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GENETIC ANALYSIS OF SOME IMMUNOLOGICAL TRAITS IN YOUNG BULLS

By

Ø. Lie

LIE, Ø.: *Genetic analysis of some immunological traits in young bulls.* Acta vet. scand. 1979, *20*, 372—386. — Bulls from a testing station, comprising 137 animals from 113 to 420 days of age, were inoculated twice with human serum albumin (HSA). The antibody titers against HSA and the total serum immunoglobulin levels were evaluated by the single radial diffusion technique. Heritability estimates indicated a genetic influence on both the immunoglobulin level and the antibody response. The influence on the primary response appeared to be the strongest one.

antibody response; immunoglobulin level; genetics

Since the discovery of X-linked agammaglobulinaemia (*Bruton* 1952) a large number of immunodeficiencies with genetic basis have been described in man and animals (*Rosen* 1975).

During the period from 1952 several experiments have produced evidence for a genetic influence not only on deficiency states, but on qualitative and quantitative traits of the immune system in general. Immunological studies and breeding experiments in rodents have revealed complex gene systems operating at several levels in regulating the immune responsiveness (*McDevitt & Tyan* 1968, *Biozzi et al.* 1972, *Dorf et al.* 1974).

Immunogenetic studies in cattle have demonstrated the genetic influence on the serum level of immunoglobulins (*Jensen & Christensen* 1975) and on the antibody response (*Sellei & Rendel* 1968, *Lie* 1977). Moreover, evidence for the inheritance of immunoglobulin allotypes in a Mendelian fashion has been presented (*Spooner & Millar* 1976).

Combined immunological and clinical studies in livestock have demonstrated the connection between certain immuno-

logical traits and resistance to infection (*Nansen* 1972, *Williams et al.* 1975, *Briles et al.* 1977). A corresponding relationship has been shown to exist in experimental animals (*Oldstone et al.* 1973, *Plant & Glynn* 1974).

The main purpose of the present work was to study the variations for some immunological traits in cattle when environmental conditions were kept standardized. The traits, which included characteristics of the antibody response to a specific antigen and the serum immunoglobulin level, were to be examined with regard to genetic and age influence. Finally, the intention was to elucidate some interrelationships of the above mentioned characters.

MATERIALS AND METHODS

Source of material. Bulls from the NRF (Norwegian Red Cattle) Testing Station at Øyer, Norway, comprising 137 animals from 113 to 420 days of age, were arranged in 15 groups of half sibs. The feeding and environmental conditions were standardized.

Immunization antigen. Human serum albumin* (HSA) was used as antigen since the bulls had presumably experienced no previous contact with this compound. Each bull should therefore possess approximately the same specific ability to produce an immune response, with genetic and age variation out of consideration.

Preliminary immunization experiments. The request for relatively high antibody titers for the application of a quick and simple evaluation method (radial diffusion) had to be balanced by the necessity to avoid serious reactions as anaphylaxis and immune complex diseases. Consequently, the decision with regard to antigen/adjuvant quantity, application modus (sub- or intracutaneous) and number and intervals of injections was taken after preliminary immunizing experiments on a number of 12 animals.

Immunization schedule. Two doses, each of 2 mg HSA in adjuvant**, were given subcutaneously to each bull with an

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* Human Albumin, ORHA, Behringwerke AG, Marburg Lahn, W. Germany.

** Adjuvant. Incomplete, Freund, Difco Laboratories, Detroit 1, Michigan, USA.

interval of about 5 weeks. The immunization dose was distributed bilaterally in amounts of 1 mg each in the region behind the scapula.

Blood sampling. Blood samples were drawn prior to injection on the day of the first immunization and on the 8th, 14th, 21st and on 37th day which was the day of the second administration. Thereafter samples were collected on the 41st, 42nd, 43rd, 44th, 48th and 65th day.

