DROSOPHILA AS AN EXPERIMENTAL MODEL IN ANIMAL BREEDING RESEARCH

Drosophila comme modèle expérimentale dans la recherche en élevage animal

Drosophila als experimentelles Modell in der Tierzuchtorschung

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In quantitative genetic research ample justification exists for the use of laboratory animals in general (Chapman, 1951 and 1961; Robertson, 1959 and 1967a; Kojima and Kelleher, 1961; Roberts, 1965; Fredeen, 1966, and Falconer, 1967), and for Drosophila in particular (F. W. Robertson, 1956). However, there is need to remind ourselves, and our administrators, of the important place laboratory animals must hold in the application of genetics to animal production. This paper further demonstrates the usefulness of Drosophila research by mentioning some recent findings with obvious implications for animal breeding, and some present problems, the solution of which would be assisted by further laboratory work. Direct extrapolation of such results to specific livestock breeding programs is not implied and should be guarded against, as previous reviewers have stressed. However, the present state of quantitative genetics makes Drosophila an efficient tool to obtain a better understanding of the nature of quantitative genetic variation and to study the general behaviour of quantitative characters in populations where this variation is being manipulated.

THE NATURE OF GENETIC VARIATION

The complexity of quantitative genetic variation in Drosophila populations has been discussed by Latter (1969). The classical interpretation of this variation by statistical partitioning tells us very little of its nature at the gene level and, with all its associated problems of estimation and application is obviously of limited value in optimising breeding programs.

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To determine the adequacy of the many assumptions of present theory (see for example Clayton et al., 1957; Robertson, 1969, and Dickerson, 1970), and to suggest improvements, a better understanding of the properties of this variation is needed. The questions which require answers, for at least the major portion of the variation in the traits of interest, have often been put—for examples, see Robertson (1966b, 1967b and 1968). Essentially we wish to know the number of loci which contribute to this variation, the distributions of allelic frequencies, effects and dominance relations and the interrelations between the characters we measure and reproductive fitness. Present methods which can be used to obtain this information have been classified by Piper (1971) as:

1. Analyses of differences between pairs of lines utilising
   a) genetic markers without the assistance of methods of crossover suppression,
   b) as for (a) but with crossover suppression involving studies
      — on whole chromosomes, and
      — within chromosomes,
   c) back-crossing with inbreeding,
   d) back-crossing with selection,
   e) redefinition of the character, and
   f) statistical methods to determine simple and sufficient models.

2. Analyses of differences between individuals in random mating populations by
   a) estimating pleitropic effects of alleles at known loci.
   b) interpreting patterns of response to directional selection, and
   c) utilising higher order moments.

After evaluating these techniques Piper concluded that for most domestic animals only (1e), (2a), (1f) and (2c) have potential and for the former two procedures this will be realised only when linkage maps are much more complete. Yet with the above armoury of techniques and a good linkage map, Drosophila research to date has not satisfactorily interpreted the variation for a single quantitative character—see Frankham (1974) for examples of controversy. Much work and refinement of present techniques, if not new techniques, is required before we can successfully interpret problems being encountered in breeding programs and predict the consequences of specific breeding procedures on our gene pools.

THE BEHAVIOUR OF QUANTITATIVE CHARACTERS

Drosophila has proved a most valuable research tool in the primary examination of the adequacy of the assumptions in general quantitative genetic theory. From such tests, and to a lesser extent from exploratory studies not specifically designed to test any aspect of the theory, improvements to the theory have been suggested.

In the early generations of directional selection there is fair agreement between the simple theory and the observed response averaged over replicate populations.
(Barker, 1967), provided such populations have no history of artificial selection (Frankham et al., 1968b). Frankham (1968) also obtained good agreement between predicted and observed response to single-sex selection for a character having sex-dimorphism in scale and a genetic correlation between sexes of less than unity.

Throughout most breeding programs numbers of individuals will be restricted and there will be only one replicate. Recently some large studies using Drosophila have examined the influence of population size and selection intensity on response to mass selection and repeatability of response.

