Effects of major histocompatibility complex on antibody response in F1 and F2 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 F1 (n = 761) and F2 (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 F2 respectively. Estimates of MHC effects in the F2 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.

Résumé – Effets du complexe majeur d’histocompatibilité sur la réponse en anticorps dans des croisements F1 et F2 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 F1 (n = 761) et une F2 (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 F2, alors que l’hérédité du caractère...
Les estimations des effets du CMH dans la F2 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 confortent 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.

**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 F1 and F2 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 F₁ animals. From the F₁ population, 243 females and 202 males were used to produce 1,033 F₂ chicks. Parents of the F₁ and F₂ populations were chosen from as many different families as possible, and were mated at random, providing in F₂ ≈ 100 chicks for each of the 10 MHC genotypes (see below). Immunization with SRBC was performed on F₁ and F₂ animals identically as in the selected lines, and Ab titers against SRBC 5 d postprimary immunization were recorded. The vaccination schedule applied to F₁ and F₂ 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 cm² with 10 chicks maximum per cage on one farm; F₁ and F₂ 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 B₁₁₄, B₁₁₉, B₁₂¹, and B₁₂₄ 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 B₁₁₄ and B₁₁₉ showed similarities for B-G with B₁₄ and B₁₉, respectively, whereas B₁₂¹ showed similarities for B-F with B₂¹ (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 F₁ and F₂ 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 F₁ and F₂ 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 \( k \)th chick,
- \( \mu \) = a constant,
- \( sex_i \) = the fixed effect of the \( i \)th sex of the chick,
- \( MHC_{j} \) = the fixed effect of the \( j \)th MHC genotype,
- \( U_{ijk} \) = the random additive genetic effect on the Ab titer in the \( k \)th 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 F1 and F2 crosses were used in the analysis of the F1 and F2 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 counterparts.

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: \[
\frac{\sum_j (Geno_{ij} - Geno_{rj})}{p},
\]
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):

\[
Ab_{ijl} = \mu + sex_i + \sum_j \beta_j Haplo_j + U_{ijl} + e_{ijl} \quad \text{(Method II)}
\]

\[
Ab_{ijkl} = \mu + sex_i + \sum_j \beta_j Haplo_j + \sum_k \Gamma_k Comb_k + U_{ijkl} + e_{ijkl} \quad \text{(Method III)}
\]

where \(\beta_j\) 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, \(\Gamma_k\) 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 F1 cross, only Method I was applied, whereas all 3 methods were compared in the F2 population, which provided all possible haplotype combinations in similar numbers of animals.

RESULTS

**Antibody titer distribution in the F1 and F2 populations**

Antibody titer distributions in the H and L lines of the 9th generation and in the F1 and F2 crosses are shown in figure 1, and mean titers are given in table I. The F1 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 F1 and F2
crosses than in the selected lines, but the F2 population did not show a greater variation of titers than the F1 cross.

**MHC distribution in the F1 and F2 populations**

Numbers of animals per MHC genotype in the F1 and F2 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 F1 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 F1 and F2 animals are given in table III. The overall effect of MHC genotypes was greater in the F2 than in the F1 population. The range of estimates was higher in the F1 than in the F2 population, but the SE of differences between genotypes were half as large in the F2 as they were in the F1 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 F1 compared to those in the F2 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 F2, 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.
Comparisons of genotype effects on the Ab response to SRBC estimated in the F2 with their effects estimated in the H, C and L lines (Pinard et al, 1993) are shown in figure 3. Results obtained from the F2 were more in agreement with those 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 F2 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

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**Table I.** Means ± SDs of antibody titers to sheep red blood cells in the high and low lines of the 9th generation and their F1 and F2 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    |
| $HGF^b \times LQ^b$ | 5.85 ± 1.34   |              |              |
| $LQ^b \times HQ^b$ | 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; $^b$ F1 reciprocal crosses; $^c$ whole F1.

**Table II.** Number of animals per B-genotype in the F1 and F2 crosses.

| Genotype | Cross |
|----------|-------|
|          | F1    | F2    |
| 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  | 50    | 103   |
| 121-124  | 88    | 108   |
| 124-124  | 57    | 105   |
| ALL      | 761   | 1033  |

Comparisons of genotype effects on the Ab response to SRBC estimated in the F2 with their effects estimated in the H, C and L lines (Pinard et al, 1993) are shown in figure 3. Results obtained from the F2 were more in agreement with those of obtained from the selected lines than from the C line.

