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## Divergent selection for humoral immune responsiveness in chickens: distribution and effects of major histocompatibility complex types

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**Summary** – Chickens were selected for 10 generations for high and low antibody response to sheep red blood cells; in addition, a randombred control line was maintained. All birds ( $n = 1\ 602$ ) from the 9th and 10th generations were typed for major histocompatibility complex B-types. All identified types were present in the control line but the selected lines showed divergent distributions. The 121 B-haplotype was predominant in the high line in the form of 121–121 B-genotype, whereas the 114 B-haplotype was most frequent in the form of 114–114 and 114–124 B-genotypes in the low line. To explain these frequency changes, effects of B-genotypes on the selected trait were estimated, using a mixed animal model. The B-genotypes were responsible for a significant part of variation of the trait within lines, but their effects differed between lines. These effects could be related partly to the changes in B-genotype distribution.

chicken / immune response / selection / animal model / major histocompatibility complex

**Résumé** – Sélection divergente sur la réponse immunitaire chez la poule: distribution et effets des types du complexe majeur d'histocompatibilité. Des poulets ont été sélectionnés pendant 10 générations sur la réponse immunitaire haute et basse à des globules rouges de mouton; une lignée témoin était également maintenue par accouplements

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au hasard. Tous les animaux ( $n = 1602$ ) des générations 9 et 10 ont été analysés pour leurs types B du complexe majeur d'histocompatibilité. Tous les types identifiés étaient présents dans la lignée témoin, alors que les lignées sélectionnées présentaient des distributions divergentes pour ces types B. L'haplotype B 121 était prédominant dans la lignée haute sous la forme du génotype B 121-121, alors que l'haplotype B 114 était le plus fréquent dans la lignée basse sous la forme des génotypes B 114-114 et 114-124. Afin d'expliquer ces changements de fréquence des types B, les effets des génotypes B sur la réponse immunitaire aux globules rouges de mouton ont été estimés à l'aide d'un modèle animal mixte. Les génotypes B étaient responsables d'une part significative de la variation du caractère intralignée, mais leurs effets étaient variables suivant la lignée. Ces effets pouvaient en partie expliquer les changements de fréquence des types B.

**poule / réponse immunitaire / sélection / modèle animal / complexe majeur d'histocompatibilité**

## INTRODUCTION

In recent years, there has been a growing interest in improving the genetic resistance of domestic species to infectious diseases. This improvement may be accomplished indirectly by selective breeding for immune responsiveness and/or for genes or marker genes for immune responsiveness and disease resistance (Warner *et al*, 1987). Moreover, advances in molecular technique have opened promising ways for directly introducing advantageous genes into animals by genetic engineering (Lamont, 1989).

Successful selection experiments for high and low antibody response to sheep red blood cells (SRBC) have been reported in mice (Biozzi *et al*, 1979) and in chickens (eg Van der Zijpp *et al*, 1988; Martin *et al*, 1990). In the former experiment, Pinard *et al* (1992) have estimated heritability for the selected trait as 0.31. However, even if the humoral response to SRBC is under polygenic control, some specific genes might play a major role, and the genes of the major histocompatibility complex (MHC) are prime candidates. The MHC genes encode highly polymorphic cell surface proteins that have been shown to play an important role in immune responsiveness and disease resistance in many species including chickens (Bacon, 1987; Gavora, 1990; Lamont and Dietert, 1990).

Estimation of MHC-type effects remains a delicate task, especially in the framework of selected outbred lines. Ignoring the relationships between individuals may, for example, often lead to overestimation of the MHC effect (Mallard *et al*, 1991). The choice of the method to estimate single gene effects separately from the background genes is therefore crucial (Kennedy *et al*, 1992).

The objectives of this study were to look for possible changes in MHC haplotype and genotype frequencies in lines of chickens divergently selected for 10 generations for antibody response to SRBC, and to estimate the MHC effects on the selected trait in order to understand the involvement of MHC in the regulation of the immune response.

