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Further studies on inherited susceptibility to Friend mouse leukemia virus

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1. INTRODUCTION

The resolution of host response to Friend virus (FV) into simple Mendelian models has been attempted with inbred strains of mice. Various mating combinations suggest at least three forms of gene expression for susceptibility: complete dominance (Odaka & Yamamoto, 1962), co-dominance (Axelrad, 1966) and recessiveness (Franker & Quilligan, 1966).

It has been suggested that these disparities may be a function of either the strain or dose of virus used in genetic assay. (DBA/2 × C57BL) F_1 hybrid mice are resistant to a 'parental' strain of FV but susceptible to a mutant strain as described by Lilly (1967). The susceptibility of (RF × C57BL) F_1 hybrids is similar to parental RF mice at one dose of virus (Odaka & Yamamoto, 1962) in contrast to their intermediate susceptibility at other dose levels (Axelrad, 1966).

Evidence that the resistance of (DBA/2 × C57BL) F_1 mice to one strain of FV is independent of the dose of virus and is probably due to a genetic threshold is presented here.

2. MATERIALS AND METHODS

Virus inocula used in these experiments were obtained from spleen brei as described by Fieldsteel, Dawson & Bostick (1961) after propagation by nineteen consecutive passes in mice of the DBA/2/Crgl sub-line. Dilutions (1:10, 1:100, 1:500) were made in phosphate buffered saline and ampoules containing aliquots of each dose were stored at −60 °C until used. The 1:10 dilution was equivalent to $10^{4.3}$ ID 50 for DBA/2 mice.

F_1 and subsequent generations were obtained by mating randomly selected individuals of the C57BL/Crgl and DBA/2/Crgl sub-lines and backcrossing twice to the DBA/2 parent strain.

F_1 and BC_1 progeny receiving each of the aforementioned virus doses were inoculated intraperitoneally at 21–24 days of age according to a previously outlined protocol (Franker & Quilligan, 1966). Splenic enlargement 21 days after infection was chosen as the continuous variable to measure host-mediated variance. In the second experimental series with BC_2 progeny obtained from 9 DBA♀ × BC_1♂ and 14 BC_1♀ × DBA♂ matings, this protocol was repeated with the 1:10 dilution of virus.

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Throughout this study the maximum number of animals per cage during the post-inoculation period was four in an attempt to reduce possible fluctuation in body/spleen weight ratios.

3. RESULTS AND DISCUSSION

The spleen-weight distribution of F_1 progeny at each virus dilution are shown in Fig. 1. These histograms closely resemble distributions consistently obtained with