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**Table III.** Estimates of B-genotype effect on the antibody response to sheep red blood cells in the F1 and F2 crosses.

| Genotype   | Estimate | Genotype | Estimate |
|------------|----------|----------|----------|
| 124-124    | -0.94<sup>a</sup> | 114-124 | -0.50<sup>a</sup> |
| 114-124    | -0.82<sup>a</sup> | 114-114 | -0.28<sup>ab</sup> |
| 114-114    | -0.79<sup>a</sup> | 121-124 | -0.18<sup>abc</sup> |
| 114-121    | -0.48<sup>ab</sup> | 124-124 | -0.17<sup>abcd</sup> |
| 121-124    | -0.47<sup>abc</sup> | 119-119 | -0.08<sup>bcd</sup> |
| 114-119    | -0.03<sup>bcd</sup> | 114-119 | -0.06<sup>bcd</sup> |
| 119-124    | 0.00<sup>bcd</sup> | 119-124 | 0.00<sup>bode</sup> |
| 119-121    | 0.07<sup>cd</sup> | 114-121 | 0.11<sup>cde</sup> |
| 119-119    | 0.45<sup>d</sup> | 121-121 | 0.21<sup>de</sup> |
|            |          | 119-121 | 0.35<sup>e</sup> |

Pr > F<sup>e</sup> = 0.0005 < 0.0001

<sup>a,b,c,d</sup> Estimates with different superscripts indicate differences (P < 0.01) between genotypes within cross. <sup>e</sup> Pr > F indicates the overall effect of B-genotypes within cross. SEs of differences between genotypes were between 0.28 and 0.32 in F1, and 0.16 in F2.

**Fig 2.** Distribution of antibody titers to sheep red blood cells of the 114-124 (---), 119-119 (-----) and 119-121 (- - -) genotypes in the F2.
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
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 \((Comb_{jk})\) were simply equal to the heterozygous effects as given in table V (data not shown).

**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 F2. 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 F2.

| Model                                  | \(R^2\) |
|----------------------------------------|---------|
| \(Ab_{jk} = \alpha + MHC_{j} + e_{jk}\) | 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 previously described; \(^b\) \(R^2 = 1 - \frac{N - p}{N - 1} \times \frac{\sigma^2_{\text{residual}}}{\sigma^2_{\text{phenotypic}}}\)

where \(N\) is the number of observations and \(p\) is the number of degrees of freedom of the model.
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 F1 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 F2 was produced. In fact, results of estimation of genotype effects in the F2 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 F2, a random background. However, the F2 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 F2 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 and linked immune response genes may not have disappeared completely in the F2.

How do the results of the F2 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 F2 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 F2 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 F2, 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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REFERENCES

