Status of quantitative genetic theory

Oscar Kempthorne
STATISTICAL LABORATORY
IOWA STATE UNIVERSITY, AMES, IA 50011

What Do We Want From Quantitative Gen

I consider that this is th ...nd that the answer is quite clear from some vie... unclear from other viewpoints.

Let me first consider the q ...stion from a "pure science" viewpoint. Mather and Jinks (1971) in their prefaces give one answer, which I quote:

> "to show the kind of evidence upon which the genetical theory of continuous variation is based, to bring out the special problems which it raises, to see how the familiar genetical concepts must be adapted to this new use, and to outline an analytical approach which can help us to understand our experimental results."

I find it very difficult to understand this statement. I wonder if I am alone. I shall return to the Birmingham school later. Falconer (1972) in his review of the Mather-Jinks book mentions the genetic architecture of metric traits. This seems to

---

[1]This paper was presented in part at the International Conference on Quantitative Genetics, held at Ames, Iowa, on August 16 to 21, 1976, and also contains what may be termed an "Epilogue" view of the conference.

Journal Paper No. J-8686 of the Iowa Agriculture and Home Economics Experiment Station, Ames, Iowa. Project 1669. This work was supported by Grants GM13827-10 and GM23339-01 from the National Institutes of Health.

Proceedings of the International Conference on QUANTITATIVE GENETICS

me to convey something. We might wonder, for instance, if a trait is determined by additive gene action, or whether there is complete dominance or overdominance or epistasis. I think this question is meaningful. We might ask if a metric trait in a population exhibits variability because of a few genetic factors of large effect or an unknown but presumably very large number of genetic factors with very small effects. If we could answer this definitely, we would have a useful result, which would suggest further activities of various sorts. In spite of this "verbiage," I still find that I have perplexity about what the "pure" quantitative geneticist is seeking.

The contrasting outlook of the applied geneticist is very simple and direct. The corn breeder would like a genetic stock that produces consistently, say, a yield of 300 bushels or more per acre under average Iowa conditions. The poultry breeder wants a stock of laying hens that has considerably greater production than the present, and so on. The applied geneticist is interested in a science and a technology that will produce superior stocks. He needs desperately some sort of theory, though in fact, a quite remarkable amount of progress was achieved over the centuries without any theory apart from "use the best." Interestingly, this prescription is still the main basis of animal breeding, but with considerable statistical sophistication in determining which animals are best.

It is almost a cliché, I suppose, that in applied quantitative genetics there is a spectrum of conditions with two extremes. One extreme is that of the animal breeder who is and has to be concerned with the upgrading of a single existent population by selective breeding. At the other extreme is the plant breeder who has a fairly wide variety of stocks, who can make up new populations very easily and who has the twofold problem of making up populations within which to select and then of having processes for selection within chosen manufactured populations. In applied quantitative genetics there is also the technological role and impact of basic biological

features of the species, particularly with respect to multiplication of stocks. Corn breeding via inbred lines is viable as an industry, whereas beef breeding is much less so.

So we have science, technology, science of technology and application of chosen technology, all of which must be integrated in practical uses.

Fisher's Theory of An Equilibrium Population

Without doubt, the basic and seminal paper in the theory of quantitative genetics is that of Fisher (1918). The paper itself gives a short account of the background of knowledge, opinion and controversy that was Fisher's basis. A definitive account would involve extensive study and would be a fascinating story in the history of science, which we may hope will be developed in the future. A review I wrote (Kempthorne, 1974) has stimulated some exploration (Norton and Pearson, 1976), and the reproduction of an hitherto unpublished paper of Fisher written in 1911 when he was a second-year undergraduate at Cambridge, a paper which contains ideas that have been brought forward independently in the subsequent decades. It is desirable, however, to give a very brief statement of the background, namely, that there was a deep and intense controversy as to whether the obvious and unquestionable fact of continuous variation of metric traits could be reconciled with the discrete processes based on Mendelian factors and Mendelian laws of inheritance. That there should have been controversy about this seems very strange, even by, say, the year 1910, and surely so by the 1920's.

The initial point of Fisher was perhaps strange to the conventional wisdom of the time but surely consonant with all that has been discovered since, including modern molecular biology, in that he took as a genetic model an indefinitely large number of segregating Mendelian loci with the possibility also of an arbitrary number of alleles at each locus. This is strongly relevant to the discoveries in the last two decades of a huge amount of genetic

segregation in populations. Also, in contrast to classical Mendelism in which the role of environment was essentially negligible and could be ignored, it was obviously necessary to allow for environmental effects on metric traits. So Fisher gave the essential elements of modelling in the study of quantitative genetics, which have been used ever since. Indeed, I shall take the viewpoint that to some extent the stance taken by Fisher has dominated thought ever since, and has perhaps limited the approaches of subsequent workers. It is a tribute, of course, to Fisher's intellect that it has proved very difficult to move beyond the basis he set.

