# STRAIN VARIATION IN MICE

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Everyone reading these papers already knows that there are a number of uniform strains of mice maintained in Great Britain. Of these the Laboratory Animals Centre maintains, according to the Catalogue of Uniform Strains, nine inbred and one random bred strain and in practice has one or two more strains that have been acquired recently. It has been my task for the past 3 years to investigate the differential characteristics of some of these strains of mouse.

Preliminary work on the response of mice from a number of our strains to histamine acid phosphate, after sensitising with pertussis vaccine and to insulin, after 24 hr. deprivation of food, gave the results shown in Fig. 1.

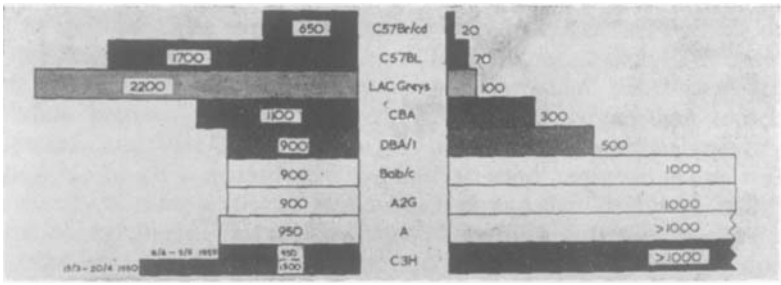


Fig. 1. Comparative sensitivities of some mouse strains for insulin and histamine acid phosphate.

In this work I used approximately equal numbers, usually between 20 and 30, of each sex of mouse, from 6 to 8 weeks of age. I estimated the approximate LD50 and ED50 of each strain by probit plots, and or Karber's method, and the histograms show the average obtained for two or three tests. It was not determined whether the difference between the ED50 of the two samples of $C_3H$ mouse was significant. Two further points of interest should be noted from the figure. The first is that the C57Br/cd mice are the most sensitive for both responses, and the second that the three white strains of mouse resemble one another in each response, possibly due to their derivation.

The lack of relation between the order of magnitude of these quantal responses in any one strain of mouse has been the stimulus for more extensive work. This has been done using strains of mouse and their $F_1$ hybrids in a study of quantal response to insulin and of quantitative response to pentobarbitone sodium. Experimental conditions were arranged to be the same for all mice used on any one day. Not more than 5 or less than 4 mice were allowed to react to insulin in one jar, and not more than 5 mice were housed in one box between tests of response to

pentobarbitone sodium. The animal room was maintained at a temperature of 70° ± 2° F. The work on both these responses has defined the necessity for using mice of known weight, sex and age when investigating differential characteristics.

In considering weight of mouse in the quantal response to insulin, significant, or closely approaching significant correlations were found of the combined results for ED50, and of the mean slopes with mean strain weight, so that a rough assessment of the reaction of a strain to this response could be made from mean strain weight. In the response to pentobarbitone sodium, for one strain of mouse, the correlation of sleeping time with weights of mouse was such, that it seemed reasonable to adjust the mean sleeping times for body weights by co-variance analysis for all strains used.

TABLE I

COMPARISON BETWEEN THREE HYBRID STRAINS OF MICE FOR DIFFERENCE IN PATTERN OF RESPONSE AND IN ED50

P = probability D = difference

| Strain | Pattern of response $BrA2F_1 > A2CF_1$ and $CA2F_1$ | | Mean ED50 |
|---|---|---|---|
| | P | D | |
| $BrA2F_1$ | | | 885 |
| $A2CF_1$ | 0·02 | + | 1,190 |
| $CA2F_1$ | 0·001 | +++ | 1,100 |

$BrA2F_1$ = C57Br/cd (F) × A2G (M).
$A2CF_1$ = A2G (F) × CBA (M).
$CA2F_1$ = CBA (F) × A2G (M).

