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Original article

Effects of major histocompatibility complex on antibody response in F_1 and F_2 crosses of chicken lines

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Summary – Lines of chickens selected for 9 generations for high (H) and low (L) antibody (Ab) response to sheep red blood cells (SRBC) were crossed to produce $F_1(n = 761)$ and $F_2(n = 1033)$ populations. All animals were typed for major histocompatibility complex (MHC) B-types. Effects of MHC genotypes and haplotypes on the Ab titer to SRBC were estimated. The MHC genotypes and remaining genotype explained 2.5% and 31% of the total variation of the Ab titer in the F_2 respectively. Estimates of MHC effects in the F_2 were similar to estimates in the selected lines. The 119 and 121 B-haplotypes were associated with a significantly higher response than the 114 and 124 B-haplotypes. These results confirm the hypothesis that changes in B-type distribution observed in the selected lines could be related to a direct or closely linked effect of MHC on the immune response.

chicken / humoral response / selection / cross / major histocompatibility complex

Résumé – Effets du complexe majeur d'histocompatibilité sur la réponse en anticorps dans des croisements F_1 et F_2 de lignées de poules. *Des lignées de poules, sélectionnées pendant 9 générations sur la réponse humorale haute et basse à des globules rouges de mouton, ont été croisées afin de produire une F_1 (n = 761) et une F_2 (n = 1033). Tous les animaux ont été analysés pour leurs types B du complexe majeur d'histocompatibilité (CMH). Les effets des génotypes et des haplotypes du CMH sur la réponse en anticorps aux globules rouges de mouton ont été estimés. Le génotype du CMH explique 2,5% de la variation totale de la réponse en anticorps dans la F_2, alors que l'héritabilité du caractère*

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est de 0,31. Les estimations des effets du CMH dans la F_2 sont semblables à celles obtenues dans les lignées sélectionnées. Les haplotypes B 119 et B 121 sont associés à une réponse immunitaire significativement plus élevée que les haplotypes B 114 et 124. Ces résultats confirment l'hypothèse que les changements de fréquence des types du CMH observés dans les lignées sélectionnées pouvaient être dus à un effet direct ou génétiquement lié du CMH sur la réponse immunitaire.

poule / réponse immunitaire / sélection / croisement / complexe majeur d'histocompatibilité

INTRODUCTION

There is accumulating evidence that disease resistance and immune response are under genetic control in most species, providing the bases for an improvement by direct selection for the trait of interest; moreover, the use of markers might add to the efficiency of selection (Shook, 1989; Weller and Fernando, 1991). But in the latter option, relationships between marker genes and the trait of interest have to be clearly established. Studies on relationships between major histocompatibility complex (MHC) types and immune traits or disease resistance have shown variability in strength and nature of association (Schierman and Collins, 1987; Van der Zijpp and Egberts, 1989). Inconsistencies might be due to several reasons: a) the MHC does not directly affect the trait and some crossing over has occurred between the MHC and immune response genes, so that the apparent effect of MHC on the immune trait depends on the linkage phase between MHC genes and immune response genes; b) the MHC is directly involved but there are epistatic effects with other background genes and/or significant genotype-environment interactions; c) only a few MHC types are present per study, so that the same haplotypes differ in relative performance (good or poor) in different populations; d) different and even inappropriate statistical methods might have been used, especially when animals are related.

High (H) and low (L) lines of chickens have been produced by divergent selective breeding for primary antibody response to sheep red blood cells (SRBC) (Van der Zijpp *et al*, 1988; Pinard *et al*, 1992). After 10 generations, the H and L lines revealed a diverging distribution in MHC types, compared to the random control line; moreover, MHC types were responsible for a significant part of variation of the immune response (Pinard *et al*, 1993). However, MHC genotypes were not know in early generations so that estimates of the MHC effect might be biased, even when using all family information (Kennedy *et al*, 1992). Moreover, the number of animals for some genotypes was limited. Therefore, a study involving crosses between the H and L lines was required to confirm the MHC association.

The objectives of this experiment were to produce F_1 and F_2 crosses from lines of chickens selected for high and low antibody response to SRBC, and to estimate the MHC genotype and haplotype effects on the immune response against a random background.