Antibody assay. Serum antibody titers against HSA were measured by the single radial immunodiffusion technique according to *Mancini et al.* (1965). The titers were expressed in diffusion units as described by *Sandvik* (1962) and modified by *Lie* (1977). The corresponding titers of the 10 serum samples drawn from the 8th to the 65th day were named Ti01, Ti02, ... Ti10, respectively.

Quantitative immunoglobulin determination. Total serum immunoglobulin levels were determined by the method of *Mancini.* Rabbit anti bovine immunoglobulin* serum and bovine immunoglobulin** (14 mg/ml in 0.9 % saline) acted as antiserum and reference standard, respectively. The corresponding levels of the samples collected before immunization and on the 43rd day were named Ig0 and Ig1, respectively, and expressed in mg per 100 ml.

Statistical methods. The statistical analyses were mainly performed by the method of least squares (*Harvey* 1960), in which the effects of the 2 main factors, age and sires, were simultaneously estimated. As illustrated in Table 1, this particular analysis was based on a 2-way classification, in which groups of half sibs and age represent the effects of sires and age, respectively. Interaction between the 2 factors was assumed non-existent.

In addition, chi-square (χ^2) values and simple correlation coefficients (r) (confirmed by t-tests) were estimated.

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* Rabbit Anti Bovine γ-globulin Serum, OTPR, Behringwerke AG, Marburg Lahn, W. Germany.

** Immunoglobulin, Bovine, ORHE, Behringwerke AG, Marburg Lahn, W. Germany.

Table 1. The distribution of the total bull material with regard to groups of age and half sibs.

		Half sib groups															Number of animals in each age group
		1453	1476	1594	1641	1647	1692	1725	1732	1756	1764	1871	1880	1883	6502	6505	
Age groups (days)	113—147			2			1	4	1	7	1			2	1	1	20
	148—161			5	1	1	1	1	4	2	2		1		1		19
	162—180			2	2	2	2	5	4	4							21
	181—220			4	3	5	2	4	10	8		1			1	1	39
	221—420	3	2	13		1	1	1	2	2	4	1	1	1	4	2	38
Number of animals in each half sib group		3	2	26	6	9	7	15	21	23	7	2	2	3	7	4	137

RESULTS

Dynamics of antibody production

The overall mean antibody response curve to HSA for the whole bull material had a typical course with peaks of the primary and the secondary response at about the 14th and the 44th day, 15 and 8 days after the first and second injection, respectively (See also Fig. 1 below). The peak titer of the secondary response was about 8-fold higher than the primary one. Many good primary responders were observed to give poor secondary responses and vice versa.

Genetic influence

All 137 bulls produced a detectable secondary response. As shown in Table 2, this was not the case with regard to the primary response. "High" and "low" groups of half sibs with

Table 2. Number of primary responders to human serum albumin within the total bull material and within extreme groups of age and half sibs.

Group	Number of animals	Primary responders	
		number	per cent
Total material	137	114	83
Half sib group 1594	25	24	96
Half sib group 1725	15	11	73
Age group 113—147 days	20	10	50
Age group 221—420 days	38	34	89

regard to the number of primary responders were recorded and some of them (for instance 1594 and 1725) differed significantly ($P < 0.04$).

Table 3. Means and standard deviations for some traits within the total bull material and within high and low responder groups of age and half sibs.

Group	Number of animals	Trait*				
		Ti02	Ti07	Ig0	Ig1	Age (days)
Total material	137	24 ± 26	125 ± 113	2070 ± 510	2330 ± 580	209 ± 76
Half sib group 1732	21	30 ± 31	181 ± 133	2090 ± 530	2350 ± 610	183 ± 28
Half sib group 1756	23	19 ± 20	86 ± 66	1990 ± 490	2270 ± 540	174 ± 33
Age group 113—147 days	20	12 ± 13	54 ± 45	2250 ± 530	2450 ± 680	132 ± 9
Age group 221—420 days	38	33 ± 32	144 ± 120	2090 ± 550	2410 ± 650	312 ± 68

* See MATERIALS AND METHODS.