Sex effect in the response to insulin is apparent from the significant qualitative difference in the pattern of response within certain strains between males and females. Pattern of response between strains is also significantly different, and I postulated for the LAC grey mice a relation between sensitivity and pattern of response. This is now confirmed for the $F_1$ strains in Table I and between the sexes of the $F_1$ strains in Table II.

TABLE II

COMPARISON BETWEEN THE PATTERN OF RESPONSE AND THE MEAN ED50 FOR MALES AND FEMALES IN FOUR HYBRID STRAINS

P = probability D = difference

| Strain | Pattern of Response M < F | | Mean ED50 | |
|---|---|---|---|---|
| | P | D | M | F |
| $A2BrF_1$ | 0·2 | — | 999 | 946 |
| $BrA2F_1$ | 0·7 | — | 882 | 877 |
| $A2CF_1$ | 0·1–0·001 | +++ | 1,230 | 973 |
| $CA2F_1$ | <0·001 | +++ | 1,142 | 1,014 |

$A2BrF_1$ = A2G (F) × C57Br/cd (M). $A2CF_1$ = A2G (F) × CBA (M).
$BrA2F_1$ = C57Br/cd (F) × A2G (M). $CA2F_1$ = CBA (F) × A2G (M).

An interesting negative confirmation is given in Table III. It is not proven that an unequal balance of sex in the mice used for this response

would affect the results of an assay, but it is significant that for all the $F_1$ strains in Table IV the male mice have the greater slope of regression between dose and response. The hypothetical strain of mouse having male and female slopes equal to the average slopes for the $F_1$ strains and the variance of the difference calculated from the $F_1$ strains variance, has a significant difference between male and female slopes. For the response to pentobarbitone sodium a sex difference develops with age, showing that for such reactions a knowledge of both the age and sex of the animals is important.

TABLE III

COMPARISON BETWEEN THE PATTERN OF RESPONSE AND THE MEAN ED50 OF THE HYBRID A2DB/1$F_1$, AND ITS PARENTS

P = probability D = difference

| Strain | Pattern of response A2DB/1$F_1$ = A2G and DBA/1 | | Mean ED50 |
|---|---|---|---|
| | P | D | |
| A2DB/1$F_1$ | | | 890 |
| A2G | 0·05–0·1 | — | 885 |
| DBA/1 | 0·05–0·1 | — | 875 |

TABLE IV

SLOPES OF THE RESPONSE TO INSULIN FOR THE MALE AND FEMALE MICE OF FOUR $F_1$ HYBRID STRAINS

| Strain | Mean slope M | Variance M | Mean slope F | Variance F |
|---|---|---|---|---|
| A2Br$F_1$ | 1·597 | 0·789 | 1·105 | 0·267 |
| BrA2$F_1$ | 3·455 | 0·975 | 1·996 | 0·140 |
| A2C$F_1$ | 2·871 | 0·342 | 1·784 | 0·586 |
| CA2$F_1$ | 1·453 | 0·310 | 0·545 | 0·318 |
| Average | 2·344 | | 1·358 | |

Hypothetical strain of mouse comprising four hybrid strains.
Significant difference M slope > F slope 0·02 > P > 0·01.

Having settled that animals of known weight, sex and age must be used, it is possible to view general strain differences. The strain difference in sensitivity to insulin has already been seen in Fig. 1. The strain difference in the precision of this response is shown in Table V. It is important that no significant within strain difference in parallelism was found, but between strain differences were apparent and significant when within strain variance was low. Of the hybrid strains the crosses between the A2G and CBA strains were interesting in that each resembles its maternal parent more closely. That between DBA/1 and A2G strains is interesting in that it resembles neither parent. A correlation of ED50 and slope of regression for this response that has been previously published brings out clearly the genetic relation between the strains of this species (Fig. 2). With the quantitative response to pentobarbitone sodium it was necessary

to consider not only the weights, sex and age of the mice but also the homogeneity of the variance of their response. The heteroscedasticity of the groups was such that significant difference was defined at a level of