What then were Fisher's ingredients? I have to be brief and almost cryptic for reasons of space and time. There is an indefinitely large number of segregating loci; these are segregating "more or less" independently; their effects are essentially additive; hence we may call on the Central Limit Theorem to infer normality of distributions of total genotypic effect; environment is additive to genotype, and is randomly associated with genotype. Fisher had become interested in human populations from an early age (i.e., < 20 years) and received a considerable stimulus from the massive effort of Karl Pearson and his associates of applying statistical or biometrical procedures to human data. These workers had accumulated much human data, which in consonance with the "biometric school," were reduced to correlations between relatives. So the question was whether the observed correlations were consonant with what was at that time a very sophisticated Mendelian model. The stage was still further restricted to the case of an existent population that had arisen by "natural" processes and could not be experimentally manipulated by the various possible activities of planned crosses, planned inbreeding, planned selection, and so on. This history is relevant, I think, because it gives perhaps an indication of why Fisher did not get involved appreciably in the theory of selection for a metric trait, even though he gave, as will be seen, nearly all the bases that subsequent workers have

used. It is also relevant to the nature of more recent work on humans, particularly with respect to mental abilities.

Fisher's work was complicated by the obvious necessity to take care of assortative mating, to which I will refer in a later section. In the area of random mating populations, Fisher established the covariances for the relationships commonly observable (i.e., without inbreeding) in human populations by a model with a single segregating locus, and then merely added over loci. It is natural that he was then concerned with the role of dominance in these covariances, which he developed with dominance generally. He was concerned a little with two-factor interactions, but after seeing how these entered into "simple" covariances for a random mating population, did not pursue the problem. He disposed of multiple allelomorphism, getting the same formal result as with two alleles. He tackled the role of linkage and, after some development, concluded that it was not important in his context; a pair of linked factors could, he thought, be replaced analytically by a single factor.

Perhaps the most curious logical fact that Fisher found in 1918 with respect to a metric trait and with no variability in fitness is the following. In a random mating single locus population with no selection, the Hardy-Weinberg law holds, and in this case one can apply the processes of linear models. With $P = G + E$, one can develop by least squares the decomposition

$$G = A + D$$

and in the population A and D are uncorrelated random variables with variances σ_A^2 and σ_D^2. The Fisherian recognition of this is not surprising, I suppose, because Fisher had developed the modern ideas of linear models and the analysis of variance essentially single-handedly, but withal we may wonder why a process of fitting such a linear model would bear a relationship to components of variance that give a simple structure to covariances of relatives.

Wright's Systems of Mating

Over somewhat the same period, more or less, Sewall Wright had been pursuing somewhat the same sort of problem, but with what I think should be characterized as a different thrust. Wright was concerned with the role of what I wish to call neutral genetic processes, and in particular inbreeding. By a neutral genetic process I mean a process in which the genetic operations of crossing and inbreeding are performed with no selection. For this, which is only a branch of Wright's total effort, he used his method of path coefficients, which is original and in general statistics highly important. This method, however, does not handle non-linear determination of a variable by prior variables except by very forced arguments (c.f., the treatment of the role of dominance, Wright, 1963). I shall abbreviate a huge history by stating two points: (a) by attaching a score to a particular gene and zero to all other genes, Wright obtained so-called genetic correlations, and (b) by supposing that phenotype is determined additively by randomly occurring genes and by randomly occurring environment that are additive in their effects, Wright determined covariances of relatives under a wide variety of circumstances and not just for an equilibrium random mating population as Fisher had done.

This process was used, after all, by Fisher in the first instance in his "proof" that normality of distribution of the metric trait would hold. In tacitly expressing criticism of this type of thinking, I have also to recognize that workers have done "what they can do," and to develop results for a wider model, involving even two loci, let alone one involving, e.g., 1000 loci, is very hard and, indeed, has not yet been accomplished. Parenthetically, the whole of theoretical population genetics is confronted with the same sort of problem. Nearly all theoretical population work uses single locus fitness, which is itself an obscure and quite inadequately thought-out and exposited concept.

Malécot's Contribution to Quantitative Genetics

Here I shall abbreviate sharply. Malécot (1948 and earlier) formulated the notion of identity by descent and gave us a calculus based solely on probability ideas. He then obtained, with the use of probabilities of identity by descent, a general formula for covariances of relatives in a population under neutral processes, i.e., random mating or pure inbreeding, with a single locus segregating and with no selection. With hindsight, we see that the problem was rather simple, but, as throughout the saga, the recognition of inherent simplicity is the truly creative act.