Genetic tendencies can also be interpreted from Table 3. The 2 half sib groups represented (1732 and 1756) differed widely with regard to the antibody titers Ti02 and Ti07. As appears from Fig. 1 the same groups differed significantly all through

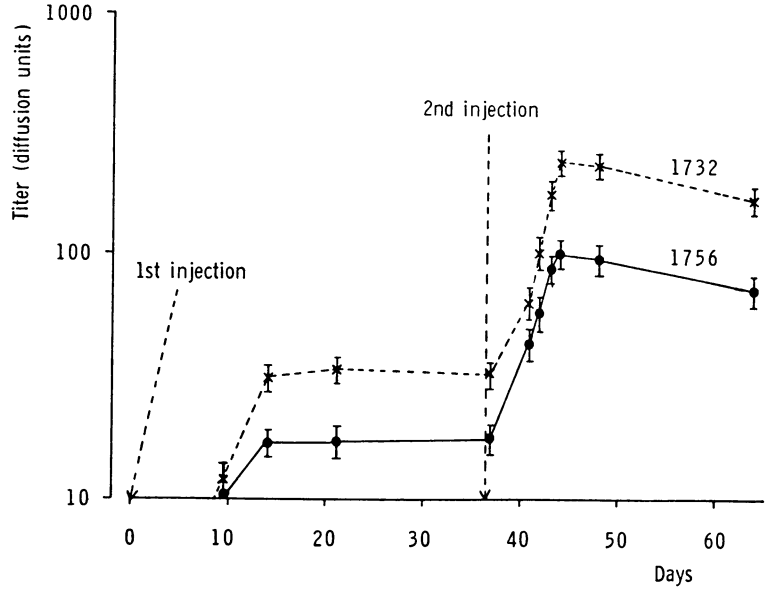

Figure 1. Titer curves for 2 groups of half sibs injected twice with human serum albumin. Vertical bars are standard errors.

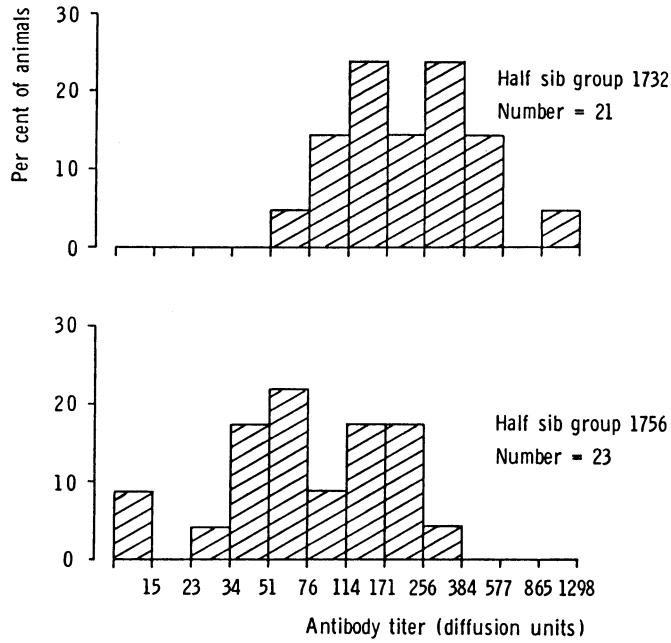

Figure 2. Frequency distribution (semilogarithmic) of peak level of secondary antibody response to human serum albumin for 2 groups of half sibs.

the course of the response curve. Fig. 2 presents the peak titer of the secondary response for the same groups of animals, the differences between groups again being highly significant ($P < 0.005$).

Two groups of half sibs which particularly contributed to the intergroup variation in the immunoglobulin level are presented in Fig. 3. They differed significantly with regard to the level of Ig0 ($P < 0.01$). Significant differences within pairs of groups in respect of Ig1 were also revealed.