**Population Size and Selection Intensity**

Barker (1967 and 1969) in particular has detailed the implications of population size and selection intensity for breeding programs. Their influence in early generations is demonstrated by some results from large replicated studies of Frankham et al. (1968a) and Hollingdale and Barker (1971)—Table 1. For a fixed number of individuals scored, realised heritabilities were greater with less intense selection. These heritabilities increased with *parent population size*, but at constant parent size there was no consistent effect of selection intensity in the short term (not shown in the Table). Jones et al. (1968) extended the study of Frankham et al. showing that the long-term response, averaged over replicates, agreed in general with the theory and increased with increase in the product of the population size and standardised selection differential. Changes in the number scored had greater influence on total response than did change in selection intensity. They also observed that after a number of generations of selection restriction of population size considerably reduced total response. Further study (with sufficient population size and replication) of the pattern of response to intense selection and of optimum strategies for population size and selection intensity is required—see for example Robertson (1970b).

**TABLE 1**

| Selection intensity (%) | Number of individuals measured |  
|---|---|---|---|
|  | 100 | 200 | 400 |
| 10 | — | 15.5 | 13.4 |
| 20 | 13.1 | 18.0 | 15.8 |
| 40 | 17.1 | 20.3 | — |
| 50 | — | — | 22.5 |

<table>
<thead>
<tr>
<th>Number of Parents</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average of all intensities</td>
<td>14.6</td>
<td>16.2</td>
<td>18.3</td>
<td>22.5</td>
</tr>
</tbody>
</table>
In studies which have examined the influence of parent population size on response, the number of individuals sampled from the base population has generally equalled the number of parents each generation thereafter. In animal breeding programs selection probably has often commenced from a small founder sample and I suspect that this tendency is now being accentuated by recent international interest in 'exotic' genotypes. Thus the genetic variability available to selection is restricted from the outset. McBride (1965) and Barker (1967) stressed the importance of founder population size to such programs and James (1971) has examined theoretically its influence on response in relation to selection intensity and parent population size. The loss in future response because of this sampling will depend on the gene frequencies in the base population and on the subsequent selection scheme.

Robertson (1966a) described briefly an experiment which showed a reduction of about 30% in long-term response to selection (10/25 pairs) for sternopleural bristle number after commencing with a founder sample of one pair, the main effect of this bottleneck being in the first few generations. D. Robertson (1969) used the same character and another cage population in a study involving a replicated factorial design of 3 founder sizes (1, 5 and 20 pairs) and 2 parent sizes (5 and 20 pairs) and observed similar reduction in total response to long-term selection with only the smaller parent size. By the twenty-fifth generation of selection the influence of founder size had disappeared in his larger parent size treatment. The population sizes had little influence on response over the first 10 generations of selection but realised heritabilities were reduced as founder size decreased. I have recently (Hammond, 1973) examined the effect of founder (1, 10 and 50 pairs) and parent (1, 10, 20, 50 and 100 pairs) sizes on response to 10 generations of selection (at 33%) for abdominal bristle number using an unbalanced factorial design with 3 founder replicates and 3 to 10 parent replicates per founder replicate. When population size was large good agreement between predicted and observed response was obtained. Small population size, particularly founder size, reduced both response (Fig. 1) and realised heritability considerably, and over the period of selection James' simple additive prediction slightly underestimated the influence of founder size. At the tenth generation the average response for the largest parent treatments of the 1 and 10 pair founder lagged that of the 50 pair founder by about 1 and 0.5 phenotypic standard deviations respectively.

The composition of the founder sample is also important to response. Is it preferable to sample a founder population from one or all available base populations? How should selection of a founder from a multiple of base populations be performed—should all founder parents come from the 'best' population, or be sampled equally or unequally from all populations? Howe and James (1973) have considered the extreme cases of this problem theoretically, viz. a founder sample composed of: 1) the best individuals of the best population for the phenotype of interest; 2) an equal number of individuals taken at random from many populations; and 3) an equal number of the best individuals from many populations. They concluded that the optimum composition of the founder population varied with different aims—if high initial mean breeding value is the aim,
method 2) is worst, while if high genetic variance is the aim, method 2) is best, although usually only slightly better than method 3). They then used 20 populations of *Drosophila* to examine these methods experimentally over 10 generations of selection and obtained results in broad agreement with the theory.