General Work on Covariances of Relatives

The gaps in desired knowledge at this stage are rather obvious. We now have a theory of covariances of relatives, assuming a single segregating locus and purely random environmental effects, which are additive, based on the equation

$$P = A + D + E$$

with obvious connotations for the symbols.

It is appropriate to focus on this because so much work in the theory of applied quantitative genetics uses this model or even the simpler model

$$P = A + E$$

with assumptions of lack of correlation and so on. To make matters even more unsatisfying, it is assumed in much theory that one needs merely to work out what happens with a single segregating locus, treating all other loci as merely contributing to random error, and then to accommodate the obviously essential ingredient of there being many loci to "add over loci."

Fisher in 1918 had observed a very curious fact for a single locus random mating population. He had obtained simple covariances and found that they involve parameters that we now denote by σ_A^2 and σ_D^2. A Hardy-Weinberg population is representable as

	A	a
A	p^2	pq
a	pq	q^2

and this 2x2 table has proportional frequencies. Did Fisher know that the analysis of variance with proportional frequencies is clear and easy? The world did not know until perhaps two decades later. The upshot of this is that Fisher became highly enamored with the additive genetic variance, defined as the variance accounted for by a linear model consisting additively of gene effects. Parenthetically, I state my opinion that attributing deep significance to this parameter for the case of an arbitrary population may well be one of the intellectual errors of Fisher. I merely state the fact that I find the section "The genetic element in variance," pages 30-37 of "The Genetical Theory of Natural Selection" (Fisher, 1930, 1958), rather incoherent, as also Fisher (1941), even though I have understood and exposited the purely linear model aspects (Kempthorne, 1957, Chapter 16) without errors, I believe. To exposit my views is impossible here. My remarks have implications, clearly, to the status of Fisher's Fundamental Theorem of Natural Selection, which has bothered, and I think correctly, very many workers.

We may surmise that Fisher knew very early, and Yates by the 30's, that the analysis of variance of a multiple cross classified population of numbers is a rather straightforward matter under one and only one circumstance, namely when the frequencies of observations in the ultimate cells are proportional. The linear additive genetic model is useful for non-Hardy-Weinberg populations only with purely additive gene action, which leads to a trivial variance analysis. Otherwise, the analysis of variance of a cross-classified structure is very difficult and not unique. Proportionality of frequences was the clue, I believe, for Cockerham (1954) for the case of two alleles at a locus and certainly the clue for myself for the general case. The outcome is that if the population

with an arbitrary number of loci and arbitrary numbers of alleles at each locus is in generalized Hardy-Weinberg equilibrium there is a simple analysis of variance; and if also there is no linkage, the linear model associated with the analysis variance gives terms that behave in a rather simple manner with respect to covariances of relatives. The upshot of this is two formulae:

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2 + \sigma_{AA}^2 + \sigma_{AD}^2 + \sigma_{DD}^2 + \ldots$$

and

$$\mathrm{Cov}(X,Y) = \Sigma(2r_{XY})^u (u_{XY})^v \sigma^2_{A^u D^v} .$$

This is described correctly, I hope, in my book (Kempthorne, 1957). This general result seemed at the time, I surmise, to be rather neat, as I suppose it is. I still find it remarkable that such pleasing formulae occur.

Let us suppose that, somehow or other, we know that the conditions necessary for these formulae hold. Should we feel that we have stripped out this situation? We have solved nicely a particular interesting problem, but having solved it we must immediately face problems of implementing the formulae and of assessing the value of what we have achieved. How good are these formulae? We shall observe covariances of relatives, and we shall then try to estimate the components of variance σ_A^2, σ_D^2, and so on, but we encounter extremely unpleasant problems. If we accept the formulae literally we have an unknown number of parameters, and to estimate the components we must necessarily have a number of different relationships between X and Y equal at least to the number of components. Fortunately, we are saved to some extent by the powering that occurs in the coefficients of the covariance formula, so that if we wish to get a good approximate idea of covariances for an arbitrary (noninbred) relationship, we can eliminate all but a few of the terms. Even here, however, the associated statistical problems are difficult as a result of the relationships between coefficients and the imprecision of sample covariances, which require

large amounts of data for even moderate precision. It would be a huge task to review the statistical literature on this. The "simple" way out is merely to delete all terms except σ^2_A, as occurs in uses of Wright's path coefficients, or all terms except σ^2_A and σ^2_D, as with Fisher, and in the simple quantitative genetic designs. As we shall see later, this is not at all bad for some purposes.