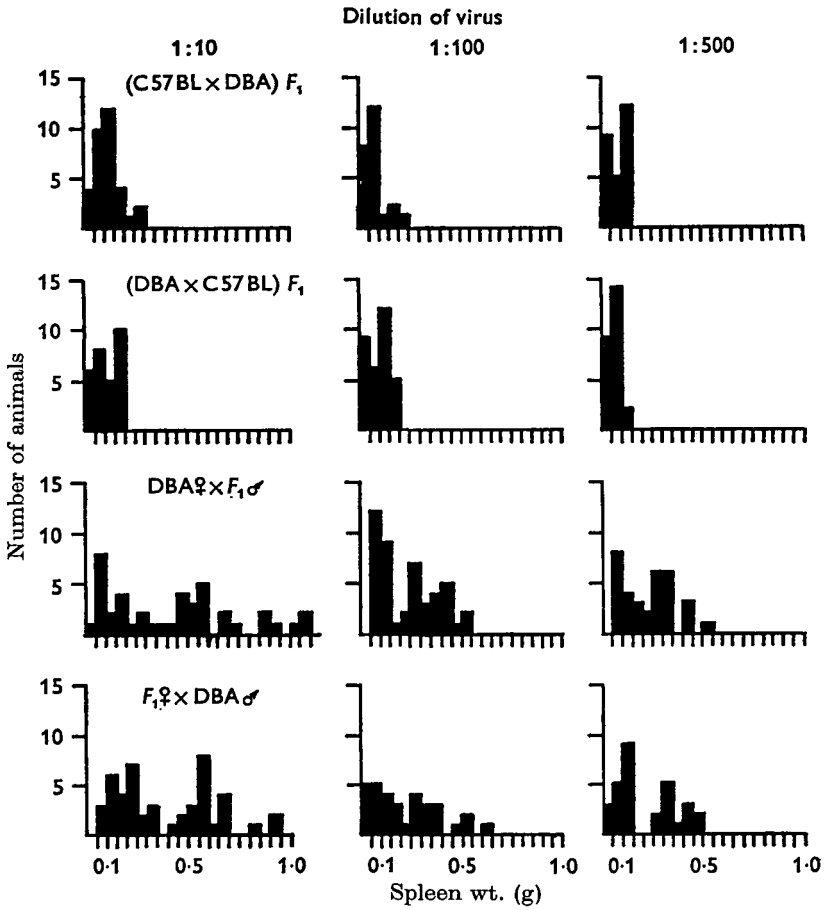

Fig. 1. Spleen weight distribution of F_1 and BC_1 progeny from reciprocal mating combinations 21 days after inoculation with three dilutions of DBA-derived Friend virus. Class values are 0·05 g.

parental C57BL mice at similar and higher doses of virus and represent non-significant deviations from normal spleen weights. The doses of virus used in these experiments induce spleen weights of 1·5 g or greater in 95% of parent DBA/2 mice.

The contribution of DBA-mediated susceptibility becomes apparent in the distributions shown for BC_1 progeny (Fig. 1). Meaningful interpretation is possible when these data are combined as in Table 1. There are two distinct modes in each

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distribution. All three distributions include a mode at the class value representing spleen weights of 0·05–0·09 g. Distributions about these low modes include individuals phenotypically similar to F_1 hybrids and therefore constitute resistant progeny. Differing class values are found for the other mode at each dilution (0·55–0·59, 0·25–0·29 and 0·30–0·34 for the 1:10, 1:100 and 1:500 dilution respectively). The distributions about these high modes should include susceptible

Table 1. *Virus dose and combined spleen weight distribution of BC_1 progeny*

Spleen wt. (g)	Number of progeny per class value		
	Dilution of virus		
	1:10	1:100	1:500
< 0·05	1	5	3
0·05–0·09	11	17	11
0·10–0·14	8	13	13
0·15–0·19	8	4	3
0·20–0·24	8	3*	2*
0·25–0·29	4	11	8
0·30–0·34	4	6	11
0·35–0·39	1*	7	1
0·40–0·44	2	5	6
0·45–0·49	6	2	2
0·50–0·54	6	4	1
0·55–0·59	13	—	—
0·60–0·64	1	1	—
0·65–0·69	6	—	—
0·70–0·74	1	—	—
0·75–0·79	—	—	—
0·80–0·84	1	—	—
0·85–0·89	2	—	—
0·90–0·94	3	—	—
0·95–0·99	—	—	—
1·00–1·04	1	—	—
1·05–1·09	2	—	—

* Intermodal point of division between resistant and susceptible progeny.

progeny. Because the extent of overlap in the bimodal distributions is small, separation of two groups of progeny may be made at the intermodal class value with the lowest frequency. This point of separation is at the 0·35–0·39 class for the 1:10 dilution and at the 0·20–0·24 class for the 1:100 and 1:500 dilutions. Dividing each distribution at the corresponding intermodal value gives almost equal numbers of resistant and susceptible animals, in agreement with the expectation of the 1:1 segregation hypothesis.

The suggested single gene difference between parental DBA/2 and C57BL mice was further tested by measuring the response of BC_2 progeny as outlined in Materials and Methods. Progeny from BC_1 parents heterozygous for C57BL-resistance would be segregating and families of such lineage would include both resistant and susceptible animals. Families without the C57BL 'gene' would be non-segregating and include no resistant progeny.