**Figure 1.** Average response to directional selection for each population size combination (founder followed by parent size - pairs) expressed as deviation from control.
Replicate Variation

In virtually all selection experiments with reasonable replication, considerable replicate variation has been described, often with an element of surprise. Both the researcher who is aiming to test the adequacy of selection theory and the animal breeder who is about to plan an improvement program require a priori estimates of the sampling variances of predicted responses. A second objective of my recent work was to examine the influence of founder and parent size on the variance of response to random and to unidirectional mass selection. In all but the smallest populations the observed variances of response to directional selection, between replicates initiated from the same founder sample, were less than those observed under random selection, and the latter were substantially greater than expected from the simple theory (Wright, 1921). Under directional selection variances of realised heritabilities were more influenced by parent than by founder size. They were in reasonable agreement with prediction (Hill, 1972) as demonstrated by the results (Table 2) for one estimator of realised heritability (the regression of cumulative response on cumulative selection differential). It is apparent that the sampling variance of this estimate from the conventional regression analysis can be severely biased.

TABLE 2

Comparison of the estimated and predicted variances of realised heritabilities, * expressed as ratios of the observed variances

<table>
<thead>
<tr>
<th>Population size Combination ++</th>
<th>$df$</th>
<th>Estimated Observed</th>
<th>Predicted Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>25</td>
<td>0.25</td>
<td>0.76</td>
</tr>
<tr>
<td>1-10</td>
<td>18</td>
<td>0.88</td>
<td>1.75</td>
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<tr>
<td>1-20</td>
<td>15</td>
<td>0.42</td>
<td>0.72</td>
</tr>
<tr>
<td>10-10</td>
<td>21</td>
<td>0.41</td>
<td>1.04</td>
</tr>
<tr>
<td>10-20</td>
<td>18</td>
<td>0.59</td>
<td>1.44</td>
</tr>
<tr>
<td>10-50</td>
<td>12</td>
<td>0.59</td>
<td>0.94</td>
</tr>
<tr>
<td>50-50</td>
<td>14</td>
<td>0.50</td>
<td>0.82</td>
</tr>
<tr>
<td>50-100</td>
<td>6</td>
<td>0.47</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* Calculated over the 10 generation period of selection.
+ «Estimated» from the conventional regression analysis and «Predicted» from Hill (1972).
++ Founder followed by parent population size (pairs).

Selection Plateaux

In many selection experiments plateaux have been recognised and in some livestock breeding programs diminishing returns to selection realised. Almost two decades ago Bell et al. (1955) posed the vital questions which must be answered in such situations before substantial further improvement is possible, viz. «Will
continued selection eventually break through these performance plateaux [and what length of time may be involved]? Will further improvement await the introduction of new genetic variation into the closed population, or is a new method of breeding or selection required for further progress? Could these plateaux possibly be due to physiological ceilings for the species or as a result of negative genetic correlations between selected characteristics? Does irradiation provide an avenue for further improvement ...? Such plateaux have been attributed occasionally to the exhaustion of additive variance, e.g. Brown and Bell (1961), but in most studies considerable additive variation has remained at a plateau. For example, a colleague of mine (Mr. B. H. Yoo) found no decrease in the additive variance of abdominal bristle number in the majority of 6 populations which were at or approaching a plateau after they were selected (50/250 pairs) for more than 85 generations and had traversed about 35 additive genetic standard deviations.

There have been valuable recent contributions to our understanding of how plateaux may be broken — see Barker (1967) for a detailed discussion of earlier work. The work of Jones (1967) and Hollingdale and Barker (1971) when considered together suggests that the worth of radiation treatment depends on the nature of the variation sampled from the base population and the subsequent selection program. It has been shown that some response barriers can be broken by subdividing the population and capitalising on genetic sampling by subsequent between-line selection (Latter, 1970), and by selecting component traits (Latte, 1973). The introduction of new variation by crossing and selection techniques has been studied by Osman and Robertson (1968) who demonstrated some incompatibility between the conditions necessary to minimise the time to obtain useful response and maximise total response. More work is certainly required on the nature of these plateaux and methods for their transgression. However, sufficient evidence exists to suggest that for a trait at a plateau in a particular population a good appreciation of the nature of its variation will be required before there is a reasonable chance for substantial progress.