Let us pass over these technical problems and consider the situation if indeed all our assumptions hold and we are able to estimate all the components of genetic variance that are involved. I think we have to have a bifurcated view. On the one hand, we are able to say what every covariance not involving inbreeding is. We know how the variance of our population is made up. But on the other hand, this is from many viewpoints a pitifully weak picture of the genetic population. We have a remarkable result because the variability in the population depends on a huge number of genotypic frequencies and genotypic effects. We have achieved a description of variance and of covariances of relatives that depends only on genetic components of variance, which, however, depend on the gene frequencies and the genotypic effects. We have in fact managed to submerge almost all the interesting facts about our population. We can, however, use this description or characterization of the population for the prediction of short-term response to weak selection under special circumstances, and this has been used very widely in the choice of breeding plans.

It is interesting that the results on the variances and covariances do not depend at all on the nature of the trait except that it be representable by an arithmetic number. So, for instance, if our trait were presence or absence of some attribute, we could score presence by 1 and absence by 0, and our description in terms of components of variance would be correct. With the model assumptions, including arbitrary genotypic effects, the results are <u>not</u> approximate.

The next easy step is to suppose that in fact the metric traits of individuals of any specified relationship can be represented by

a multivariate normal distribution. We are, then, clearly in business, because the multivariate normal distribution is specified totally by the mean vector and the variance-covariance matrix. Also, this distribution has the property that the distribution of any set of variances conditional on other variables is also multivariate normal, and the conditional expectation function given the values of some variables is linear. So by adjoining multivariate normality we have a huge simplification, which is widely used in animal breeding. The question of linearity of relationships between relatives assumed with normality was raised by Kempthorne (1960), and it was interesting that the question is raised by A. Robertson in this volume.

Complications of the Preceding

1. Genetic Mechanism

It is obvious that even if we have a generalized Hardy-Weinberg population at equilibrium, the phenomenon of linkage must be accommodated. I shall not give any review of this. Definitive work is by Schnell (1961, 1963) and van Aarde (1975). The upshot is that formulae can be developed, but they depend on the whole panorama of segregation parameters. This very difficult work has had very little impact on our quantitative genetic thinking, and in saying this, I am not being at all critical of it. We have to develop larger outlooks so that we can contemplate the formulae and give them some intuitive meaning. I expect this to be done by some fresh mind.

2. Population Structure

What results we have are for a generalized Hardy-Weinberg population. What can we do for populations that do not have this structure or some other very special structures to be discussed later? I suppose we have been completely stopped. We can only observe our populations and attempt a purely empirical statistical description. But perhaps someone will have ideas.

At this point it is appropriate to say a few words about Fisher (1918) again. In a remarkable effort, Fisher obtained some theoretical ideas about a population with assortative mating which is at equilibrium. Fisher developed a theory of covariances of relatives under a model with additive and dominance effects but with no epistasis for an equilibrium assortative mating population, in which the number of loci is "very large," the effects associated with any locus are "very small," and environment acts additively and at random. In spite of efforts to establish the validity of the whole development, obscurities remain (I have seen unpublished work by Vetta). It is necessary at least to mention Wright's work (1921) on assortative mating, which perforce, because of the method, deals with only additive gene action. It seems that neither Fisher's nor Wright's work has been extended in any essential way.

It would be remiss not to comment on the use of this work. Except by psychologists, the work has been almost (but not quite) ignored. I shall not give references, but will merely confine myself to the statement that the ideas were taken up, notably, by C. Burt and Arthur Jensen. In the latter case, a huge amount of controversy, often very bitter, has arisen. I have only a brief, perhaps cryptic, comment. The model is highly naive genetically, and, more critically, environmentally. In my opinion, there have been errors in statement and in logic on all sides. The whole episode is most unfortunate, and many of the unfortunate aspects are, I opine, due to the participants. The topic of "race" and IQ should be buried because there is in the foreseeable future no possibility of eliminating extreme naiveté of genetical, environmental and statistical modelling. The only viable approach to educability and education is by way of very carefully designed (with randomization) experiments on environmental factors. This has been the path followed by the best psychological and educational research of this century, as in the Milwaukee experiment (Heber et al, 1972).

3. Consanguineous Mating

An obvious potentially useful approach to understanding the

nature of quantitative inheritance is to make use of consanguineous mating, which leads, of course, to inbreeding. And, of course, inbreeding has been used extensively in applied quantitative genetics even before the time and ideas of Mendel. What then can be said, following the traditional route, about covariances of relatives with inbreeding?

It seems that if we obtain a population of generalized Hardy-Weinberg inbred structure, and then use random mating, the basic formulae remain valid, with the coefficients $2r_{XY}$ and u_{XY} properly defined to take account of the initial inbreeding (see Section 20.6 of Kempthorne, 1957). This work is restricted, however, to cases in which the relatives considered are not inbred.

