus and the sex determination locus showed that enforced heterozygosis of the Y chromosome can result in sheltering of the lethal in populations subject to genetic drift, provided that the product of the recombination rate and the effective population size is sufficiently small. MAYO (1981) extended NEI's approach to other sex chromosome systems.

RASMUSON (1980), studying the related question of the effect of a self-incompatibility locus on the frequency of a lethal allele, showed that the lethal resists extinction under complete linkage. However, LEACH, MAYO and MORRIS (1986) demonstrated that RASMUSON's conclusions fail under partial linkage, with associations required for the maintenance of the lethal. Unlike the earlier studies, neither model incorporated a mechanism (for example, mutation) that could maintain the lethal in the absence of incompatibility.

Proximal and ultimate consequences of incompatibility on selection within the t-complex: Suppression of recombination between the MHC and the t-complex in $+/t$ individuals promotes the maintenance of existing associations. At high complementarity equilibria, which are characterized by the absence of antigens that occur on both t-complex haplotypes, the expression of incompatibility influences the genotypic distribution at the t-complex through two effects. First, in $+/t$ mothers, the preferential conception or gestation of zygotes derived from sperm bearing the +-haplotype shelters the lethal by reducing the pro-

TABLE 1

Summary of tests of local stability

Initial state	Introduction	Outcome
Central equilibrium	All novel antigens	Unstable
High complementarity equilibrium	All novel antigens	Unstable
	Class A to C conversion	Stable for small *a*
	Class B to C conversion	Unstable for intermediate range of *b*; single class B retained for small *a*

duction of *t*/*t* offspring. Second, +/+ mothers, which express incompatibility against two antigens associated with the +-haplotype and none associated with the *t*-haplotype, produce more +/*t* offspring than expected in the absence of incompatibility.

Both effects, the sheltering of the *t*-haplotype by +/*t* mothers and the favoring of the *t*-haplotype by +/+ mothers, contribute toward an increase in its frequency (see APPENDIX 3). Consequently, the expression of incompatibility of the form studied exacerbates the disagreement between the predicted and observed frequencies of the *t*-haplotype (see LEWONTIN and DUNN 1960). Although incompatibility improves offspring viability by reducing the rate of formation of *t*/*t* zygotes, its ultimate effect is to increase the frequency of the lethal and depress the mean fitness of the population.

The origin and maintenance of high complementarity associations

Incompatibility actively encourages the initial increase of all novel antigens. This effect is well-known in models of self-incompatibility systems in plants (WRIGHT 1939) and of maternal-fetal incompatibility systems in mammals (WARBURTON 1968). Table 1 summarizes the results of the local stability analyses described in preceding sections, which indicate that prezygotic and postzygotic incompatibility retains this property even in the presence of associations with the *t*-complex. Incompatibility permits the evolution of associations from a state of complete independence and, in conjunction with rare combination events, modifies the number of antigens associated with each *t*-complex haplotype.

Origin of associations: Near states of complete independence between the MHC and the *t*-complex, the invasion of novel antigens that occur on only one of the *t*-complex haplotypes induces all resident antigens to become associated with the alternative haplotype. A similar phenomenon was described by THOMSON and KLITZ (1987), who studied the generation of associations between neutral MHC alleles and alleles under selection at linked loci. In the present study, the advantage of rarity conferred by the expression of incompatibility on the novel antigen causes a subsequent increase in the frequency of *t*-complex haplotypes identical by descent to the particular haplotype on which the novel antigen was introduced (hitchhiking, MAYNARD SMITH and HAIGH 1974). Viability selection at the *t*-complex itself tends to maintain the equilibrium frequencies of +-haplotypes and *t*-haplotypes; consequently, the hitchhiking of the particular *t*-complex haplotype that bears the novel antigen entails a decline in frequency of other haplotypes of the same kind. The nearly complete suppression of recombination between the +-haplotype and the *t*-haplotype satisfies the requirement of tight linkage, under which hitchhiking can influence allelic and chromosomal frequencies (see review by THOMSON 1977).