Population Structure

In some selection programs it is desirable to maximise both the initial rate of response and total response. Such objectives are partly incompatible since selected populations are necessarily of finite size, but the population structure to achieve them will depend on the nature of the variation in the base population (Wright, 1939; Madalena and Hill, 1972). Madalena (1970) and two of my colleagues (Mr. K. A. Rathie and Mr. B. H. Yoo) have compared experimentally population structures involving between-line selection and crossing with selection in single populations. In neither study were large gains obtained from the sub-lining methods but in each case this was probably due to variation for the character under selection being mostly additive. As Madalena and Hill pointed out, the methods were originally proposed by Wright to prevent loss by recombination of favourable epistatic combinations and further comparisons of them would be useful.
Inbreeding

The adverse effect of a high rate of inbreeding on many production characters has long been recognised and Wright's (1922) inbreeding coefficient for a single additive locus has many uses in prediction. However, its ability to predict attainment of homozygosity has not been satisfactorily examined experimentally, although earlier work suggests it overestimates loss of heterozygosity (F. W. Robertson, 1956) and, in a check of the static quantitative theory, Kidwell and Kempthorne (1966) observed that «inbreeding did not behave as expected». Rum- ball and Franklin (1974) tested the simple theory by studying the genotypic frequencies, under close inbreeding (full-sib and double-first-cousin), of 6 electrophoretic markers over 17 generations. They commenced with 120 full-sib and 60 double-first-cousin lines and found that agreement between observed and predicted differed for each system. Homozygosity was less than expected in the full-sib lines but not significantly different from expected in double-first-cousins. With each system, loss of heterozygosity was similar between loci (3 unequally spaced loci on each of 2 chromosomes) suggesting that selection was not acting on the markers themselves but on linked complexes.

Genetic Associations Between Characters

Knowledge of genetic associations between characters will be required to optimise breeding procedures and/or predict correlated responses of characters not under selection, for in virtually no breeding program will only one character be of interest. But genetic covariances between characters can change rapidly with selection and genetic drift (Bohren et al., 1966) and most of the limited experimental evidence suggests that the use of genetic correlations would be hazardous unless they were reassessed at short intervals. Recently Jones et al. (1969) observed that the realised genetic correlations between several bristle systems were very different in 42 different populations (initiated from the same base population) after more than 20 generations of selection. When these correlations were averaged over populations they were similar to estimates on the base population. Sheridan and Barker (1974a) compared predicted and realised responses in four replicates selected (20 pairs and 20 % selection) for one or both of two bristle characters in both directions. A feature of their results was the considerable replicate variation in realised responses and genetic correlations, although when the latter were averaged over replicates they were similar to estimates from the base population. Their average realised responses in both single and two-trait lines were less than predicted using the base population estimates. But the responses in the two-trait lines agreed with prediction based on realised correlations from the single-trait lines. After 22 generations of two-trait selection the treatment trends in the genetic correlations were contrary to the generally accepted expectations; concurrent selection resulted in significantly larger correlations than divergent selection (Sheridan and Barker, 1974b). The substitution of a gene or chromosome segment under selection for the primary trait may produce no change, a positive change, or a negative change in a secondary trait. In addition it has been shown by Latter (1973) that joint effects of substitution of pairs of chromosome segments or genes may show important interaction for the secondary
trait while showing additivity for the primary trait. Thus the number of possible genetic models is very large.

Many characters of interest are complexes of interrelated components. Latter (1970) showed that negative genetic correlations between such components may be generated by selection, thereby restricting response. His study also indicated «that appropriate allelic substitutions may sufficiently alter the developmental or physiological processes involved that quite different genetic relationships among the components are induced».

The correlated responses to which I have been referring, and for which the evidence suggests our present theory has limited predictive value, will be linear with time. Robertson (1970a) has pointed out however, that correlated responses in fitness components are likely to increase with the square of the number of generations. Over the last two decades Robertson has repeatedly attempted to kindle interest in this even more difficult area (see for example Robertson, 1967b and 1970a) which is of vital and increasing importance to breeding programs (Ferrando and Schaller, 1970). The first extensive exploratory study was performed more than a decade ago when Latter and Robertson (1962) attempted to measure changes in fitness under inbreeding and artificial selection for three characters. However, the amount of physical work involved in studies in this area and the lack of good predictive theory has discouraged the extensive laboratory work required, but I consider that Drosophila will play a major role.