The initial attack on this, for a base population of Hardy-Weinberg structure, was that by Wright, already referred to in which a single locus is segregating and the genes have additive effects. In that case, the covariance of two relatives X and Y is simply equal to $2r_{XY}\sigma_A^2$, where σ_A^2 is the genotypic and the additive variance in the base population. Furthermore, the coefficient $2r_{XY}$ is very simple to obtain by using a simple calculus on identity by descent, exposited, for example, by Kempthorne (1957, Chapter 5). Essentially all the results for simple cases had been derived at around 1920 by Wright. It is perhaps a comment on the state of animal breeding theory that there has been essentially no use of any theory more general than this very naive one.

The problem is, as one would expect, that a general theory of covariances of relatives, which may be inbred, is extremely difficult. The basic work in this area deals with a single locus and was done by Gillois (1964) and Harris (1964). The fact that comes to light immediately is that there are fifteen different possibilities with regard to identity by descent of four genes at a single locus is found to involve parameters of genotypic variation and covariance and five functions of relationship. A review of this work is impossible here. Extension of this to, say, the case of several loci has been pursued by Harris (1964) and Gallais (see

his paper and references in this volume). An alternative attack by means of identity-by-descent is described in this volume by Weir and Cockerham. It seems that this work generates a huge number of parameters that will not be estimable with the usual amount of resources and I wonder if it will aid understanding.

An alternative route was considered by Kempthorne (1957). Here the game, confined to a single segregating locus, is to consider an inbreeding process, e.g., parent-offspring mating or full sibbing starting from a Hardy-Weinberg population, and to obtain covariances of relatives of particular relationships, e.g., parent in generation n and offspring in generation (n+1), or full-sibs in generation n. The virtue of this work is that, over and above the results of Wright, it does take account of dominance. This line of work has been largely ignored, perhaps because it has not been examined, or perhaps because it is not fertile, though this seems doubtful. The topic is treated, with references to related work, in Kempthorne (1957, Chapter 17). Clarification and extension of that work might be useful. The case of continued selfing lends itself to special treatment; in population genetics theory it behaves as a particular case of mutation with large mutation rates. Each individual has one parent, and all the complexities owing to an individual having two parents, which are usually "swept under the rug" by the use of haploid models, do not arise. The case of continued selfing with arbitrary epistasis but without linkage is treated by Kempthorne (1957, Chapter 20), but the results have not been found stimulating.

To reinforce an opinion stated earlier, the results obtained in these cases do not have any relation to additive variance defined in a least squares sense. This is part of my basis for rejecting completely any general force to this Fisherian concept, except in the case of random mating populations, and, of course, in the case of additive gene action when the notion of partition of variance is unnecessary.

A Partial Evaluation of the Above

I have already made some comments in the above exposition, to which I add the following. The situation we are trying to model, and to model correctly and effectively, is incredibly complex. That we have been able to develop some theory, no matter how simplified, is remarkable, and as we shall see later some of the theory has been useful to obtain approximate ideas about selection. My task, however, is not to praise or condemn but to try to evaluate.

Let us put aside all the genetic complexities and consider the general nature of the modelling. The basis throughout the above has been that we have primitive zygotes containing nothing but the genotype as biochemical "stuff," of course, and that the primitive zygote is placed in a random environment. When the modelling is described in these harshly critical terms, its potential naiveté is displayed. It is obvious in mammals that there is cytoplasm and extra-nuclear material. It is obvious that the fertilized egg lives its early life in a special environment--that given by its mother. It is obvious that that environment is itself determined partially by nuclear forces, and it is obvious that purely environmental forces can influence the mother and the envrionment of the fetus. Various small efforts have been made on maternal effects, e.g., Kempthorne (1957, Section 15.11) and Willham (1963). One might think that this sort of phenomenon is confined to mammals, but flowering plant species, e.g., corn, have a facet that is somewhat similar logically. The endosperm of a plant surely contributes to the phenotypic expression and is part of the environment of the supposed diploid nucleus. In some respects, then, it is necessary to consider a special sort of triploid effect, and this has been done by van Aarde (1976, Variability attributable to direct effects of endosperm genotype, unpublished). The phenomenon is documented from classical Mendelian work by van Aarde, and associated biometric theory is worked out. Whether this will have impact, I do not know, but we can surely see that attaching a score to the nuclear sperm

and one to the nuclear ovum is but a naive, if necessary, beginning.

Yet another critical matter is that the environment of an individual is determined by the population in which that individual grows. Implications of this have been pursued by Griffing in several publications, including this volume.

The phenomena just alluded to enter, of course, in the matter of humans and of IQ, but have, I believe, been essentially ignored. To add to the naiveté of the work, this aspect has been swept under the rug. It is comforting that at least one study, the famous Milwaukee one (Heber et al, 1972), which is experimental, takes real cognizance of the role of the mother after birth.

Other deficiencies of the area of quantitative genetic theory relate to the existence of sex. On the one hand, one has the phenomenon of sex chromosomes. On the other hand, it seems rather clear that expression of a nonsex-limited character will in general depend on the status of the individual with regard to sex chromosomes.