While the finding that incompatibility can generate associations between the MHC and the *t*-complex raises the formal possibility of the origin of high-complementarity states by this means, the observation of the close relationship among *t*-specific antigens derived from different semispecies (NIZETIC, FIGUEROA and KLEIN 1984; FIGUEROA *et al.* 1985) argues against this scenario. The primary significance of the results obtained from the analysis of introductions near the central equilibrium is to suggest that the state of complete independence between the MHC and the *t*-complex is not stable over evolutionary time. Under all rates of segregation distortion exceeding 0.5, the expression of incompatibility promotes the maintenance of some level of association, even if the high complementarity associations tend to erode.

Maintenance of high complementarity associations: The occurrence of rare recombination events between the MHC and the *t*-complex raises the question of the maintenance of high complementarity states over evolutionary time. In the absence of incompatibility, the introduction in low frequency of an antigen associated with only one *t*-complex haplotype on the alternative haplotype fails to result in genetic change at a geometric rate. In contrast, incompatibility modifies the relative numbers of antigens associated with each *t*-complex haplotype by actively favoring or excluding recombinant haplotypes. The analysis described in preceding sections indicates that high-complementarity states are not maintained under very high rates of segregation distortion.

Segregation distortion rates estimated in mice cap-

tured from natural populations exceed 0.90 (DUNN 1957); however, the rate of distortion is subject to extensive modification by genetic factors situated throughout the genome (GUMMERE, MCCORMICK and BENNETT 1986). For values of the rate (k) of transmission of the t-haplotype in $+/t$ males between 0.90 and 0.95, the maintenance of a single t-specific antigen requires that no more than between 3 and 5 +-specific antigens occur in the same population. Many more antigens of both kinds can be maintained under lower rates of segregation distortion.

Although over 100 alleles per locus within class I and about 50 alleles per locus within class II have been identified (SILVER 1982), the number maintained in a single population depends on the mating structure and other factors that determine effective population size (WRIGHT 1939, 1964; FISHER 1958; EWENS 1969). NADEAU *et al.* (1981) reported between one and four common antigens at the D and K loci in samples of mice from natural populations. Incomplete censusing of the population and the inability to distinguish among antigens for which sera were not available imply that the actual numbers lie above these values. If the common antigens occurred in approximately equal frequencies, the set scored as blanks likely included one or more additional common antigens, increasing the estimates to four common antigens at the D locus and five at the K locus for the sample denoted BJE. Correction for sample size (NADEAU *et al.* 1981) increases these values by an additional antigen. Unfortunately, the investigators did not systematically distinguish between +-haplotypes and t-haplotypes, although males suspected of being heterozygous at the t-complex were excluded from the analysis. The high frequency of t-haplotypes in natural populations (in the range 0.18 to 0.25 (LEWONTIN and DUNN 1960)) suggests that one of the common antigens among the blanks may have been associated with the t-haplotype. Decreasing the estimates corrected for blanks and sample size by one antigen returns the estimate for the number of antigens associated with the +-haplotype in the BJE population to about four or five. KLEIN and FIGUEROA's (1981) compilation provides similar estimates of the number of common alleles (see Figure 3 in KLEIN and FIGUEROA 1981). These values lie close to the upper bound predicted by the model under which high complementarity equilibria are maintained.

In summary, the present analysis indicates that incompatibility maintains and shapes associations between the MHC and the t-complex. The high complementarity state that is stable over evolutionary time involves a single antigen associated with the t-haplotype and no more than three to five antigens associated with the +-haplotype in any single population. If these conditions fail, the population is expected to converge to a state of partial association, in which antigens occur primarily, though not exclusively, with one of the t-complex haplotypes.

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APPENDIX 1

Recursion equations

To illustrate the form of the recursions, the equations that determine the frequencies of antigen homozygotes are presented:

$$Tu'_{ii} = gx_i[(u_{ii} + v_{ii}/2)/N_1(ii) + \sum_{j \neq i} (u_{ij} + v_{ij})/(2N_1(ij))] \quad \text{(A1.1)}$$

$$Tv'_{ii} = gx_i[(w_{ii} + v_{ii}/2)/N_1(ii) + \sum_{j \neq i} (w_{ij} + v_{ji})/(2N_2(ij))] \quad \text{(A1.2)}$$
$$+ gy_i[(u_{ii} + v_{ii}/2)/N_1(ii)$$
$$+ \sum_{j \neq i} (u_{ij} + v_{ij})/(2N_2(ij))]$$

$$Tw'_{ii} = \sigma gy_i[(w_{ii} + v_{ii}/2)/N_1(ii) + \sum_{j \neq i} (w_{ij} + v_{ji})/(2N_2(ij))], \quad \text{(A1.3)}$$

in which the functions of the genotypic frequencies are defined in (4), (6), and (7); and T represents the normalizer that ensures that the genotypic frequencies in the next generation sum to unity.