However, all the above presented group differences should be considered only as tendencies as they include age effect and are based on the comparisons of extreme pairs of groups.

In order to separate the effect of age from that of sires the method of least squares was used on a material comprising all 137 bulls (15 groups of half sibs and 5 age groups). The analysis confirmed the assumption of genetic influence, as significant differences between groups of half sibs in respect both to the

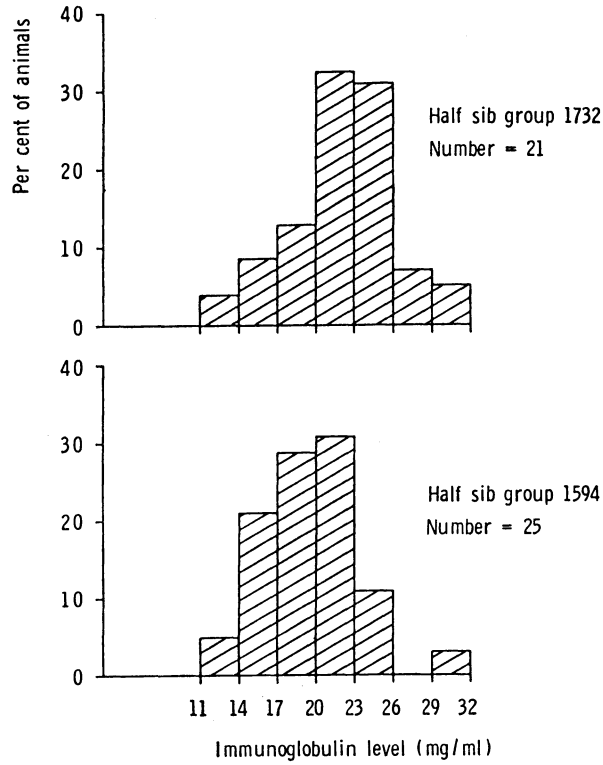

Figure 3. Frequency distribution of serum immunoglobulin level for 2 groups of half sibs.

antibody titer as well as to the serum immunoglobulin level were revealed. Consequently, some of the immunological traits in question turned out with heritability estimates significantly different from zero (Table 4). The results demonstrate a genetic influence on both the total immunoglobulin level and the antibody response, with the influence on the primary response as the strongest one. As for the primary response, the antibody titer at certain points of time (Ti02 and Ti03) seemed to be under genetic influence to a far greater extent than was the case with the peak titer.

Effect of age

The influence of age on the character "per cent responders" (Table 2) seemed obvious, the oldest animals having a much higher percentage than the youngest ones ($P < 0.005$). The same

Table 4. Heritability estimates (h^2) for some immunological traits in bulls immunized with human serum albumin.

Trait*		Heritability (h^2)		± standard error	Level of significance (P)
Primary response	Ti02	0.56	±	0.33	0.005
	Ti03	0.31	±	0.31	0.06
	Ti (p-peak)**	0.14	±	0.19	0.12
Secondary response	Ti07	0.15	±	0.19	0.11
	Ti08	0.16	±	0.19	0.10
	Ti (s-peak)**	0.18	±	0.21	0.09
Immunoglobulin level	Ig0	0.54	±	0.34	0.01
	Ig1	0.26	±	0.27	0.07

* See MATERIALS AND METHODS.
** Primary and secondary response peaks, respectively.

tendency is indicated in Table 3, the oldest animals being the best responders with regard to the titers Ti02 and Ti07. However, the influence of age on the immunoglobulin level appeared more obscure. The analysis of least squares, which included all 5 age groups, confirmed these tendencies, the age effect on response being significant ($P < 0.02$). On the other hand, no significant influence of age on the total immunoglobulin level could be demonstrated.

Fig. 4 presents the relationship between age and antibody response, which seemed to be a curvilinear function.