MATERIALS AND METHODS

Crossing of selected lines

Chickens were selected from an ISA Warren cross base population, for high (H) or low (L) total antibody (Ab) titer 5 d postprimary immunization with 1 ml 25% sheep red blood cells (SRBC) at 37 d of age (Van der Zijpp *et al*, 1988; Pinard *et al*, 1992). From the 9th generation, 26 males and 55 females of the H line were mated with 53 females and 31 males of the L line, respectively, to produce 761 F_1 animals. From the F_1 population, 243 females and 202 males were used to produce 1 033 F_2 chicks. Parents of the F_1 and F_2 populations were chosen from as many different families as possible, and were mated at random, providing in $F_2 \approx 100$ chicks for each of the 10 MHC genotypes (see below). Immunization with SRBC was performed on F_1 and F_2 animals identically as in the selected lines, and Ab titers against SRBC 5 d postprimary immunization were recorded. The vaccination schedule applied to F_1 and F_2 chicks was identical to the one used during the selection. However, the housing system and environment differed: birds from the H and L lines were reared in cages of 50 per 100 cm^2 with 10 chicks maximum per cage on one farm; F_1 and F_2 birds were housed free on the floor on 2 different farms, respectively.

Typing for MHC haplotype

Major histocompatibility complex haplotypes were determined by direct haemagglutination, using alloantisera obtained from the lines. Four serotypes, provisionally called B^{114}, B^{119}, B^{121}, and B^{124} were identified previously in the selected lines. 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^{114} and B^{119} showed similarities for B-G with B^{14} and B^{19}, respectively, whereas B^{121} showed similarities for B-F with B^{21} (Pinard *et al*, 1991; Pinard and Hepkema, 1992). A MHC genotype was defined as the combination of 2 haplotypes. Serological typing was performed on all the F_1 and F_2 chicks and segregation of the haplotypes was checked for consistency within families; inconsistent data (3% of the data) were removed from the analysis.

Statistical analysis

Effects of MHC genotype on the Ab response were estimated in the F_1 and F_2 populations, using the following mixed model:

$$Ab_{ijk} = \mu + sex_i + MHC_j + U_{ijk} + e_{ijk}$$

Where :

Ab_{ijk} = the Ab titer of the kth chick,
μ = a constant,
sex_i = the fixed effect of the ith sex of the chick,
MHC_j = the fixed effect of the jth MHC genotype,
U_{ijk} = the random additive genetic effect on the Ab titer in the kth chick and
e_{ijk} = a random error.

The sex effect corrected for a higher Ab response to SRBC in females than in males. All relationships from the base population until the F_1 and F_2 crosses were used in the analysis of the F_1 and F_2 data, respectively. The mixed model was applied assuming a heritability of 0.31, as estimated previously from data of all lines (Pinard *et al*, 1992). Solutions for the model were obtained using the PEST-program (Groeneveld, 1990; Groeneveld and Kovac, 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 by an F-value calculated by PEST, which allows use of all relations between animals. The overall effect of genotypes was estimated by testing, jointly, n-1 independent differences between genotypes, with n being the number of genotypes.

Heterozygote superiority was estimated for each available combination by testing the difference between the heterozygote genotypes and the average of their homozygous counterparts. The overall heterozygote superiority was estimated by testing the difference between all the heterozygote genotypes and the average of their homozygous conterparts.

The haplotype effect was estimated by 3 methods. In method I, the effect of haplotype i was estimated by testing the difference between genotype combinations, comprised of the haplotype i and their counterparts, comprised of a reference haplotype r, as follows: $\frac{\Sigma_j(Geno_{ij} - Geno_{rj})}{p}$, with $Geno_{ij}$ and $Geno_{rj}$ 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. Methods II and III were applied in the following haplotype models, as adapted from Østergard (1989):

$$Ab_{ijl} = \mu + sex_i + \Sigma_j \beta_j Haplo_j + U_{ijl} + e_{ijl} \quad \text{(Method II)}$$

$$Ab_{ijkl} = \mu + sex_i + \Sigma_j \beta_j Haplo_j + \Sigma_k \Gamma_k Comb_k + U_{ijkl} + e_{ijkl} \quad \text{(Method III)}$$

where β_j is the linear regression coefficient on $Haplo_j$, which is the number of the jth MHC haplotype (2 = homozygous, 1 = heterozygous or 0 = absent) in the lth chick, Γ_k is the linear regression coefficient on $Comb_k$, which is the kth heterozygous combination, and all the other terms are as previously described.