APPENDIX 2

Genotypic frequencies in the absence of incompatibility

The mean fitness (T) corresponds to the single root in the interval [1/2, 1] of the following cubic:

$$(2T - 1)(2k - 1)^2 - (1 - \sigma)(1 - T)[4T^2 - (2k - 1)^2] = 0. \quad \text{(A2.1)}$$

This root determines the frequencies of the wild-type allele among eggs ($p = u + v/2$) and sperm (x):

$$x = T[2(T - 1) + (2k - 1)]/(2k - 1) \quad \text{(A2.2a)}$$

$$p = x/(2T - 1), \quad \text{(A2.2b)}$$

which in tern determine the genotypic frequencies:

$$u = px/T \quad \text{(A2.3a)}$$

$$v = (px + qx)/T \quad \text{(A2.3b)}$$

$$w = qy\sigma/T, \quad \text{(A2.3c)}$$

in which q ($q = 1 - p$) represents the frequency of the t-haplotype among eggs.

APPENDIX 3

Determination of the high complementarity equilibria

Under recessive lethality of the t-haplotype ($\sigma = 0$), the mean fitness of the population depends on the rate of production of t/t individuals:

$$T = 1 - vy(b - 1 + g)/(2bN_3), \quad \text{(A3.1)}$$

in which N_3 is given by (11c). Simultaneous solution of (10a) and (10b) produces expressions for $u(Hom)$ and $u(Het)$ in terms of T and v (which determines x and y). Substitution of these expressions into (3) (with $w(Hom) = w(Het) = 0$), produces an equation in T and v. Elimination of T from this equation using (A3.1) produces a polynomial of the sixth degree in v. Ignoring terms of the order $(1 - g)^2$ and smaller reduces this polynomial to:

$$a[T - 1/2 - ku - (1 - g)(1 - vy)x/(2a)] + (1 - g)kux(a - 1)/a = 0, \quad \text{(A3.2)}$$

which, with (A3.1), generates a cubic in v alone.

APPENDIX 4

Introductions near the central equilibrium and the high complementarity equilibria

Novel class A antigen near high complementarity equilibria: Changes in the frequency of a rare, new class A antigen are determined, up to terms of the first order in the frequency of the rare genotypes, by:

$$Tu'_{.R} = u_{.R}[F + x(a - 1 + g)/(N_1a)]/2 + v_{R.}[(1 - k)F + x/(2N_{R.})] \quad \text{(A4.1a)}$$

$$Tv'_{R.} = u_{.R}[v/(2N_3) + y/N_1]/2 + v_{R.}[(1 - k)v/N_3 + y(b - 1 + g)/N_{R.}]/2, \quad \text{(A4.1b)}$$

in which $u_{.R}$ and $v_{R.}$ are defined in (13); N_1, N_2, and N_3 are given by (11); T and the genotypic frequencies in the resident population are obtained from (10), (12), and APPENDIX 3; and

$$F = u(Hom)/N_1 + u(Het)/N_2 + v/(2N_3) \quad \text{(A4.2a)}$$

$$N_{R.} = (g - 1)y/b + 1. \quad \text{(A4.2b)}$$

Novel class B antigen near high complementarity equilibria: The single recursion governing changes in the frequency of a new class B antigen is:

$$Tv'_{.R} = v_{.R}[kF + x(a - 1 + g)/(2aN_1)], \quad \text{(A4.3)}$$

in which $V_{.R}$ is given by (14) and all other variables are as defined in (A4.1).

Conversion of a class A antigen to class C near high complementarity equilibria: Linearized recursions in the variables corresponding to $+/t$ individuals that are homozygous for the converted antigen (v_{RR}), and those that are heterozygous for the antigen (see (14)) are given by:

$$Tv'_{RR} = v_{RR}g[kF + x/(2N_1)]/a + v_{.R}g[kF + x/(2N_2)]/a \quad \text{(A4.4a)}$$

$$Tv'_{.R} = v_{RR}[(a - 1)kF - (1 - g)ku(Het)/N_2 + (a - 1)x/(2N_1)]/a + v_{.R}[(a - 1)kF - (1 - g)ku(Het)/N_2 + x(a - 2 + g)/(2N_2)]/2, \quad \text{(A4.4b)}$$

in which the remaining quantities are as defined in (A4.1).