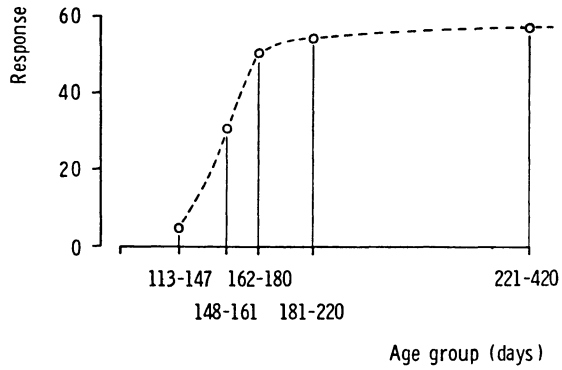

Figure 4. Relationship between age and antibody response in bulls immunized with human serum albumin. The criterion of response capacity is the peak titer of the secondary response. Graphically this is expressed as percentage of animals in each age group with peak titers above the mean level for the total number of animals.

Correlations between immunological traits

Table 5 presents some estimates of simple correlations between some of the immunological traits within the single animal. The results suggest positive correlation between antibody response and serum immunoglobulin level, irrespective of whether the immunoglobulin assays were carried out before or after the immunization (Table 5, I—IV). A positive correlation between primary and secondary response titers was also found to exist (Table 5, V). Although the Ig1 level for the total bull material was found to be significantly higher than Ig0 ($P < 0.001$, Table 3), the analysis stated a highly significant correlation ($P < 0.001$) between these immunoglobulin levels (Table 5, VI).

Table 5. Mean correlation coefficients (r) between some immunological traits in bulls immunized with human serum albumin. All estimates are significant at the level of 5 %.

No.	Trait 1*	Trait 2*	Mean correlation
I	Ti01—Ti03**	Ig0	0.37
II	Ti05—Ti08**	Ig0	0.28
III	Ti01—Ti03	Ig1	0.25
IV	Ti05—Ti08	Ig1	0.35
V	Ti01—Ti03	Ti05—Ti08	0.48
VI	Ig0	Ig1	0.41
VII	Ti01—Ti03	$\frac{1}{t}$ (p)***	0.85
VIII	Ti05—Ti08	$\frac{1}{t}$ (s)***	0.92
IX	Ti01—Ti03	Ti (p-peak)	0.57
X	Ti05—Ti08	Ti (s-peak)	0.69

* See MATERIALS AND METHODS.

** Titers of the rising phases of the primary and the secondary response, respectively.

*** Rate of antibody production for the primary and the secondary response, respectively.

In Fig. 5 idealized titer curves for "high" and "low" responders are presented. These curves indicate some relationship between rate and magnitude of the antibody response. The reciprocal value of the period of time ($\frac{1}{t}$) from the point of immunization till the antibody titer reached a certain level (TiC) was used as a criterion for rate of antibody production. With regard to the secondary response, the rate had to be determined with

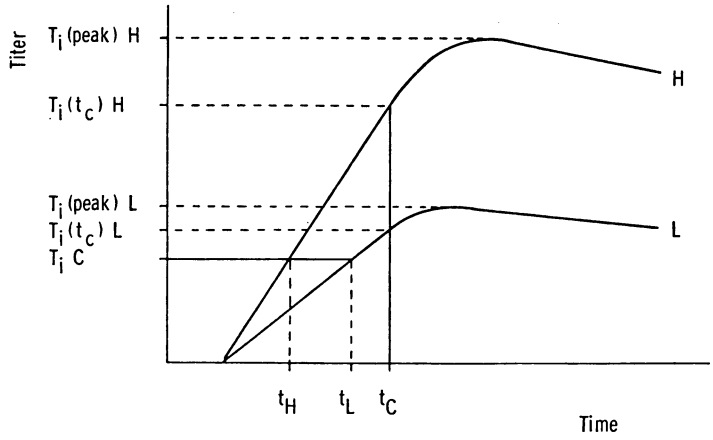

Figure 5. Approximation of relationships between rate and magnitude of the antibody response.