In the F_1 cross, only Method I was applied, whereas all 3 methods were compared in the F_2 population, which provided all possible haplotype combinations in similar numbers of animals.

RESULTS

Antibody titer distribution in the F_1 and F_2 populations

Antibody titer distributions in the H and L lines of the 9th generation and in the F_1 and F_2 crosses are shown in figure 1, and mean titers are given in table I. The F_1 cross did not show any positive heterosis effect, and the titer of the cross between L line females and H line males was even lower (5.85) than the mean parent value (9.06). The Ab titers appeared to be more normally distributed in the F_1 and F_2

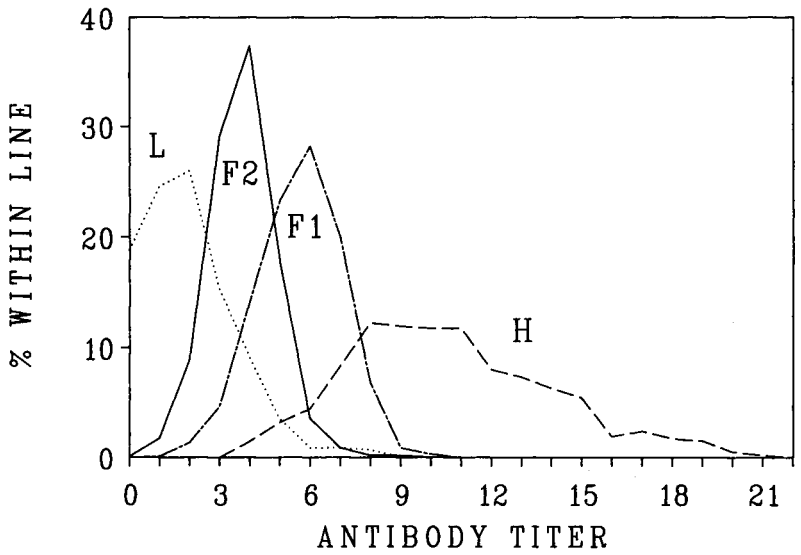

Fig 1. Distribution of antibody titers to sheep red blood cells of the high (H, - -) and low (L, . .) lines of the 9th generation, H × L = F_1 (- .) and F_1 × F_1 = F_2 (——) crosses.

crosses than in the selected lines, but the F_2 population did not show a greater variation of titers than the F_1 cross.

MHC distribution in the F_1 and F_2 populations

Numbers of animals per MHC genotype in the F_1 and F_2 crosses are given in table II. Sexes were equally represented in each class. It was not possible to obtain homozygous 121–121 animals in the F_1 cross because the 121 B-haplotype was not present in the L line of the 9th generation (Pinard *et al*, 1993).

Estimation of MHC genotype effects on the antibody response

Estimates of MHC genotype on the Ab response to SRBC in F_1 and F_2 animals are given in table III. The overall effect of MHC genotypes was greater in the F_2 than in the F_1 population. The range of estimates was higher in the F_1 than in the F_2 population, but the SE of differences between genotypes were half as large in the F_2 as they were in the F_1 cross. The ranking of genotypes according to their Ab titer estimates did not differ greatly between the 2 populations; only the 124-124 and the 114-121 B-genotypes showed relatively low estimates, and the 119-119 B-genotype a relatively high estimate in the F_1 compared to those in the F_2 animals. No significant changes in the estimate were observed when taking other input heritability values between 0.2 and 0.4 (data not shown). In the F_2, the distributions of Ab titers within genotypes were normal and ranged between those of the 114-124 and 119-121, as shown in figure 2.

Table I. Means ± SDs of antibody titers to sheep red blood cells in the high and low lines of the 9th generation and their F_1 and F_2 crosses.

Line	*Antibody titer*		
	Whole line	*Male parent*[a]	*Female parent*[a]
L	1.94 ± 1.57	0.00 ± 0.00	2.89 ± 1.71
H	10.62 ± 3.38	15.23 ± 1.55	11.67 ± 3.46
H♂ × L♀ [b]	5.85 ± 1.34		
L♂ × H♀ [b]	5.46 ± 1.44		
F_1[c]	5.66 ± 1.64	5.47 ± 1.42	5.83 ± 1.34
F_2	3.77 ± 1.13		

[a] Males and females from the line, used to produce the next cross; [b] F_1 reciprocal crosses; [c] whole F_1.