Conversion of a class B antigen to class C near high complementarity equilibria: The linearized recursions in the variables corresponding to the three kinds of rare genotypes generated by this conversion are:

$$Tv'_{RR} = v_{RR}g[(1 - k)v/N_3 + y/N_{RR})]/(2b) + v_{R.}g[(1 - k)v/N_3 + y/N_{R.})]/(2b) + u_{.R}g(v/2 + y)/(2bN_3) \quad \text{(A4.5a)}$$

$$Tv'_{R.} = v_{RR}(b - 1)[(1 - k)v/N_3 + y/N_{RR})]/(2b) + v_{R.}[(b - 1)(1 - k)v/N_3 + y(b - 2 + g)/N_{R.})]/(2b) + u_{.R}(b - 1)(v/2 + y)/(2bN_3) \quad \text{(A4.5b)}$$

$$Tu'_{.R} = v_{RR}\{(1 - k)[F - v(1 - g)/(N_3b)] + x/N_{RR})\}/2 + v_{R.}\{(1 - k)[F - v(1 - g)/(N_3b)] + x/N_{R.})\}/2 + u_{.R}[F - v(1 - g)/(N_3b) + x(a - 1 + g)/N_3)]/2, \quad \text{(A4.5c)}$$

in which the genotypic and gametic frequencies are obtained from APPENDIX 3, F from (A4.2a), N_3 from (11c), and now

$$N_{RR} = (g - 1)y/b + 1 \quad \text{(A4.6a)}$$

$$N_{R.} = (g - 1)2y/b + 1. \quad \text{(A4.6b)}$$

Novel class A antigen near the central equilibrium: The rare genotypes generated by this introduction [p_R and x_R,

see (19)] evolve according to:

$$Tp'_R = p_R/2 + x_R[(1 - H_A)/N_1 + H_A/N_2] \quad \text{(A4.7a)}$$

$$Tx'_R = p_R[x + 2(1 - k)y]/4 \quad \text{(A4.7b)}$$
$$+ x_R[(1 - H_A)/N_1 + H_A/N_2][p + 2(1 - k)q]/4,$$

in which H_A is given by (17); T, p ($p = u + v/2$), q ($q = w + v/2$),y, and x ($x = 1 - v$) are obtained from (8) under lethality of the t-allele and from APPENDIX 2 under partial viability; and

$$N_1 = (g - 1)/c + 1 \quad \text{(A4.8a)}$$

$$N_2 = (g - 1)2/c + 1. \quad \text{(A4.8b)}$$

Novel class B antigen near the central equilibrium: Linearized recursions in q_R and y_R (see (19)) are given by:

$$\mathrm{Tq'_R = q_R(x + \sigma y)/2} \quad \text{(A4.9a)}$$
$$\mathrm{+ y_R[(1 - H_A)/N_1 + H_A/N_2](p + \sigma q)}$$
$$\mathrm{Ty'_R = q_R(2kx + \sigma y)/4} \quad \text{(A4.9b)}$$
$$\mathrm{+ y_R[(1 - H_A)/N_1 + H_A/N_2](p + 2k\sigma q)/2,}$$

in which the remaining quantities are as defined in (A4.8).

APPENDIX 5

Threshold numbers of antigens required to exclude conversions of *t*-specific antigens

High complementarity equilibria resist conversion of a class B antigen to class C if:

$$b^2\{ax(k - 1/2) + (a - 1)[(1 - k)(1 + 4kp) + u/2]\}$$
$$+ ba^2[(1 - k)(p + x + 4kp) \quad \text{(A5.1)}$$
$$- 2y(k - 1/2)] + a^2y(k - 1/2) > 0.$$

For $b = 1$, this condition reduces to:

$$a^2\{u[4k(1 - k) + 1] + 3 - 4k^2\}$$
$$+ a[u(1 + 3k - 2k^2 + (1 - k)(1 + 6k)] \quad \text{(A5.2)}$$
$$- \{u[4k(1 - k) + 1] + 2(1 - k)(1 + 2k)\} > 0.$$