## MATERIALS AND METHODS

### Selection lines

The selection experiment has been described in detail elsewhere (Van der Zijpp *et al.*, 1988; Pinard *et al.*, 1992). Briefly, chickens were bidirectionally selected from an ISA Warren cross base population for 10 generations. The selection criterion was the total antibody (Ab) titer, 5 d postprimary immunization with 1 ml 25% sheep red blood cells (SRBC) diluted in phosphate-buffered saline. Antibody titers measured against SRBC were expressed as the  $\log_2$  of the reciprocal of the highest blood plasma giving complete agglutination. In addition to the high (H) and low (L) lines, a random-bred control (C) line was maintained. Every generation, there were  $\approx$  300 chicks each in the H and L lines and 250 chicks in the C line, from which  $\approx$  25 males and 50 females in the H and L lines and  $\approx$  40 males and 70 females in the C line were used to produce the next generation. In the 9th generation, the inbreeding level was 7.3, 3.6 and 9.4% in the H, C and L lines, respectively. The numbers of birds in the H, C and L lines of the ninth and tenth generations are given in table I.

**Table I.** B-genotype frequencies (in %) in the H, C and L lines of the 9th and 10th generations, ordered by decreasing number (No) of birds per genotype in the L line.

Genotype	H		C		Line L		H	C	L
	Generation		Generation		Generation		No of	No of	No of
	9	10	9	10	9	10	birds	birds	birds
114-114	0	0	2.9	4.6	33.8	44.6	0	13	256
114-124	0.5	0.5	12.2	4.0	38.1	29.1	3	31	234
114-119	0	0	10.7	11.2	11.5	8.1	0	39	69
124-124	2.2	0	20.5	7.9	8.9	10.5	8	54	64
119-124	2.2	8.7	15.6	26.3	7.7	5.0	26	72	45
119-119	2.5	0	6.4	9.2	0	2.7	9	27	7
114-121	7.4	0	3.4	8.5	0	0	27	20	0
121-124	12.7	11.6	8.8	14.5	0	0	70	40	0
119-121	12.7	12.1	12.2	9.2	0	0	71	39	0
121-121	59.8	67.1	7.3	4.6	0	0	356	22	0
No of birds	363	207	205	152	417	258	570	357	675

### Typing for MHC haplotype

Major histocompatibility complex haplotypes were determined by direct haemagglutination, using alloantisera obtained from the lines. Four serotypes, provisionally called B<sup>114</sup>, B<sup>119</sup>, B<sup>121</sup>, and B<sup>124</sup> were identified in the tested birds. As compared to known reference B-types, none of the serotypes identified in the lines was identical

for both B-F and B-G. Only B<sup>114</sup> and B<sup>119</sup> showed similarities for B-G with B<sup>14</sup> and B<sup>19</sup>, respectively, whereas B<sup>121</sup> showed similarities for B-F with B<sup>21</sup> (Pinard *et al*, 1991; Pinard and Hepkema, 1992). A MHC genotype was defined as the combination of 2 haplotypes. Serological typing was performed on the parents of the 8th generation, on all the females and the selected males of the 8th generation, and on all the birds of the 9th and 10th generations. Only the results of MHC typing in the 9th and 10th generations were used in the analysis. Segregation of the haplotypes was checked for consistency within families over generations, and inconsistent data were removed from the analysis.

### Statistical analysis

Comparison of MHC type frequencies between the lines was performed by  $\chi^2$  tests.

Effects of MHC genotype on the Ab response were estimated within lines using the following mixed model:

$$Ab_{ijklm} = \mu + generation_i + sex_j + line_k + MHC_{kl} + U_{ijklm} + e_{ijklm}$$

Where:

$Ab_{ijklm}$  = the Ab titer of the  $m$ th chick,

$\mu$  = a constant,

$generation_i$  = the fixed effect of the  $i$ th generation (9, 10),

$sex_j$  = the fixed effect of the  $j$ th sex of the chick,

$line_k$  = the fixed effect of the  $k$ th line (H, C, L),

$MHC_{kl}$  = the fixed effect of the  $l$ th MHC genotype within the  $k$ th line,

$U_{ijklm}$  = the random additive genetic effect on the Ab titer in the  $m$ th chick  
and

$e_{ijklm}$  = a random error.