Table II. Number of animals per B-genotype in the F_1 and F_2 crosses.

Genotype	*Cross*	
	F_1	F_2
114-114	65	96
114-119	87	108
114-121	201	100
114-124	50	101
119-119	50	97
119-121	88	105
119-124	75	110
121-121	0	103
121-124	88	108
124-124	57	105
ALL	761	1 033

Comparisons of genotype effects on the Ab response to SRBC estimated in the F_2 with their effects estimated in the H, C and L lines (Pinard *et al*, 1993) are shown in figure 3. Results obtained from the F_2 were more in agreement with those of obtained from the selected lines than from the C line.

The relative importance of the MHC genotype and the remaining genotype on the variation of the Ab titer in the F_2 were calculated by comparing the coefficients of determination using different models (table IV). When used alone in the model, the MHC genotype explained only 4.4% of the total variation, which could still be the result of partial confounding effects between MHC genotype and the effects of the sex and of U_k. It is, therefore, better to look at the difference in R^2 between a full model with and without MHC effect. Including MHC effect in the full animal model increased the variation explained by an additional 2.5%. The R^2 value of

Table III. Estimates of B-genotype effect on the antibody response to sheep red blood cells in the F_1 and F_2 crosses.

Cross			
F_1		F_2	
Genotype	*Estimate*	*Genotype*	*Estimate*
124-124	-0.94^{a}	114-124	-0.50^{a}
114-124	-0.82^{a}	114-114	-0.28^{ab}
114-114	-0.79^{a}	121-124	-0.18^{abc}
114-121	-0.48^{ab}	124-124	-0.17^{abcd}
121-124	-0.47^{abc}	119-119	-0.08^{bcd}
114-119	-0.03^{bcd}	114-119	-0.05^{bcd}
119-124	0.00^{bcd}	119-124	0.00^{bcde}
119-121	0.07^{cd}	114-121	0.11^{cde}
119-119	0.45^{d}	121-121	0.21^{de}
		119-121	0.35^{e}
Pr> F^{e}	0.0005	< 0.0001	

^{a,b,c,d} Estimates with different superscripts indicate differences ($P < 0.01$) between genotypes within cross. ^{e} Pr > F indicates the overall effect of B-genotypes within cross. SEs of differences between genotypes were between 0.28 and 0.32 in F_1, and 0.16 in F_2.

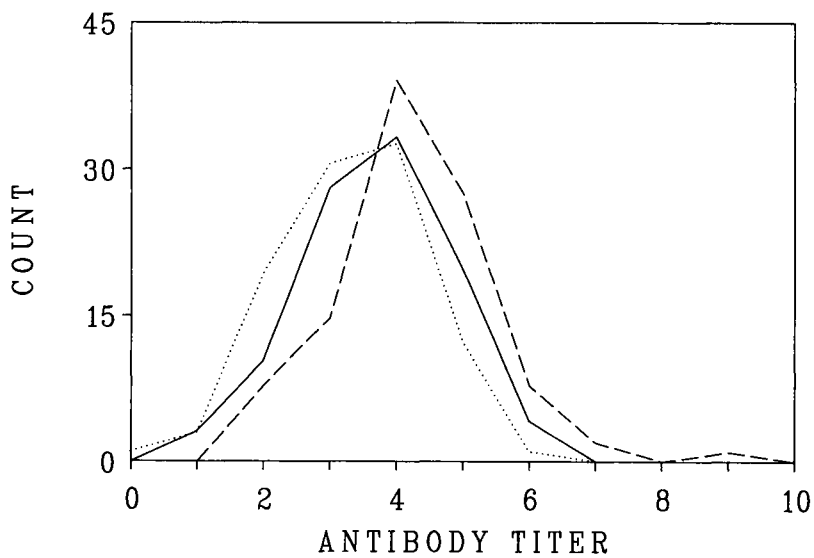

Fig 2. Distribution of antibody titers to sheep red blood cells of the 114-124 (. .), 119-119 (____) and 119-121 (- -) genotypes in the F_2.