H and L: High and low responders, respectively.

Ti(peak)H and Ti(peak)L: Peak titers.

Ti(t_C)H and Ti(t_C)L: Titers at a certain point of time (the time of blood sampling).

TiC: A certain level of the antibody titer.

t_H and t_L: The periods of time from immunization till the titers reach a certain level.

t_C : A certain point of time related to the time of blood sampling.

correction for differences in antibody levels due to the primary response. This correction was done by calculating the rate within groups of animals with approximately the same titers prior to the second immunization. The overall mean correlation between this rate and the antibody titers at certain points of time in the rising phases of the response curve was found to be very high (Table 5, VII and VIII). For the primary as well as the secondary response positive correlations were found between the titer at a certain point of time and the peak titer (Table 5, IX and X).

DISCUSSION

The heritability estimates of the immunological traits investigated here correspond fairly well with the results from several genetic analyses in small animal models (*Stiffel et al.* 1974, *Siqueira et al.* 1976, *Feingold et al.* 1976), from family studies in man (*Grundbacher* 1974) and from immunogenetic surveys in herds (*Jensen & Christensen* 1975).

The main reason for the big errors and the wide range of

heritability estimates (0.14—0.56) in this study is the very limited material. On the other hand, significant heritability estimates out of 137 observations require strictly standardized environmental conditions. It should be emphasized that this point is the main advantage of the bull material in this study.

Among points of possible interest from this study is also the finding that the primary response seemed to be under genetic influence to a greater extent than the secondary response (Table 4). However, since the response is subject to genetic control at 2 independent levels: antigen recognition (the ability to respond) and antibody synthesis (magnitude of response), this finding is perhaps not unexpected. The qualitative level is undoubtedly more distinctly expressed through the primary response than through the secondary one, even if both responses are recorded as quantitative traits. This point of view is also supported by the observation that the primary response in this experiment to a larger extent than the secondary one acted as a trait with tendencies towards a classification into groups of "responders" or "non-responders". In mice similar "qualities" have been comprehensively studied through antibody responses to simple synthetic antigens. Those responses have been characterized as traits which are under a dominant, determinant-specific type of genetic control (*McDevitt & Tyan* 1968). These traits, though quantitatively recorded, are inherited in a Mendelian way and probably controlled by a limited number of immune response (Ir) and cell interaction (CI) genes which in the mouse are closely related to the major histocompatibility complex (H-2) (*Katz* 1977). The specific nature of the Ir controlled responses in mice cannot directly be compared with the general and more unspecific responsiveness to the rather complex antigen in the present experiment. However, the main point is that both the specific level of response, antigen recognition, as well as the unspecific one, antibody synthesis, even in this experiment do exist. Secondly, there are undoubtedly differences between the primary and the secondary response regarding to what extent these levels are observed. In the secondary response the quantitative level of reaction (magnitude of response) is the predominant one. Consequently, this response is recorded as a typical quantitative and determinant-nonspecific trait which is, to a larger extent than the primary one, modified by polygenes and environmental factors. The rather low correlation found

between the primary and the secondary response supports this theory (Table 5, V), indicating that the primary and the secondary response in this particular experiment to a certain degree might be different characters or at least characters with different degree of genetic control.

The answer to whether the primary or the secondary response should be the best criterion for the general immune defence, can be given by correlation to disease data. However, with only one immunogen of medium complexity used, there is reason to believe that the general responsiveness, which is predominantly expressed through the secondary response, would be the most useful criterion. On the other hand, by the use of various simple immunogens, specificity patterns might be more easily revealed through the primary response. These patterns could make it possible to differ between groups of half sibs in a way that might be of great value in the characterization of the immune system together with traits of general responsiveness.