The fixed effect of generation accounted for environmental differences between generations 9 and 10. The sex effect corrected for a higher Ab response to SRBC in females than in males. Relationships between individuals from the 10 generations and Ab data of the 9th and 10th generations were used in this study. The mixed model was applied assuming a heritability of 0.31, as estimated previously (Pinard *et al*, 1992). Solutions for the model were obtained using the PEST program (Groeneveld, 1990; Groeneveld and Kovak, 1990), which is a generalized procedure to set up and solve systems of mixed model equations containing genetic covariances between observations.

Differences between genotypes within lines were tested as orthogonal contrasts using the  $F$  test values as estimated by PEST. The overall effect of genotypes in a line was estimated by testing, jointly against the error variance term  $\sigma_e^2$ ,  $n - 1$  independent differences between genotypes, with  $n$  being the number of genotypes in the line.

Heterozygote superiority was estimated within-line for each available combination of haplotypes by testing the difference between the heterozygote genotypes and the average of their homozygous counterparts. The overall heterozygote superiority in a line was estimated by testing the difference between these heterozygote genotypes and the average of their homozygous counterparts.

The effect of haplotype  $i$  was estimated within-line by testing the difference between genotype combinations comprised of the haplotype  $i$  and their counterparts comprised of a reference haplotype  $r$ , as following:  $\frac{\sum_j(\text{Geno}_{ij} - \text{Geno}_{rj})}{p}$ , with  $\text{Geno}_{ij}$ , and  $\text{Geno}_{rj}$  being the estimated effects of MHC genotypes comprised of haplotypes  $i$  and  $j$ , and  $r$  and  $j$ , respectively, and  $p$  being the number of pairwise combinations.

## RESULTS

### *MHC distribution in the different lines*

Frequencies of MHC genotypes and haplotypes in the 9th and 10th generations for the H, C and L lines are given in tables I and II, respectively. Frequencies of genotypes and haplotypes were significantly ( $P < 0.01$ ) different between lines in the 9th and in the 10th generation. In the C line, all 10 possible genotypes were present, with a predominance of the 119-124 B-genotype, and the 119 and 124 B-haplotypes were prevalent. The distribution of MHC genotype and of MHC haplotype in the H line was opposite to those in the L line. The 121-121 B-genotype predominated in the H line, whereas the 114-114 and 114-124 B-genotypes were most frequent in the L line. In the H line, the 121 B-haplotype frequency reached 79% at the expense of the 114 B-haplotype, which tended to disappear. On the contrary, the 121 B-haplotype disappeared between the 8th and the 9th generation in the L line (data not shown). In the L line, the 114 B-haplotype was found most compared to the 124, and especially the 119 B-haplotypes.

Heterozygous birds were in the majority in the C line, whereas homozygous birds were most frequent in the H line and to a lesser extent in the L line. This tendency was more pronounced in the 10th generation.

### *Estimation of MHC genotype effects on the Ab response*

Estimates of MHC genotype effects on the Ab response to SRBC are given in table III. The overall effect of MHC genotypes was greater in the selected lines than in the C line, and the total genetic variance explained by MHC genotypes was greater in the H and C lines than in the L line. This high genetic variance in the H line arose from extreme estimate values of the 114-124, 119-119 and 124-124 B-genotypes despite their low frequency value. The ranking of genotypes according to their estimates of effects on the Ab titer differed between lines, especially between the C line and the H line. No significant changes in the estimates were observed when taking other input values for heritability between 0.2 and 0.4 (data not shown).

**Table II.** Frequencies (in %) of B-haplotype and of heterozygote birds in the H, C and L lines of the 9th and 10th generations, ordered by decreasing haplotype frequency in the L line.