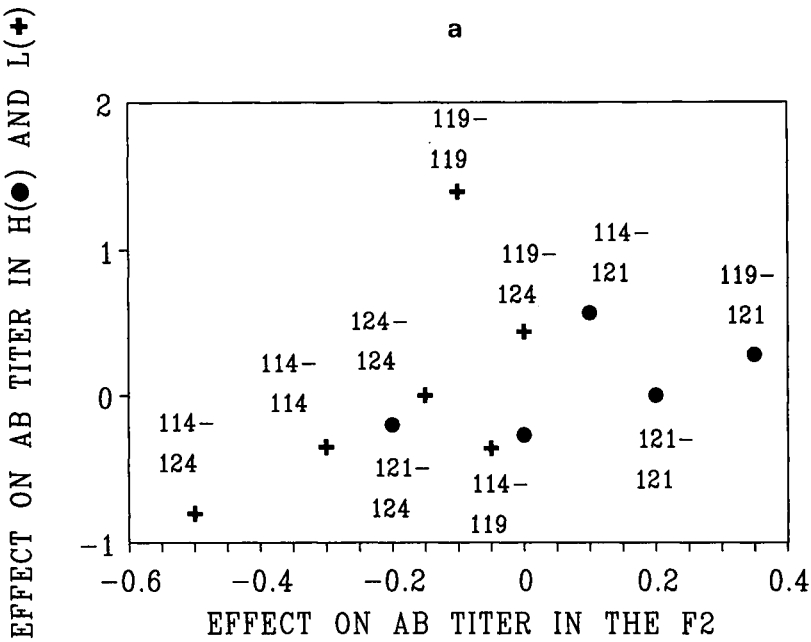

Fig 3a. Effects of MHC genotypes on antibody titers to sheep red blood cells estimated in the high (H, •) and low (L, +) lines according to their effects on antibody titers to sheep red blood cells estimated in the F_2. Results of the H and L lines are from Pinard *et al* (1993), and rare genotypes in the H line were not considered.

31.1 when putting only U_k as an effect was close to the input heritability (0.31) as expected.

Estimation of heterozygote superiority

In the F_1 population, no significant effect of heterozygote superiority, overall or for any available combination, was found (data not shown). No significant effect of overall heterozygote superiority was shown in F_2 animals either (table V); however, the 114-124 and 119-121 B-genotypes demonstrated a significant heterozygous disadvantage and advantage, respectively.

Estimation of MHC haplotype effects on the antibody response

Results of the estimation of MHC haplotype effect in the Ab titer in the F_1 and F_2 populations, using Method I, are given in table VI. In the F_1 population, the 119 B-haplotype was significantly associated with the highest estimate, whereas in the F_2 animals, the estimated Ab titers of the 119 and 121 B-haplotypes were significantly higher than for the 114 and 124 B-haplotypes. As compared to the results obtained with Method I, using Method II in the F_2 population did not significantly change the relative values of haplotypes. Haplotype effects estimated

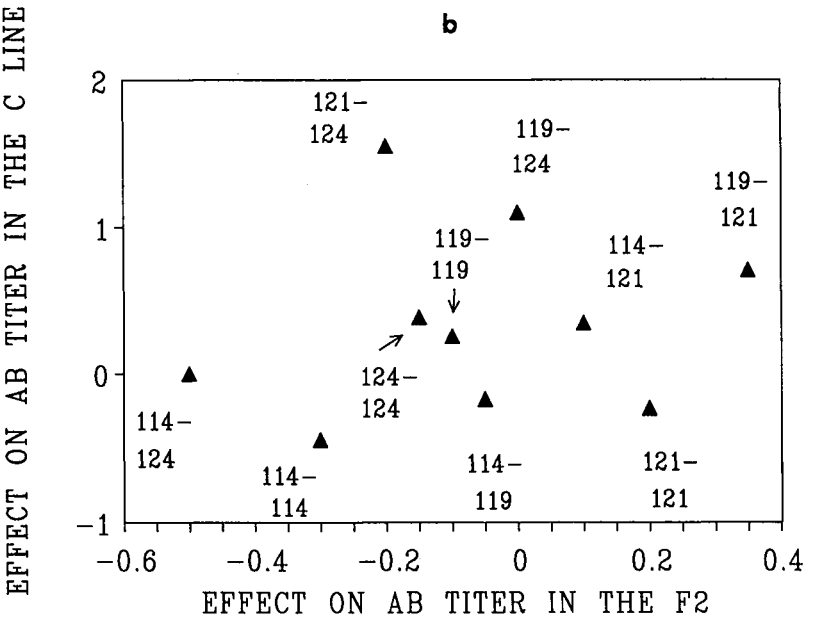

Fig 3b. Effects of MHC genotypes on antibody titers to sheep red blood cells estimated in the control (C, ▲) line according to their effects on antibody titers to sheep red blood cells estimated in the F_2. Results of the C line are from Pinard *et al* (1993).