The existence of these well-established biological phenomena presents a deep dilemma to workers in quantitative genetic theory. On the one hand, the theory that incorporates them is much more complicated, and naturally, the biologist abhors complexity. On the other hand, the elucidation of the effects, even very approximately, requires planned experiments that are impossible, or nearly so (e.g., transplantation of fertilized eggs), and also requires huge experiments and difficult technical statistical problems. But this should not be a source of surprise since, in the last resort, the task is to model correctly the whole panorama of biological life and this is not going to be achieved by observing, even if very accurately, a few correlation coefficients or a few components of variance. A final remark with reference to human IQ and with respect to behavioral genetics needs to be made. It is surely obvious that the model of the nuclear genotype plus random environment is so naive as to vitiate any substantive conclusions, but the

use of such models can thicken our journals and lead in some cases to totally unnecessary deep societal conflict.

The Biometrical Genetics Approach

It is interesting that Fisher (Fisher, Immer and Tedin, 1932) also initiated a quite different approach to quantitative genetics. In the foregoing, gene frequencies and gene effects are hidden in the parameters, and this has unfortunate consequences. What is another approach? With the notion of completely inbred lines, a suggestion is immediate, namely, to work with inbred lines. If we take two inbred lines and form their F_2, we have got rid of the gene frequency problem because all gene frequencies are 0, 1 or ½. We have P_1 and P_2; we can get F_1, F_2, BC_1, BC_2, and so on. Furthermore, we can use bulked populations, and we can look at population means. This was pursued by several, and a report up to the late 40's is given by Mather (1949); a summary of this work with brief evaluation is given by Kempthorne (1957, Chapter 21). The simple aspect of this is the nature of means of derived populations given in a highly related line of work by Anderson and Kempthorne (1954). This line of thought has been continued, e.g., by Eberhardt and others. The general line of this basic work is very important because it raises the question of scaling, which somehow "falls between the cracks" in the lines of work discussed earlier. The problem is a general one, associated with factorial experiments and error; one wants error to be additive and from a single distribution; one wants zero-interaction of the factors. Obviously, one can work with any 1-1 function of the observations. Rather obviously too, it is unlikely that a transformation that will achieve one of the desiderata will achieve the other.

I shall pass over any discussion and merely state that the results reported by Mather and Jinks (1971) and in various other works are quite emphatic, in my opinion, in indicating that non-removable epistasis is a general phenomenon (as one would expect). This poses an interesting question; attempts to show epistasis by

analysis of second-degree statistics have been unsuccessful. This is a direct contrast. The reason I believe is simply that components of variance involve gene frequencies, and epistatic effects are smeared with small weights so as to be lost in the general variance characterization.

The next step in the biometrical approach, of which the basic ideas were presented by Fisher, Immer and Tedin (1932), uses selfing and the analysis of variance for hierarchical structures. But then comes the problem of developing a genetic interpretation of the components of variance. These are, of course, related to covariances of relatives, but with special non-Hardy-Weinberg populations. With no epistasis and no linkage, this is fairly easy, but otherwise not at all so. One may refer to Mather and Jinks (1971).

An extensive experimental effort with maize was made on somewhat the same lines in North Carolina (Comstock et al, 1958). A critical evaluation of that effort would be useful.

But supposing one has gone through the suggestions in this direction. What precisely has one achieved? I am not alone, I know, in having considerable doubts. This should be debated very seriously in the literature, but it is not. It is very easy to conduct the experiments of biometrical genetics; they provided Ph.D. thesis topics by the dozen, which are no more than imitative, and are, when questioned seriously, as uninformative as the original ones. A very popular experimental design uses some type of diallel cross. One view on the nature of the information these give is presented in this volume by K. Hinkelmann. Another view with, it seems, the different background that the inbred are a definite fixed set and not a random sample from a population, was developed by Hayman and Jinks, and is presented by Mather and Jinks (1971). I am not alone in finding this analysis very opaque. Also, as D. S. Falconer has said, the information it supposedly leads to has, it seems, no implication with regard to selection.

The punch line in the Mather-Jinks theory is the notion of effective factors and the interpretation of effective factors. The notion itself is essentially, but with minor modifications, the Castle-Wright formula of the distant past, a formula based on purely additive gene action, which requires very strong and, it would seem, unwarrantable assumptions. The associated genetic "entities" are called by them "super-genes." I have the view that the whole concept here, rather like that of polygene (which is, I think, a mistaken one), is not viable nor useful. I suggest to the critical reader Chapter 11 of Mather and Jinks. I now give a few quotations, which motivate my doubts:

p. 325 "Since..., the super-genes which the chiasmata distinguish will not be of constant content. They will be variable even within a generation,...." "Finally, since chiasmata vary in position, a further breakdown of the effective factors must occur in later generations. The total number of factors found in these later generations will generally be greater than the first estimate. The effective unit of inheritance is thus a unit only for one generation, and even within this period it may well be a statistical rather than a physical unit."

p. 360 "The demonstrations of polygenic linkage,..., carries with it the demonstration that no permanent system of effective factors can be derived." "A second consequence of the breakdown of the factors is that they can be used as units only in a temporary sense."

finally,

p. 360 "They enable us to force behavior in the near future, to predict minimal limits and rates of advance under selection for one or two generations."