Haplotype	H		Line C		L	
	Generation		Generation		Generation	
	9	10	9	10	9	10
114	4.0	0.2	16.1	16.4	58.6	63.2
124	9.9	10.4	38.8	30.3	31.8	27.5
119	9.9	10.4	25.6	32.6	9.6	9.3
121	76.2	79.0	19.5	20.7	0	0
Hetero <sup>1</sup>	35.5	32.9	62.9	73.7	57.3	42.3

<sup>1</sup> Hetero: % of heterozygote birds within lines.

**Table III.** Estimates of B-genotype effect on the Ab response to SRBC in the H, C and L lines of the 9th and 10th generations.

H		Line C		L	
Genotype	Estimate	Genotype	Estimate	Genotype	Estimate
114-124	-2.89 <sup>a</sup>	114-114	-0.44 <sup>a</sup>	114-124	-0.80 <sup>a</sup>
119-124	-0.27 <sup>b</sup>	121-121	-0.23 <sup>a</sup>	114-119	-0.36 <sup>ab</sup>
121-124	-0.10 <sup>b</sup>	114-119	-0.17 <sup>a</sup>	114-114	-0.35 <sup>ab</sup>
121-121	0.00 <sup>b</sup>	114-124	0.00 <sup>a</sup>	124-124	0.00 <sup>b</sup>
119-121	0.28 <sup>b</sup>	119-119	0.26 <sup>ab</sup>	119-124	0.44 <sup>b</sup>
114-121	0.57 <sup>bc</sup>	114-121	0.35 <sup>ac</sup>	119-119	1.40 <sup>b</sup>
119-119	2.14 <sup>cd</sup>	124-124	0.39 <sup>ac</sup>		
124-124	3.13 <sup>d</sup>	119-121	0.71 <sup>ac</sup>		
		119-124	1.10 <sup>bc</sup>		
		121-124	1.56 <sup>c</sup>		
$Pr > F^1$	0.0002	0.0235		0.0074	
$\sigma_G^2$	0.38	0.31		0.13	

a,b,c,d Estimates with different superscripts indicate differences ( $P < 0.05$ ) between genotypes within lines. <sup>1</sup>  $Pr > F$  indicates the overall effect of B-genotypes within lines.  $\sigma_G^2 = \sum_i p_i (est_i - \bar{est})^2$ : total genetic variance arising from the MHC loci in generation 9;  $p_i$  and  $est_i$  are, respectively, the frequency in the 9th generation and the estimate of the  $i$ th genotype, and  $\bar{est}$  is the average genotype estimate ( $\sum_i p_i est_i$ ).

**Estimation of heterozygote superiority**

Estimates of heterozygote superiority for each available combination and overall lines are given in table IV. In the C line, a moderately positive general effect of heterozygous genotypes was demonstrated. This positive effect appeared in the 119-124 B-genotype, and was marked in the 121-124 B-genotype. In the L line, a general heterozygous disadvantage was non-significant. This negative effect, however, was significant only for the 114-124 B-genotype. In the H line, not all the heterozygous combinations could be evaluated because of missing genotypes. In the H line, there was a significant negative effect of heterozygous genotypes overall, and of the 121-124 and the 119-124 B-genotypes.

**Table IV.** Heterozygote *versus* homozygote superiority ( $\pm$  SE) in the H, C and L lines of the 9th and 10th generations.

<i>Genotype</i>	<i>Line</i>		
	<i>H</i>	<i>C</i>	<i>L</i>
114-119		-0.79 $\pm$ 0.58	-0.89 $\pm$ 0.56
114-121		0.68 $\pm$ 0.70	
114-124		0.03 $\pm$ 0.57	-0.63 $\pm$ 0.24 **
119-121	-0.79 $\pm$ 0.47	0.70 $\pm$ 0.52	
119-124	-2.91 $\pm$ 0.72 **	0.78 $\pm$ 0.40 *	-0.26 $\pm$ 0.65
121-124	-1.66 $\pm$ 0.50 **	1.48 $\pm$ 0.48 **	
ALL <sup>1</sup>	-1.79 $\pm$ 0.42 **	0.60 $\pm$ 0.31 *	-0.59 $\pm$ 0.38

\*,\*\*: Significant superiority at the 0.05 and 0.01 levels, respectively; <sup>1</sup> ALL indicates the overall superiority within lines.

