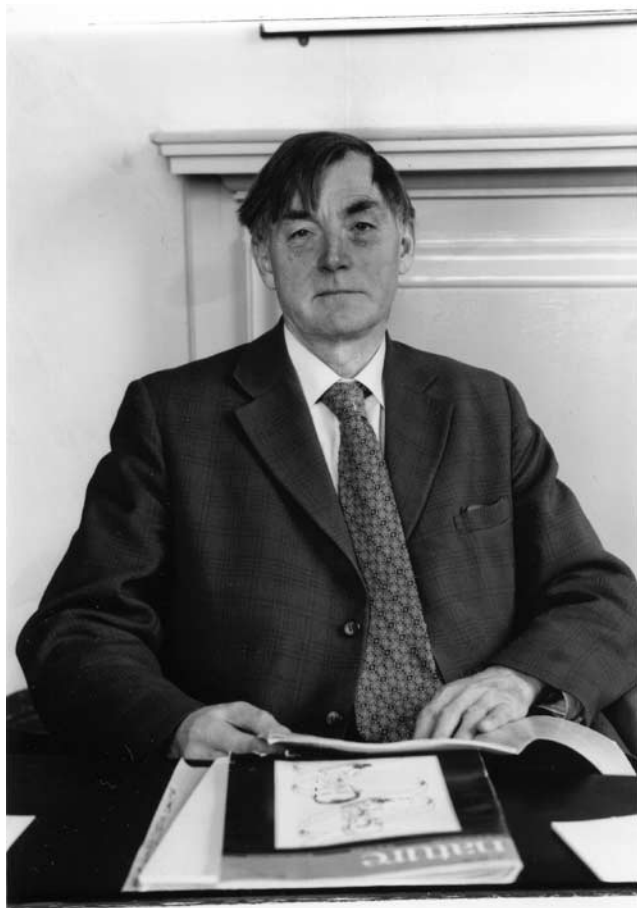


NEWS AND COMMENTARY

Douglas Scott Falconer (1913–2004)

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Douglas Falconer's early work was on linkage and genetic analyses of major Mendelian mutations in mice, including the discovery of the first sex-linked mouse mutation (Falconer, 1952a). He continued this interest throughout his career, publishing 17 papers on this topic. His major contributions, however, were in the area of genetic analyses of quantitative traits, for which variation is determined by segregating alleles at multiple interacting loci with individually small effects, and whose expression is contingent on the environment. In particular, he is best known for his work on response to artificial selection in mice, the concept of the cross-environment genetic correlation, development of the theory for understanding the genetics of complex

human diseases in terms of an underlying continuous liability, and of course, his highly acclaimed textbook, *Introduction to Quantitative Genetics*, first published in 1960.

In order to understand the impact of Douglas' work and that of his colleagues in the Agricultural Research Council (ARC) Unit at Edinburgh, it is necessary to cast our minds back to the late 1940s and early 1950s and examine the state of understanding of quantitative genetics at that time. Much of the population and statistical genetic foundations had been laid by Fisher (1918), Wright (1952), Haldane (1932) and Mather (1949), while Lush (1937) developed the early applications to animal breeding. However, there were many unanswered theoretical and empirical

questions to be addressed. How effective is artificial selection in changing mean values of a trait? For how long does response to selection continue? How closely do observed responses to selection match theoretical predictions? What deductions about the nature of genetic variation can be made from results of selection experiments? How important is recombination and linkage in patterning natural variation for quantitative traits and governing response to selection? The latter questions arise from the puzzle of abundant genetic variation for quantitative traits, yet relatively stable mean values in most populations. Could this be explained by the action of the population genetic processes of mutation, natural selection, migration and genetic drift on genes affecting quantitative traits; or are genes affecting such traits of a qualitatively different sort than those affecting Mendelian variation? The latter hypothesis was espoused by Mather (1941, 1949), who proposed that natural variation for quantitative traits was caused by multiple polygenes with individually undetectable but similar and supplementary, largely additive, effects, organized in balanced polygenic systems of alleles increasing and decreasing the trait value.

In his *Genetics Perspective* Falconer (1993), Douglas describes the early years of the ARC Unit. In addition to Douglas and CH Waddington, the original staff included A Robertson, JM Rendel, RA Beatty, FW Robertson, ECR Reeve and JH Sang. Their remit was to conduct research on quantitative genetics of farm animals, rabbits, mice, and *Drosophila*. The rather forward-thinking premise was that breeding methods would be first tried in *Drosophila*, taking advantage of the rapid generation time and large numbers that could be reared economically. Methods that worked would then be tried on mammals; general principles inferred from successes in *Drosophila* and mammals could then be applied to farm animals.

Strong predictions regarding the response of quantitative traits to artificial selection arise from extrapolating population genetic models of response of single genes to selection. Assuming that many genes affect the trait, and that allele frequencies are not correlated with the magnitude of their effects, one expects a symmetrical response to divergent selection for increasing and decreasing values of the trait, the rate of which should gradually decline as frequencies of genes affecting the trait in each direction approach fixation.

