The remaining five days records were omitted from analysis. I calculated the variances using the data which they excluded and found the combined variances (with the degrees of freedom in parentheses) to be: 0·0346 (45) for *C57BL*; 0·0849 (43) for *C3H*; 0·0396 (44) for the F_1 hybrid; and 0·0213 (44) for 'Mousery' animals. The variance for the F_1 hybrid is smaller than that for the *C3H* strain, but greater than that for *C57BL*, although not statistically significant. The variance for the 'Mousery' mice appears to be the smallest among them. The relative order is obviously different from that which they obtained (estimate of variance: 0·0552 for *C57BL*; 0·0778 for *C3H*; 0·0165 for F_1 hybrids; and 0·0176 for 'Mousery') based on two-days records. However, perhaps their selection of data was due to their lack of understanding of the biological nature of the experiment.

The other ten papers cited by Biggers, McLaren and Michie dealt with normal variation and not with variation of biological responses. Such data might be a basis for speculation, but could not be 'definitive' evidence for conclusions about biological responses. There seems to be a lack of distinction between normal variation and biological response.

It is clear that at the present time no one has sufficient amounts of critical evidence for the generalization which these investigators have made. It is true that Mather suggested the possibility of using F_1 hybrids in bio-assay, and Lerner pointed out that heterozygotes have better self-regulating ability than homozygotes. Moreover, I believe that under ordinary environmental conditions and without treatment, the F_1 hybrids may be more homogeneous in morphological traits than inbreds, but to equate this morphological homogeneity with response to chemical or biological stimuli requires further experimental evidence.

It is well established that there are species differences in sensitivity and that, in bio-assay, preference is given to certain species for certain assays; for example, metamorphosis in the tadpole for assay of thyroid hormone; comb-growth of chicken for androgen; crop-gland secretion of pigeon for lactogenic hormone; and uterus growth in mice for œstrogen. I believe that there are differences also in sensitivity between races, breeds and strains within species as well. Indeed, some differences have been shown to exist between mouse strains, as already illustrated in my article in *Nature*, **185**, 514; 1960. Inbred strains can be very useful for assays of certain substances. This has been well illustrated and discussed by Becker and Berg (*Poultry Sci.*, **38**, 362) in a paper in which they compared inbred and hybrid chickens in high and low planes of nutrition.

Finally, I reiterate that I do not underestimate the potentiality of F_1 hybrids for use in bio-assays. It has been claimed that the heterozygotes are better 'buffered' than the homozygotes, but differences between them in the mechanisms of reactivity are poorly understood. Our understanding of genetic pathways in the polygenic systems are practically nil, and reliable data from comparisons in bio-assay values between inbreds and F_1 hybrids are limited. Assay substances from synthetic and biological sources are numerous, and their end-points in assay vary widely from physiological and morphological measurements to rates of survival. In these circumstances, it seems wise to use an empirical approach, as I have, rather than to draw conclusions which might mislead the experimenter into believing that there is more evidence available for his making a choice of animal material than actually exists.

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Dr. Chai has now raised a criticism of an earlier paper of ours (*J. Genet.*, **54**, 440; 1956). As explained in the paper in question, estimates of variance of response derived from animals which have acquired a degree of resistance through previous exposure to the drug have no simple interpretation. Our "selection of data" consisted of using only estimates of variance derived from mice not previously exposed to the drug. Furthermore, it is not statistically legitimate to pool variance estimates, as Chai has done, when the estimates are derived from the same mice on different occasions and when the responses on different occasions are correlated. As for Chai's distinction between "variation of biological responses" and "normal variation", in so far as these two categories can usefully be distinguished, it is not easy to see why they should not be subject to the same underlying mechanisms of genetic and developmental homœostasis. We have discussed these matters more fully elsewhere (*New Biol.*, **19**, 48; 1955).

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Development of resistance to drugs, particularly those affecting the central nervous system, is well known. The analysis which Drs. McLaren and Michie made, testing the significance of this, was not convincing, for their interpretation (that response to 'Nembutal' is affected by previous dose) was based on only part of their results. The primary concern in pooling or comparing variances of different groups should be that the variance is independent of the mean, not that there was, or was not, previous exposure to the drug. McLaren and Michie used the logarithmic scale for correcting the dependence of the variance on the mean. This transformation was not adequate, as they themselves stated, ". . . this applies too strong a correction and results in a negative correlation between variance and mean". When I analysed their results, I noticed that they pooled the variance-estimate in the two-day tests and compared the variances without considering that the means were different and the transformation not adequate. Transformation of data for biological responses is often a troublesome matter and it is difficult to obtain an adequate scale. I reiterate that although "variation of biological response" and "normal variation" may be subject to the same underlying genetic and developmental mechanisms, further experimental evidence is necessary before this can be accepted as fact. Furthermore, there is little information available regarding differences in variability between inbred and F_1 hybrids in characters which have different evolutional significance. Speculation with regard to homœostasis, a concept which is theoretical and controversial, should not be substituted for proof.

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