The high correlation stated between the rate of production and the titer at a certain point of time (Table 5, VII—VIII), justifies the use of the last-mentioned character as criterion of production rate. This particular trait is more easily available because the certain point of time is defined in relation to the time of blood sampling. Moreover, the titer at a certain point of time might even be the best criterion for the response capacity in general as, in the rising phase of the response curve, it includes both the magnitude and the rate of reaction.

Another point to be underlined is the finding that the primary response titers at certain points of time were under genetic control to a higher degree than was the primary response peak (Table 4). This could be explained with the suggestion that the rate of production, which was found to be strongly expressed through the titer at a certain point of time, is more a character of quality than is the peak of the response. With regard to combating infections, this finding might perhaps be of interest. A high rate of antibody production might in that case be of greater value than a high antibody titer.

The repeatability of the total immunoglobulin level within animals which is expressed through the correlation between Ig0 and Ig1 (Table 5, VI) corresponds fairly well with the heritability (h^2) estimates of this character. The repeatability can be regarded as the upper limit of the heritability, and therefore it is likely to suggest that the true value of h^2 is situated below

this level. There is no contradiction between this conclusion and the heritability estimate for Ig0.

It is reasonable to consider the immunoglobulin level as resulting from multiple specific antibody responses to naturally occurring immunogens. Consequently, the positive correlation stated between the anti HSA response and the immunoglobulin level, both prior to and after the immunization, is not unreasonable (Table 5, I—IV). However, only further studies including correlations to disease data can give the answer to whether immunoglobulin levels or single specific responses are the most useful markers for the general immune defence against infectious diseases. The finding of a significantly elevated immunoglobulin level (Table 3) in the course of the specific antibody response to HSA may be interpreted in an analogous way. It is possible that the specific response to HSA is one reason for this elevation as the titers of the secondary response were found to be correlated with Ig1 to a larger extent than with Ig0 (Table 5, II and IV). Alterations of environmental conditions and conditions related to the animal (age) might also explain the difference between Ig0 and Ig1 to some extent. However, the main point to be underlined is that the antibody response as a whole seems to be correlated with Ig0 to a degree as large as that with Ig1.

With regard to the estimated age effect on the antibody response, the tendency illustrated in Fig. 4 might be of interest in connection with vaccination programmes. Based on the assumption that responses to different antigens are well correlated (*Siqueira et al.* 1976, 1977), it might be assumed that the bulls develop their response capacity within approx. 180 days of age. On the other hand, it is well known that several antigens induce poorly correlated responses. Consequently, this finding should not be considered conclusive.

The findings reported here might to some extent contribute to the understanding of immunity and genetics in cattle. A matter of greater importance in this field of work, however, is to find out if and to what extent the genetically controlled immunological traits are correlated to disease resistance. Consequently, a comprehensive and systematic characterization of the general immune defence of the bulls through further immunogenetic studies is necessary. Moreover, correlation analyses between all investigated traits in the bulls and the frequency of infectious diseases in their half sibs and offspring from dairy herds have

to be carried out to reveal genetic markers of disease resistance. There is reason to believe that in some future, immunogenetic markers will be included in the breeding value of bulls in order to accelerate the genetic progress in disease resistance of cattle.

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SAMMENDRAG

Genetisk analyse av noen immunologiske karakterer hos ungokser.

Etthundreogtrettisju ungokser fra en testingsstasjon i alderen fra 113 til 420 dager ble immunisert to ganger subkutant med humant serum albumin (HSA). Antistofftiteret mot HSA samt det totale serum immunoglobulinnivå ble kvantifisert ved radial diffusjon. Arvbarhetsestimatene tyder på en genetisk innflytelse på såvel immunoglobulinnivå som på den spesifikke antistoffrespons mot HSA. Denne innflytelsen synes å være sterkest på den primære antistoffrespons.

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Reprints may be requested from: Øystein Lie, the National Veterinary Institute, P.O.Box 8156 Dep., Oslo 1, Norway.