I am mystified because a lack of quasi-permanence in the so-called "super-genes" would seem to preclude any role in selection theory and because I do not see in the presentation any suggestions on how the results of the biometric analysis are to be used in deciding on a selection scheme. Falconer (1972, pp. 416-417) says:

> "The book disappointed me in two respects. First, one feels that the detailed and precise genetical knowledge gained from the analyses must have some practical use in application to plant breeding. Yet applications are hardly ever mentioned and are nowhere discussed in any detail. Second, there is very little comment by the authors on the results obtained.... I can only urge the authors to write another book to give us the benefit of their knowledge and experience of these more general problems."

I close with a general imprecise comment. It is quite clear, I think, that a model for quantitative inheritance must be statistical with respect to the Mendelian loci as well as with respect to individuals. A specification of genetic structure by single gene effects seems to be quite inviable. Can the Mather-Jinks ideas be fertile in this type of direction? We were very sorry that the Birmingham School was not represented at the conference to react to questions of this sort.

The Theory of Genetic Selection

From the viewpoint of human needs, the theory of quantitative genetics must be judged on the basis of whether it suggests schemes of selection and predicts successfully the results of selection schemes applied to real populations of importance to mankind. In the preceding parts of this essay, I have discussed our available theory for a population and the biometric relationships of relatives that may arise or be obtained by random mating or inbreeding. There are considerable gaps, as we have seen, but we should not blind our sight to the theoretical knowledge we do have. So now we turn to the theory of selection.

It is of some interest that the basic step was given by Fisher in 1918 (p. 403), though Fisher's interest was in the correlation of relatives, and in selection only insofar as assortative mating would induce changes in genotypic frequencies. I shall use Fisher's notation so that the reader may verify my account. It is curious that the "gem" lay hidden for a very long time. Consider a population with genotypic array $\overline{P}AA + 2\overline{Q}Aa + \overline{R}aa$, at a particular

locus. As I have indicated, the Fisher model has a "large number" of loci with "very small" effects. Consider the subgroup of the population for which the metric trait has value x measured from the population mean. Let the effects of the AA, Aa and aa subgenotypes on the metric trait be a, d, -a, respectively, with mean m. Then using the normal distribution, Fisher shows that the frequency of the AA, Aa, aa subgenotypes in this subgroup of the population are given respectively by P, 2Q and R, where

$$P \doteq \overline{P}\,\{1 + \frac{x}{\sigma^2}(a-m)\}$$

$$Q \doteq \overline{Q}\,\{1 + \frac{x}{\sigma^2}(d-m)\}$$

$$P \doteq \overline{R}\,\{1 + \frac{x}{\sigma^2}(-a-m)\} \quad .$$

Let us now change the notation a bit, and take a special case of Hardy-Weinberg structure. Write $\overline{P} = p^2$, $\overline{Q} = pq$, $\overline{R} = q^2$ with $P = p'^2$, $Q = p'q'$, $R = q'^2$, so that the prime indicates the frequencies for the chosen or selected subgroup. Then

$$p'^2 \doteq p^2 \{1 + \frac{x}{\sigma^2}(a-m)\}$$

$$p'q' \doteq pq \{1 + \frac{x}{\sigma^2}(d-m)\}$$

$$q'^2 \doteq q^2 \{1 + \frac{x}{\sigma^2}(-a-m)\} \quad .$$

We see then that the gene frequencies in the chosen group are

$$p' \doteq p\,\{1 + \frac{x}{\sigma^2}[p(a-m) + q(d-m)]\}$$

$$q' \doteq q\,\{1 + \frac{x}{\sigma^2}[p(d-m) + q(-a-m)]\} \quad .$$

For later purposes, it is useful to denote these by $p'(x)$, $q'(x)$, respectively. With a diploid model, AA, Aa, aa, relative "selective (viability) values" $1 + s_2$, $1 + s_1$, and $1 + s_0$, respectively, population $p^2AA + 2pqAa + q^2aa$, then

$$p'^2 = \frac{p^2(1+s_2)}{p^2(1+s_2) + 2pq(1+s_1) + q^2(1+s_0)} \quad , \text{ etc.,}$$