**Estimation of MHC haplotype effects on the Ab response**

In the C and L lines, all possible combinations of haplotypes were present. Therefore, in these lines, the choice of a reference haplotype did not affect either the ranking, or the value of the differences between haplotype estimates. Results are presented in table V taking the 119 B-haplotype as the reference. In the H line, haplotype effects were not estimated because it was not possible to write a linear combination of genotypes, which would estimate the difference between 2 haplotypes. The estimated Ab titer of the 114 B-haplotype was significantly lower than the estimate of the 119 B-haplotype in the L line (table V). In the C line, the estimated Ab titer of the 114 B-haplotype was significantly lower than the estimates of the 121 and 124 B-haplotypes in the C line.

**Relationship between the effects of MHC types on antibody response and their frequency**

To determine whether the differences in MHC genotype and haplotype distribution between the lines could be explained by differences in genotype or haplotype effect

**Table V.** Estimates of B-haplotype effect on the antibody response to SRBC in the C and L lines of the 9th and 10th generations.

<i>Line</i>			
<i>C</i>		<i>L</i>	
<i>Haplotype</i>	<i>Estimate</i>	<i>Haplotype</i>	<i>Estimate</i>
114	-0.54 <sup>a</sup>	114	-1.00 <sup>a</sup>
119	0.00 <sup>ab</sup>	124	-0.61 <sup>ab</sup>
121	0.12 <sup>b</sup>	119	-0.00 <sup>b</sup>
124	0.28 <sup>b</sup>		

The 119 B-haplotype was taken as a reference; <sup>a,b</sup>: estimates with different superscripts indicate differences ( $P < 0.05$ ) between haplotypes within lines.

on the selected trait, frequencies of MHC types and their estimated effects on the Ab titer were compared. When not considering the extreme values of rare genotypes in the H line, remaining genotype estimated effects were not significantly different from each other; therefore, results from the estimation of MHC genotype effect on the Ab response from the H line will not be considered.

The ranking of estimates of haplotype effects on the Ab response in the L line (table V), was in total agreement with the distribution of these haplotypes in the selected lines (table II). Likewise, the ranking of the 114, 119 and 121 B-haplotype effects estimated in the C line could explain the haplotype distribution in the selected lines.

Genotypes which were most frequent in the L line had also, on the whole, lower effects on the Ab response than genotypes which were rare in the L line, as estimated in the L line (fig 1) and in the C line (fig 2). Genotypes which were most frequent in the L line had globally lower effects on the Ab response in the C line than genotypes which were most common in the H line (fig 2). The major exception was the 121-121 B-genotype which was most frequent in the H line, but had a low effect on the Ab response in the C line (fig 2).

In conclusion, estimation on MHC genotype and haplotype effects on the Ab response in the C and L line could explain the observed distribution of MHC types in the L line and only partly those observed in the H line.

## DISCUSSION

Changes of gene frequency may be due to genetic drift, difference in fitness of certain genotypes, or, in case of selection, to direct effect or linkage with genes affecting the selected trait (Falconer, 1989). Even after 10 generations, genetic drift is not likely to explain such dramatic changes of MHC type frequency in opposite directions. Moreover, previous genetic analysis of 9 generations did not show any apparent genetic drift, and inbreeding, which affects genetic drift, was low (Pinard *et al*, 1992). Associations between MHC types and fitness traits have been demonstrated in avian (Gavora *et al*, 1986; Nordskog *et al*, 1987) and mammalian