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Table 2. *Spleen weight distribution within BC_2 families receiving 1 : 10 dilution of virus*

Family no.	Spleen wt. mean (g)	Number of progeny per class value (0·10 g)														
		0·10	0·10	0·20	0·30	0·40	0·50	0·60	0·70	0·80	0·90	1·00	1·10	1·20	1·30	1·40
1	28·3	—	3	1	—	1	1	—	—	—	—	—	—	—	—	—
2	29·8	2	4	—	2	—	1	—	—	—	—	—	—	—	—	—
3	32·0	1	2	1	—	—	—	2	—	—	—	—	—	—	—	—
4	38·8	—	5	—	—	1	—	—	—	1	—	1	—	—	—	—
5	42·7	1	1	1	—	—	4	1	—	—	—	—	—	—	—	—
6	45·8	2	—	1	—	—	—	—	1	—	—	1	—	—	—	—
7	46·7	—	2	2	—	—	—	—	—	1	—	—	—	1	—	—
8	49·4	1	2	—	—	—	—	—	—	—	1	—	1	—	—	—
9	57·0	—	—	3	—	—	—	—	—	1	—	—	—	1	—	—
10	58·3	—	1	—	2	—	—	1	—	1	—	—	1	—	—	—
11	62·1	—	1	1	—	—	—	2	2	—	—	—	1	—	—	—
12	63·5	—	—	—	—	2	1	2	1	—	1	—	—	—	—	—
13	72·5	—	—	1	—	—	—	—	4	3	—	—	—	—	—	—
14	73·0	—	—	—	—	—	2	1	—	1	—	1	—	—	—	—
15	73·3	—	—	—	—	—	1	—	1	2	—	1	—	1	—	—
16	73·3	—	—	—	1	1	—	—	—	2	2	—	—	—	—	—
17	75·0	—	—	—	—	—	2	2	—	2	—	—	1	—	—	—
18	76·4	—	—	—	—	1	2	—	—	2	—	2	—	—	—	—
19	77·2	—	—	—	—	3	—	1	1	1	4	—	1	—	—	—
20	78·3	—	—	—	—	—	1	—	3	1	—	1	—	—	—	—
21	87·0	—	—	—	—	—	1	—	—	1	2	1	—	—	—	—
22	113·0	—	—	—	—	—	—	1	1	1	—	—	1	—	—	1
23	117·0	—	—	—	—	—	—	1	—	—	—	—	1	1	1	1
	Totals	7	21	11	5*	9	16	14	14	20	10	8	7	4	1	2

* Intermodal point of division between resistant and susceptible progeny.

Family spleen weight means and the distribution within each BC_2 family (the wide range of variates makes a larger class value necessary) are shown in Table 2. The distribution for all BC_2 progeny is bimodal with a low mode (0·10 g class) for resistant individuals, a high mode (0·80 g class) for susceptible animals and a point of division at about 0·35 g. Families containing individuals on both sides of this intermodal point should be segregating. If this is done it will be found that families 1–11 and 13 are segregating and the remaining 11 families are non-segregating. Using this method the probability of misclassification is small. For families of five the probability is about 3 %. Since the average family size here is 6·5, the probability of misclassification is less than 3 %.

Within segregating BC_2 families an expected ratio of 1 : 1 for resistant : susceptible animals is computable despite the ambiguity of genotype in mice with spleen weights ranging from 0·30–0·40 g. There are 39 resistant and 32 susceptible with 4 unclassified. Omission of this small number (less than 6 %) does not alter the Mendelian expectation.

Unlike data from a relevant study (Bloom & Falconer, 1964), suggestion of clear-cut monofactorial control of susceptibility is precluded. Spleen weight mean of the BC_2 susceptible progeny receiving the 1 : 10 dilution of virus is $0{\cdot}828 \pm 0{\cdot}01$ g in contrast to a mean of $0{\cdot}593 \pm 0{\cdot}01$ g for BC_1-susceptible animals. These means differ significantly ($P = < 0{\cdot}01$) and this difference suggests the presence of genetic modifiers.

A second Mendelian unit for susceptibility (Lilly, 1967) cannot be inferred from these data. Analysis of the inheritance of a continuous variable as described here does not permit resolution beyond the single gene difference with any meaningful accuracy.

SUMMARY

Analysis of F_1, BC_1 and BC_2 progeny from matings of inbred DBA/2 and C57BL mice confirm the existence of a single major gene for C57BL-resistance to Friend virus. The doses of virus used did not obscure expression of this Mendelian unit.

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