Table IV. Contributions of the effects of the MHC genotypes and the animal value to the total variance in antibody titer to sheep red blood cells in the F_2.

Model[a]	R^{2b}
$Ab_{jk} = \alpha + MHC_j + e_{jk}$	4.4
$Ab_k = \alpha + U_k + e_k$	31.1
$Ab_{ik} = \alpha + sex_i + U_{ik} + e_{ik}$	31.7
$Ab_{ijk} = \alpha + sex_i + MHC_j + U_{ijk} + e_{ijk}$	34.2

[a] The factors in the model are as previouly described; [b] $R^2 = 1 - \frac{N-p}{N-1} \times \frac{\sigma_e^2 \text{ residual}}{\sigma^2 \text{ phenotypic}}$ where N is the number of observations and p is the number of degrees of freedom of the model.

by Method III were in fact equivalent to the additive effects of haplotypes, which could be obtained from the estimated effects of the corresponding homozygous genotype combinations; and the specific heterozygous combination effects ($Comb_k$) were simply equal to the heterozygous effects as given in table V (data not shown).

Table V. Heterozygote *versus* homozygote superiority (± SE) in the F_2 cross.

Genotype	*Hetero sup*
114-119	0.13 ± 0.13
114-121	0.15 ± 0.13
114-124	- 0.28* ± 0.14
119-121	0.29* ± 0.13
119-124	0.12 ± 0.13
121-124	- 0.20 ± 0.13
ALL[a]	0.04 ± 0.07

[a] ALL indicates the overall superiority; *: significant superiority at the 0.05 level.

Table VI. Estimates (± SEs) of B-haplotype effect on the antibody response to sheep red blood cells.

F_1		F_2					
Method I		*Method I*		*Method II*		*Method III*	
Haplo	*Est*	*Haplo*	*Est*	*Haplo*	*Est*	*Haplo*	*Est*
124	0.00[a]	124	0.00[a]	124	0.00[a]	114	- 0.14[a]
114	0.03 ± 0.13[a]	114	0.03[a]	114	0.01[a]	124	- 0.09[ab]
121	0.22 ± 0.19[a]	119	0.27[b]	119	0.18[b]	119	- 0.04[ab]
119	0.68 ± 0.15[b]	121	0.33[b]	121	0.28[b]	121	0.11[b]

The 124 B-haplotype was used as a reference. [a,b]: Estimates with different superscripts indicate differences ($P < 0.01$) between haplotypes within crosses. Standard errors of differences between haplotypes in the F_2 were all equal to 0.08, 0.07 and 0.08 by using Methods I, II and III, respectively.

DISCUSSION

When parental lines are crossed, the amount of heterosis shown by the F_1 may be defined as its deviation from the mid-parent value (Falconer, 1989). Crossing effects are due to differences in the allelic frequencies between the 2 parental lines. In this experiment, the 2 lines that were crossed came from the same base population. However, after 9 generations of selection, they differed greatly for MHC haplotype frequency and probably for other immune response genes associated with the response to SRBC (Pinard *et al*, 1993). No heterosis was demonstrated here. Nevertheless, the reciprocal crosses showed similar Ab titer values although their respective mid-parent values differed, indicating maternal or sex-linked effects. When crossing lines of mice at their selection limit for Ab response to SRBC, positive heterosis was shown and was interpreted as partial dominance of the character high responder (Biozzi *et al*, 1979). In a similar experiment with White Leghorn chickens, crossing of lines, which were selected for high and low Ab response

to SRBC, showed a positive heterosis effect after 3 generations of selection (Siegel and Gross, 1980), but no heterosis effect was shown after 9 generations (Ubosi *et al*, 1985). In our lines, environmental effects were responsible for more than 2 titer points of variation in Ab titer during the selection (Pinard *et al*, 1992). Therefore, selected lines and F_1 should not be compared on their phenotypic values because they were kept in 2 separate environments.