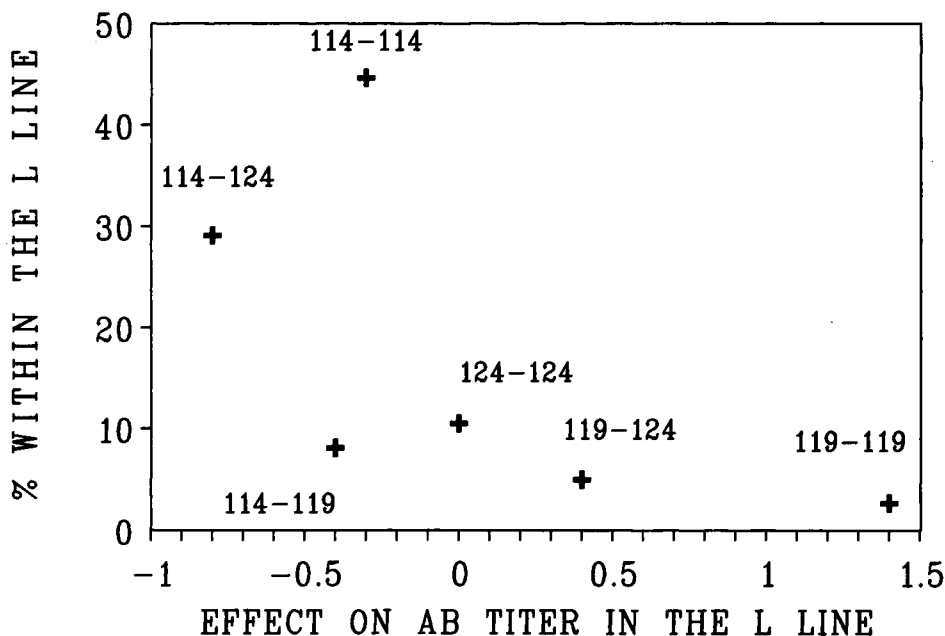
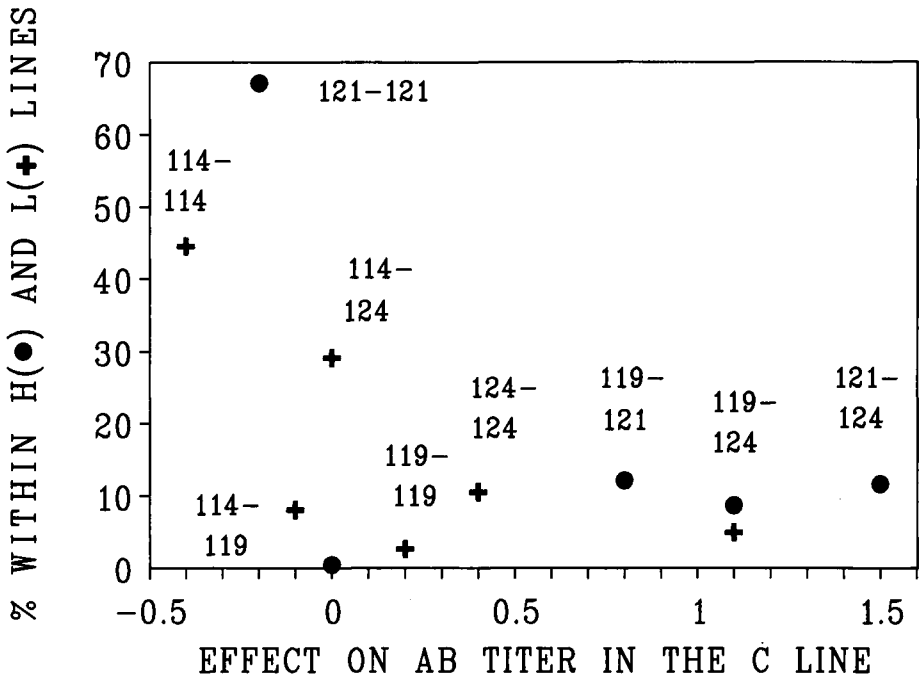


Fig 1. Frequencies of B-genotypes in the low (L,+) line of the tenth generation, according to their effect on the Ab titer to SRBC, estimated from the low line.

species (Melnick *et al*, 1981; Østergard *et al*, 1989; Gautschi and Gaillard, 1990). Therefore, a possible effect of natural selection cannot be excluded. This, however, cannot explain the opposite changes in MHC type distributions in the H and L lines, as compared to the C line. The significant differences in effect of the MHC genotype on the selected trait are evidence for a direct or closely linked effect of MHC genes on the Ab response to SRBC.