Batra TR, Lee AJ, Gavora JS, Stear MJ (1989) Class I alleles of the bovine major
histocompatibility system and their association with economic traits. J Dairy Sci
72, 2115-2124
Bentsen HB, Klemetsdal G (1991) The use of fixed effects models and mixed models
to estimate single gene associated effects on polygenic traits. Genet Sel Evol 23,
407-419
Biozzi G, Mouton D, Heumann Am, Bouthillier Y, Stiffel C, Mevel JC (1979)
Genetic analysis of antibody responsiveness to sheep erythrocytes in crosses between
lines of mice selected for high or low antibody synthesis. Immunology 36, 427-438
Biozzi G, Mouton D, Stiffel C, Bouthillier Y (1984) A major role of the macrophage
in quantitative genetic regulation of immunoresponsiveness and antiinfectious im-
munity. Adv Immunol 36, 189-234
Buus S, Sette A, Colon SM, Miles C, Grey HM (1987) The relation between
major histocompatibility complex (MHC) restriction and the capacity of Ia to bind
immunogenic peptides. Science 235, 1353-1358
Falconer DS (1989) *Introduction to Quantitative Genetics*. Longman Scientific and Technical, New York, 3rd edn
Grey HM, Sette A, Buus S (1989) How T cells see antigen. *Sci Am* Nov, 38-46
Groeneveld E (1990) *PEST User’s Manual*. Illinois Univ, Urbana, IL
Groeneveld E, Kovac M (1990) A generalised computing procedure for setting up and solving mixed linear models. *J Dairy Sci* 73, 513-531
Kaufman J, Salomonsen J (1992) B-G: We know what it is, but what does it do? *Immunol Today* 13, 1-3
Kennedy BW, Quinton M, van Arendonk JAM (1992) Estimation of effects of single genes on quantitative traits *J Anim Sci* 70, 2000-2012
Loudovaris T, Brandon MR, Fahey KJ (1990) The major histocompatibility complex and genetic control of antibody response to sheep red blood cells in chickens. *Avian Pathol* 19, 89-99
Lundén A, Sigurdardóttir, Edfors-Lilja I, Danell B, Rendel J, Andersson L (1990) The relationship between bovine major histocompatibility complex class II polymorphism and disease studied by use of bull breeding values. *Anim Genet* 21, 221-232
Mallard BA, Wilkie BN, Kennedy BW (1989) Genetic and other effects on antibody cell mediated immune response in swine leucocyte antigen (SLA)-defined miniature pigs. *Anim Genet* 20, 167-178
Mouton D, Heumann AM, Bouthillier Y, Mevel JC, Biozzi G (1979) Interaction of H-2 and non H-2 linked genes in the antibody response to a threshold dose of sheep erythrocytes. *Immunogenetics* 8, 475-486
Østergard H, Kristensen B, Andersen S (1989) Investigation in farm animals of associations between the MHC system and disease resistance and fertility. *Liv Prod Sci* 22, 49-67
Pinard M-H, Hepkema BG (1992) Biochemical and serological identification of major histocompatibility antigens in outbred chickens. In: Selection for immunoresponsiveness in chickens: effects of the major histocompatibility complex and resistance to Marek’s disease. Ph D diss, Univ Wageningen, The Netherlands, 43-59
Pinard M-H; Hepkema BG, van der Meulen MA, Nieuwland MGB, van der Zijpp AJ (1991) Major histocompatibility complex haplotypes in chickens selected for high and low antibody production. *Anim Genet* 22 (suppl 1), 117-118
Pinard M-H, van Arendonk JAM, Nieuwland MGB, van der Zijpp AJ (1992) Divergent selection for immune responsiveness in chicken: estimation of realized heritability with an animal model. *J Anim Sci* 70, 2986-2993
Pinard M-H, 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, 191-203
Schierman LW, Collins WM (1987) Influence of the major histocompatibility complex on tumor regression and immunity in chickens. *Poult Sci* 66, 812-818
Scott TR, Oduho GM, Glick B, Hagan F, Briles WE, Yamamoto Y (1988) Erythrocyte alloantigen diversity and some immunological effects of the B system in related New Hampshire strains. *Poult Sci* 67, 1210-1217
Shook GE (1989) Selection for disease resistance. *J Dairy Sci* 72, 1349-1362
Siegel PB, Gross WB (1980) Production and persistence of antibodies in chickens to sheep erythrocytes. 1. Directional selection. *Poult Sci* 59, 1-5
Ubosi CO, Siegel PB, Gross WB (1985) Divergent selection of chickens for antibody production to sheep erythrocytes: age effect in parental lines and their crosses. *Avian Dis* 29, 150-158

Vainio O, Toivanen P, Toivanen A (1987) Major histocompatibility complex and cell cooperation. *Poult Sci* 66, 795-801

Van der Zijpp AJ, Egberts E (1989) The major histocompatibility complex and diseases in farm animals. *Immunol Today* 10, 109-111

Van der Zijpp AJ, Blankert JJ, Egberts E, Tilanus MGJ (1988) Advances in genetic disease resistance in poultry. In: *Advances in Animal Breeding* (Korver S, van der Steen HAM, van Arendonk JAM, Bakker H, Brascamp EW, Dommerholt J, eds) Pudoc, Wageningen, The Netherlands, 131-138

Watts TH, Mc Connel HM (1987) Biophysical aspects of antigen recognition by T cells. *Annu Rev Immunol*, 5, 461-475

Weller JI, Fernando RL (1991) Strategies for the improvement of animal production using marker-assisted selection. In: *Gene-Mapping Techniques and Applications* (Schook LB, Lewin HA, McLaren DG, eds) Marcel Dekker Inc, NY, 305-328

**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.