Ultimately, limits to selection will be reached at which all favorable alleles are fixed and no genetic variation remains. Douglas' results of artificial selection on mice, and those of his colleagues with *Drosophila* (eg, Clayton *et al.*, 1957; Clayton and Robertson, 1957), rather surprisingly revealed that these predictions generally did not hold in practice.

For example, after 30 generations of selection for increased, and 24 generations of selection for decreased 6-week body weight in mice, Douglas observed that the absolute magnitude of response appeared equal in both directions (Falconer, 1955). However, Douglas proposed that one should describe the selection response in a manner that takes account of the amount of selection applied. He invented the concept of realized heritability (h^2), obtained by regressing the cumulated selection response on the cumulated selection differential, the latter weighted by the number of progeny measured. (Douglas credits the origin of this concept to his colleague B Wolfe.) When described in this manner, it was apparent that the resulting realized heritabilities were markedly different in the high ($h^2 = 0.18$) and the low ($h^2 = 0.52$) lines. This is an important result, as it indicates that predictions of response to selection from heritabilities estimated from correlations among relatives in the base population could be misleading. Further, asymmetrical responses to selection *de facto* imply that one or more of the assumptions underlying the simple prediction must be false. For example, alleles increasing size may have been more frequent than those decreasing size in the base population; there might be directional dominance, and/or inbreeding depression that could accelerate response in one direction and hinder it in the other. Douglas had the biological insight to realize that in this case the asymmetry was most likely attributable to a maternal effect. He speculated that 6-week body weight could be partitioned into weaning weight at 3 weeks, which is largely determined by the mother; and growth between 3 and 6 weeks, which is largely a property of the individual. Remarkably, the asymmetrical response was due to weaning weight alone. For some reason, selection for reduced body size was accompanied by a correlated response in decreased mothering ability, but there was not a concomitant increase in mothering ability in the lines selected for increased weight. In addition to the unexpected asymmetrical responses, neither realized heritability nor phenotypic variance tended to decline, as predicted, over the course

of the experiment; indeed, the phenotypic variance of the small line actually increased. Douglas also proposed that the relationship of body size to fitness could at least be partially assessed by comparing the expected and realized selection differentials. These were nearly equal in the large line, but the realized selection differentials were much lower than the expected differentials in the small line as selection proceeded, indicating that natural selection was countering artificial selection for reduced body size.

To assess whether patterns of response to artificial selection differ between traits, Douglas initiated long-term divergent selection for litter size (also an important character in farm animals). An immediate and unexpected feature of this selection response was that response was opposite to the direction of selection for the first two generations, although continued selection yielded an average realized h^2 of 0.17 (Falconer, 1955). This anomalous result was attributed to a negative nongenetic maternal effect whereby females reared in large litters were smaller, and had smaller litters. Again, the selection response was asymmetrical, with realized $h^2 = 0.08$ in the high line, and $h^2 = 0.23$ in the low line (Falconer, 1963). In this case, Douglas demonstrated quite elegantly that the asymmetry was because the 'trait' selected, 'litter size', is actually a composite of ovulation rate and embryonic survival rate. Increased litter size was due to an increase in the ovulation rate. Ovulation rate was not changed in the line selected for decreased litter size; a decrease in embryo survival accounted for this response. An explanation that fits these observations is that genes affecting embryonic survival would be deleterious recessives and rare in the initial population, and hence selection for reduced litter size would increase their frequency and consequently yield a greater response than reducing the frequency further in the high line. Segregation of rare recessive alleles affecting embryo survival could lead to a limit to selection for high litter size at which some genetic variance remains. If so, inbreeding with continued selection, followed by crossing the newly derived inbred lines, could break the selection limit by purging some of the deleterious alleles. This was exactly what was observed when this experiment was conducted (Falconer, 1971).

Douglas also made a major contribution to the practical problem of deciding in what environment artificial selection should be applied, if the selected individuals are to be reared in a wide range of environments. Should selection be conducted in a good environment,

giving maximal expression to the desired character, or should it be carried out under the conditions in which the organisms will eventually live? Douglas showed that the answer depends on the extent to which the trait exhibits genotype by environment interaction (GEI). If the rank order and relative magnitudes of phenotypic expression for genotypes affecting the trait are the same across a range of environments, then there is no GEI and it does not matter in which environment the selection is conducted. However, if the expression of the trait changes rank or magnitude among the different genotypes, there is GEI and it might be best to select in the environment in which the organisms will ultimately be reared. Douglas showed that the magnitude of GEI could be quantified by the cross-environment genetic correlation, r_{GE} , in which the same character measured in two environments is considered to be two different characters. The magnitude of GEI declines as r_{GE} approaches unity, and increases as r_{GE} approaches zero. Thus, the answer to the question regarding the appropriate environment in which to select comes from evaluating the relative magnitude of the correlated to the direct response to selection (Falconer, 1952b). Here, the correlated response (CR_Y) is the response of the trait in the environment (Y) in which it is expected to perform, given selection in a different environment (X), and the direct response (R_Y) is for selection in the environment in which the organisms will ultimately be reared. Assuming equal selection intensities in the two environments, $CR_Y > R_Y$ if $r_{GE} h_X > h_Y$, where h_X and h_Y are, respectively, the square roots of the heritabilities of the trait in the environment in which selection is made, and the environment in which the individuals are expected to ultimately perform. If the genetic correlation is low, selection should be conducted in the environment in which the strain is expected to perform, as was demonstrated by Douglas' classic experiment describing direct and correlated responses of growth weight of mice reared on high and low 'planes' of nutrition (Falconer, 1960a).