TABLE V

SUMMARY OF THE COMPARISON OF THE PARALLELISM OF THE REGRESSION BETWEEN THE CONVULSIVE RESPONSE AND THE DOSE OF INSULIN BY MEANS OF THE $\chi^2$ summation for FIRST TEST ONLY

P = probability D = difference

| Strains | No. of tests | Mean slopes | Within strain comparison | | Between LAC grey mice and other strains | |
|---|---|---|---|---|---|---|
| | | | P | D | P | D |
| Inbred | | | | | | |
| A2G | 6 | 1·929 | 0·5 | — | 0·01–0·001 | +++ |
| A2G | 2 | 1·962 | 0·1–0·2 | — | 0·1–0·2 | — |
| CBA | 3 | 0·905 | 0·1–0·2 | — | 0·2–0·3 | — |
| DBA/1 | 2 | 2·842 | ca 0·5 | — | 0·02–0·05 | + |
| Hybrid | | | | | | |
| $A2CF_1$ | 3 | 1·815 | 0·2–0·3 | — | 0·1–0·2 | — |
| $CA2F_1$ | 3 | 0·985 | 0·8–0·9 | — | *ca* 0·99 | — |
| $BrA2F_1$ | 3 | 1·825 | 0·99 | — | *ca* 0·05 | + |
| $A2BrF_1$ | 2 | 1·625 | 0·2–0·3 | — | 0·7–0·8 | — |
| $A2DB/1F_1$ | 2 | 1·283 | *ca* 0·8 | — | 0·99 | — |

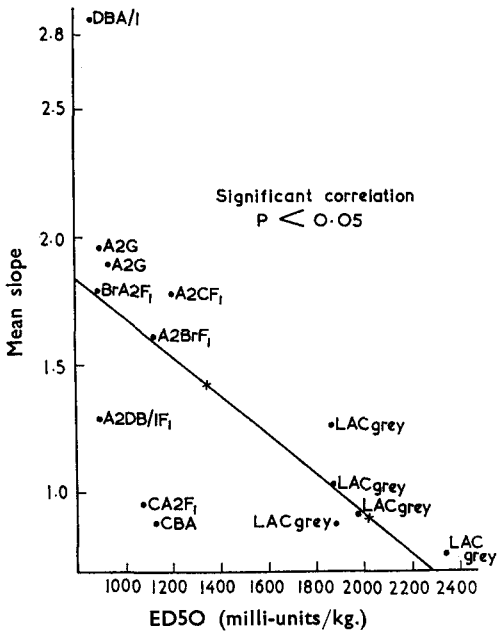


FIG. 2. Correlation of ED50 and mean slope of the regression in some strains of mouse.

probability 0·001. Fig. 3 shows the differences obtained in sensitivity and precision for some inbred and hybrid strains as compared with the

A2G strain. There is some indication that for this response both sensitivity and precision in parent strains are reflected in these characteristics of the hybrid strains.

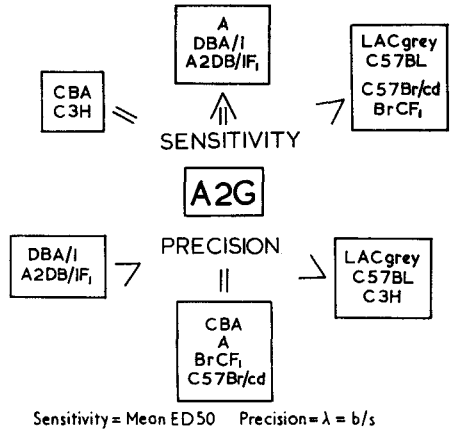


FIG. 3. Comparison of the sensitivity and precision of the response to pentobarbitone sodium in the A2G strain with that in other uniform strains of mouse.

In conclusion it may be said that uniform strains of mice vary significantly in their quantal and quantitative responses. Both the order of sensitivity of these responses and their precision must be determined empirically for each strain, in mice with known weight, and of similar age and sex.