The MHC type frequencies were not measured in the initial base population or in the first generations of selection. However, the control line was produced from the base population by random mating and displayed in the 10th generation all haplotype combinations, whereas the selected lines presented divergent distributions of MHC types. Given the relatively low level of inbreeding in the C line, it thus seems reasonable that the frequencies in the C line represent the distribution of MHC types in the base population, and that the MHC type frequencies have changed in the selected lines.

Changes in MHC gene frequency, or at least, differences in MHC type distributions between lines selected for immune responsiveness or disease resistance have been reported (Gavora *et al*, 1986; Heller *et al*, 1991). In a similar experiments to ours with chickens selected for high and low immune response to SRBC, differences in allelic frequency in 6 alloantigen systems including the B-system were found in an analysis of data from generations 10 to 13 (Dunnington *et al*, 1984; Martin *et al*, 1990). Interestingly, these authors reported that the most frequent B-haplotype in the H line was the 21, which shares B-F antigens with the 121 B-haplotype, which



**Fig 2.** Frequencies of B-genotypes in the high (H,●) and low (L,+) lines of the tenth generation, according to their effect on the Ab titer to SRBC, estimated from the control (C) line.

was also predominant in our H line (Pinard and Hepkema, 1992). Typing for MHC antigens in lines of mice divergently selected for Ab response to SRBC (Biozzi *et al*, 1979) also revealed 2 distinct haplotypes in the 2 lines (Colombani *et al*, 1979).

Estimation of MHC genotype effect and of heterozygote advantage produced different results between the lines. Immune responsiveness to various antigens like SRBC has been demonstrated to be influenced by non-MHC as well as by MHC genes (Palladino *et al*, 1977; Gyles *et al*, 1986; Kim *et al*, 1987; Lamont and Dietert, 1990). Significant interactions between MHC and the selected background genome were also reported in a similar selection experiment to ours (Dunnington *et al*, 1989). In addition, specific heterozygote advantage may result from genetic complementation between both MHC and non-MHC genes.

In segregating populations, the estimation of single gene effects can lead to biased results because of the likely confounding effects between the marker gene and the polygenes (Bentsen and Klemetsdal, 1991). Selection is an extra source of bias because the birds being selected are likely sharing advantageous alleles for both the marker gene and the polygenes. Kennedy *et al* (1992) showed that unbiased estimates of a single gene effects can be obtained by mixed model analysis from a selected population if all the genotypes are known. In our experiment, the genotypes were not determined in the early generations. And we chose to use the data complete for both the Ab titer and the genotypes from the last 2 generations, instead

of using data from all generations with an unknown genotype. Indeed, Carnier and Arendonk (1992) demonstrated by simulation that including observations in previous generations of which genotype information was missing resulted in larger biases. In our estimation, bias due to selection could not be eliminated by the use of the complete relationship matrix only. This bias might have contributed to the differences in genotypic effects observed between the lines.

The present and previous results (Pinard *et al*, 1992) are in agreement with a polygenic control of antibody response to SRBC. Moreover, one of the loci involved might be part of, or linked to, the B-complex. However, the linkage and the nature of the interactions between MHC or MHC-linked genes and other immune response genes are not known. Besides, during 10 generations of multiple matings, recombinations between MHC-linked and other immune response genes might have occurred, causing altered linkage (Pevzner *et al*, 1978; Lamont; 1989).

In conclusion, results of the estimation of MHC effect from selected populations should be considered with caution, especially when the genotypes are not known in all the generations. In our experiment, estimation of MHC effect may be obtained from the control line, providing a larger number of birds. Alternatively, one could study a F<sub>2</sub> population that will be produced from the high and low lines.

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