Many complex human diseases are affected by multiple interacting loci and the environment, but the phenotypic expression falls into only two classes – affected and not affected. Douglas showed that the inheritance of such traits could be studied by assuming an underlying, normally distributed liability, with a threshold liability above which individuals are affected, below which they are not. Given observations of the proportion of individuals affected

in the general population and in relatives of affected individuals, Douglas showed that the heritability of liability could be readily computed by invoking the properties of the normal distribution (Falconer, 1965). Essentially, he regarded the heritability of liability as a realized heritability, regressing the response (liability in relatives) on the selection differential (mean liability of affected individuals). This method has been widely adopted for estimating heritabilities of human complex diseases (eg, Falconer, 1967), and, more recently, in mapping quantitative trait loci for diseases and other threshold traits (Xu and Atchley, 1996).

It is not an exaggeration to say that Douglas' most lasting legacy and widest influence has been through the text, *Introduction to Quantitative Genetics*. Much of what we now regard as classic quantitative genetics theory and experimentation was done by the group in the Edinburgh ARC Unit in the late 1940s and 1950s, and published in the primary literature. The first version of the book (Falconer, 1960b) thus grew out of a need for a reference for lectures on quantitative genetics and animal breeding given in Edinburgh. The beautiful clarity of writing and impeccable logic exposing difficult concepts ensured its wide adoption worldwide: the first edition was translated into French, Portuguese, Polish, and Romanian. Douglas undertook a major revision, published in 1981, to update the previous 20 years' work, and two more minor revisions, in 1989 and in 1996. I was very honoured when Douglas asked me to coauthor the fourth edition, which expanded on the genetics of natural populations and added a new chapter on methods for mapping quantitative trait loci, which had undergone a revolution since the printing of the third edition with the development of abundant, polymorphic molecular markers. I have learned much from

Douglas Falconer, and along with his many friends, colleagues and students, will miss him greatly.

Biographical outline

Douglas Falconer was born on March 10, 1913 at Old Meldrum, Aberdeenshire, and died in Edinburgh on February 23, 2004, following a fall at home. His early education was in Edinburgh at Cargilfield and the Edinburgh Academy. He contracted tuberculosis after leaving the Edinburgh Academy, and spent 5 years (1931–1936) recovering prior to undertaking his B.Sc. in Zoology at St. Andrew's University, from which he graduated in 1940. Douglas received his Ph.D. from the University of Cambridge in 1943, for which he studied the behavior of wireworms (Falconer, 1945a,b) with James Gray. Douglas was a Lecturer in Queen Mary College, London, then was based at Cambridge, from 1943 to 1945; and was a research Assistant to RA Fisher in the Department of Genetics at Cambridge from 1945 to 1947, where he began his work with mice.

Douglas was appointed to the scientific staff of the Genetics Section of the Agricultural Research Council (ARC) Animal Breeding and Genetics Research Organization (ABGRO) in 1947, which relocated from Hendon to Edinburgh that year. Douglas remained in Edinburgh for the rest of his career, where he and his co-workers defined the field of modern quantitative genetics. The Genetics Section was initially directed by CH Waddington, who held the Buchanan Chair in Animal Genetics at the University of Edinburgh. It became the ARC Unit of Animal Genetics in 1957, with Douglas as Deputy Director. In 1968, following Waddington's resignation, Douglas was appointed as Director of the ARC Unit, and joined the University of Edinburgh faculty with a Personal Chair in Genetics. He

was Head of the Department of Genetics from 1969 to 1977, and retired in 1980, at which time the ARC Unit of Animal Genetics was closed. Although retired, Douglas remained active as Professor Emeritus until failing health in the late 1990s curtailed his activity. He received many honors for his contributions to quantitative genetics, including an Sc.D. from the University of Cambridge in 1969, election as a Fellow of the Royal Society of Edinburgh in 1972, and as a Fellow of the Royal Society of London in 1973. Douglas is survived by his wife, Margaret, whom he married in 1942, and their two sons. *TFC Mackay is at the Department of Genetics, Campus Box 7614, North Carolina State University, Raleigh, NC 27695, USA.*

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