Because of a possible bias in estimates of genotype effects from selected lines (Kennedy *et al*, 1992; Pinard *et al*, 1993), an F_2 was produced. In fact, results of estimation of genotype effects in the F_2 were more similar to the estimated effects in the selected lines than in the C line (fig 3), giving credibility to the analysis performed in the selected lines. The average genetic value of the C line, as measured by the mean estimated breeding value, did not change during the selection (Pinard *et al*, 1992) and the C line displayed, as the F_2, a random background. However, the F_2 background had a relatively great frequency of high and low immune response genes, whereas the C background had low, average, and high genes from the base population. Thus, besides the fact that estimation of genotype effects in the C line could be hampered by low numbers of animals, differences of effects between the F_2 and the C line may be interpreted as interaction between MHC and other immune response genes. Moreover, linkage disequilibrium created in the selected lines between MHC genes and linked immune response genes may not have disappeared completely in the F_2.

How do the results of the F_2 contribute to the understanding of the role played by MHC haplotypes during selection? In the Biozzi lines of mice at their selection limit, analysis of the F_2 cross showed that MHC haplotypes found in the H and the L lines segregated, respectively, with a higher and a lower immune response (Mouton *et al*, 1979). In our experiment, a selection limit was not reached. Nevertheless, the MHC haplotypes most frequent in the L line (114 and 124) and in the H line (119 and 121) were associated in the F_2 with the lowest and highest Ab titer, respectively. These results confirm the previous assumptions (Pinard *et al*, 1993) that the changes of MHC type frequency observed in the selected lines were not the result of chance, but could be explained by a direct or closely linked effect of MHC types on the selected Ab response. However, the magnitude of MHC effects (2.5% of the total variation) could not fully explain the interline difference.

Associations between MHC genes and the Ab response to SRBC have already been shown in chickens (Scott *et al*, 1988; Loudovaris *et al*, 1990), mice (Mouton *et al*, 1979) and miniature pigs (Mallard *et al*, 1989). Immunological knowledge of MHC can support the hypothesis of a direct involvement: when injected, the T-dependent SRBC antigens are phagocytized and processed by macrophages, and finally presented to T-helper cells, inducing, in collaboration with B-cells, the production of Ab against SRBC (Biozzi *et al*, 1984). The T - B cell interaction has been shown in chickens, as in mammalian species, to be MHC class II (B-L) restricted as is the presentation of processed peptides to T-cells (Vainio *et al*, 1987). Efficiency of the response may be related to the varied ability of MHC molecules to bind and present antigens to T-cell receptors (Watts and Mc Connell, 1987; Buus *et al*, 1987), as combined to the T-cell repertoire (Grey *et al*, 1989). Finally, Kaufman and Salomonsen (1992) proposed some models for a possible role of class IV (B-G) genes in the selection of B-cells. Positive and negative complementation

in these different paths could explain, respectively, the heterozygous advantage and disadvantage observed for the combinations of the 2 best (119 and 121) and the 2 worst (114 and 124) B-haplotypes, regarding their effect on antibody response to SRBC.

In the case of non-additivity of some MHC-linked genes, a genotype model should be preferred because it is the most complete and allows parallel estimations of the general and specific heterozygous effects. In the F_2, all possible haplotype combinations were present in a balanced design. This is often not the case; a genotype model should be, then, also used to avoid the risk of having haplotype effects completely dominated by one genotype. However, it can be of practical interest to search for favorable alleles, for example in cattle breeding where only sires are MHC-typed and extensively used, by using haplotype models such as type II or adapted from this method (Batra *et al*, 1989; Lundén *et al*, 1990). Bentsen and Klemetsdal (1991) proposed a haplotype model including a general heterozygous effect but it is obvious that this hypothesis should be tested before being applied. In the case of additivity, all 3 haplotype models would give the same estimate; otherwise, the differences between models I and II will depend on the relative value of heterozygous genotypes.

In conclusion, selecting for higher immune response may be achieved by choosing the best specific haplotype combination in a particular genetic stock or line crosses. In many species, it is not easy to utilize the non-additive genetic variation in practice. The typical multiple-line cross, which is used in commercial poultry breeding may, however, provide the necessary tool.

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ERRATUM

Pinard MH, Van Arendonk JAM, Nieuwland MGB, Van der Zijpp AJ (1993) Divergent selection for humoral immune responsiveness in chickens: distribution and effects of major histocompatibility complex types. *Genet Sel Evol* 25(2), 191-203.

On page 196, table II, frequency (in %) of the 124 B-haplotype in generation 10 of the low (L) line should be 27.5, instead of 27.75 as printed.