The result of such correlations between selected characters and reproductive fitness will be plateaued responses. Rathie and Barker (1968) compared four different treatments (4 replicates and 20 pairs of parents) of regular cycles of intermittent selection and continuous selection, expecting greater total response in some of the former treatments. However, the treatment average responses were lower for intermittent selection and there was no greater response per generation of selection. Their measures of reproductive fitness declined more under continuous selection, but they concluded that the slower average response per unit of time with intermittent selection would bar its use unless reproductive fitness was particularly important.

Heterosis

With increasing recognition of the importance of components of reproductive fitness in animal production, breeders will attempt to include them among the characters to be improved. But the majority of these components display considerable heterosis, so their inclusion poses problems. Two decades ago Bell et al. (1955) indicated the need to understand the nature of the variation in such heterotic traits before they could be utilised effectively in breeding programs (see also Donald, 1968); but we remain ignorant. Although Drosophila would not appear to be overendowed with easily scored heterotic characters, it should certainly be of use in this problem area.

Familiarity with genetic variation

Finally, I wish to consider an important role of laboratory animal research in general—that is, to enable the animal breeder to be familiar with the
behaviour of quantitative genetic characters. This need has not been fully appreciated in some sectors even though it has been mentioned several times (Robertson, 1959; Chapman, 1961; Fredeen, 1966, and Falconer, 1967).

It is necessary to comprehend experimental quantitative genetics to be generally proficient in:

1. The design, analysis and interpretation of animal breeding research. Chapman (1961) termed this the salutary effect of laboratory research because «the results which occur with large numbers of rapidly reproducing organisms over many generations often point up, in rather dramatic form, the dangers of generalisation from results based on small numbers, few generations, specific traits, and only partially defined experimental conditions». Falconer (1967) pointed out that wasted time and money through faulty design of laboratory experiments is not disastrous and would be well spent if a similar mistake in an experiment with large animals was avoided.

2. Realising where the theory is inadequate. Learning by experience allows the researcher to substitute generalised patterns of response for the restricted theory. For example, the present theory tells us little of what happens when selection is relaxed or how fitness declines with selection. There is a tendency at training centres for simulation techniques to replace laboratory work, but these two teaching tools should be considered complementary rather than alternatives to obtain an appreciation of the limitations of the theory.

3. Staying abreast of theoretical and experimental developments. The learning experience should be a continuing process and workers in applied animal breeding research should be encouraged to do experiments with laboratory animals. Fredeen (1966) considered how laboratory animal research should be integrated with large animal breeding research.

There remains a tendency for some institutions concerned with applied animal breeding research to relegate studies with laboratory animals to the early formal training of their staff. Laboratory work at such institutions can be both a stimulus and an incentive to retain top geneticists to direct breeding programs because as Fredeen (1966) suggests, it will «sustain their interests, in fact ... whet their ability and scientific knowledge ... Such experience would not only enhance their competence to deal with large animal research but also ... would greatly improve the quality of the advice they can offer to industry».

In this paper I have attempted to place some recent studies and current problems, as seen from Drosophila research, in context with the application of genetics to livestock improvement. It is apparent that the lowest common denominator of the present situation is the need for a better understanding of quantitative genetic variation, and in this Drosophila has a major role to play.

**SUMMARY**

Some recent developments in Drosophila research are considered with respect to the major roles of laboratory animals in livestock improvement. The examples and present problems referred to demonstrate that for the present Drosophila should retain a prime place in quantitative genetic research, particularly in interpreting the nature of, and increasing the familiarity with, quantitative genetic variation.
RESUME

Certains récents travaux dans la recherche de Drosophila ont été considérés du point de vue des majeurs rôles des animaux de laboratoire employés pour l'amélioration du bétail. Les exemples et les problèmes actuels mentionnés démontrent qu'à présent Drosophila doit retenir un lieu principal dans la recherche génétique quantitative, particulièrement en ce qui concerne l'interprétation betrachtet. Die betreffenden Beispiele und die gegenwärtige Aufgaben beweisen, tischen quantitativen Schwankung sowie Steigerung der Vetraulichkeit mi derselben.

ZUSAMMENFASSUNG


REFERENCES