$$= p^2\{(1+s_2)\ [1 - s_2p^2 - 2s_1pq - s_0q^2]\}$$

$$\doteq p^2\{1 + s_2 - s_2p^2 - 2s_1pq - s_0q^2\}$$

$$= p^2\{1 + s_2(1-p^2) - 2s_1pq - s_0q^2\} .$$

Above, we have

$$p'^2 = p^2\{1 + \frac{x}{\sigma^2}\ [a - p^2a - 2pqd + q^2a]\}$$

$$= p^2\{1 + \frac{x}{\sigma^2}\ [a(1-p^2) - 2pqd + q^2a]\} .$$

We may verify that there is a correspondence between the representations if we take

$$s_2 = \frac{x}{\sigma^2}\, a,\ s_1 = \frac{x}{\sigma^2}\, d,\ s_0 = \frac{x}{\sigma^2}\,(-a) .$$

We may then consider a group of the population, selected on the basis of the metric trait, and we accommodate this if we replace x by the average x, which we may write as $i\sigma$ where i is the standardized differential. Hence quantitative selection merges with qualitative selection by using

$$s_2 = i\,\frac{a}{\sigma}\ ,\ s_1 = i\,\frac{d}{\sigma}\ ,\ \text{and}\ s_0 = i\,\frac{(-a)}{\sigma} .$$

So we see that if we may assume that effects at a single locus are small, so that σ is essentially constant, and the standardized differential is kept constant, selection for a metric trait may be regarded as constant genotypic viability selection with regard to this locus. This line of thought is sometimes attributed to Haldane.

We may also note for the single locus case that

$$p'-p = i\,\frac{p\alpha}{\sigma}$$

where α is the least-squares "effect" of A versus a. If we consider a haploid population pA + qa with weak viability selective values 1+s and 1 for A and a, respectively, then

$$p'-p \doteq spq \ .$$

We see that the haploid model corresponds in effect to the diploid one if

$$\frac{i\alpha}{\sigma} = sq$$

or

$$i \left[\frac{p(a-m) + q(d-m)}{\sigma} \right] = sq \ .$$

If $d = 0$, $m = (p-q)a$, then we have

$$i \frac{qa}{\sigma} = sq \quad \text{or} \quad s = i \frac{a}{\sigma} \ .$$

So diploid metric trait selection with respect to a single locus of small effect may be approximated with respect to gene frequency, if there is no dominance, by a haploid model with constant genotypic viability selection. Obviously, the case with dominance cannot be so approximated. The haploid representation has been used extensively, particularly by A. Robertson.

It is not my intention in this essay to make a eulogy of R. A. Fisher, and indeed the reader will have noted some critical remarks. But it seems that the field of quantitative genetics has spent decades pursuing lines of development Fisher set down in 1918 (actually mainly before 1916) and often has failed to read and understand the first steps he made.

In the 1918 paper Fisher gave (page 403) the regression of offspring on parent in the form

$$\frac{\sigma_A^2}{\sigma_P^2}$$

in modern terms. He did not feel it necessary, one supposes, to state specifically what other regressions were and what the implications are. It is a trivial consequence of this that if we select individuals on the basis of their value for the metric trait, and we mate these to the whole population, then the offspring mean is equal to

$$\tfrac{1}{2}\frac{\sigma_A^2}{\sigma_P^2}\,\mathrm{Ave}(x)$$

which with normality of the trait and selection of the upper portion p of the population so that $\mathrm{Ave}(x) = (z/p)\sigma_P$, comes out to be

$$\tfrac{1}{2}\frac{z}{p}\left(\frac{\sigma_A^2}{\sigma_P^2}\right)\sigma_P$$

which is recognized as the "work horse" formula of quantitative selection.

Suppose we mate the group measuring x_1 at random with the group measuring x_2. Then, working with the case of 2 alleles for simplicity of exposition (but not of development) we are mating a subpopulation having gene frequency $p'(x_1)$ with a subpopulation having gene frequence $p'(x_2)$. Then the offspring (sub)population has array

$$[\,p'(x_1)A + q'(x_1)a\,]\quad[\,p'(x_2)A + q'(x_2)a\,]\ .$$

The argument can be pursued.

We see that we can do a number of interesting computations on this Fisherian basis. We can consider perfect phenotypic positive assortative mating, perfect phenotypic negative assortative mating, and intermediate cases. We can consider a wide variety of matings based on phenotype and on genetic operations of inbreeding. I hope to present an integrated account elsewhere. I shall, here, merely make the comment that the additive genetic variance defined in a least squares sense, which Fisher was so fond of, is not a useful parameter. And, to give what I regard as the 'coup de grace,' even if it were useful, it cannot be estimated from obtainable data.

The above argument is strongly dependent, it is clear, on there being (a) a single locus segregating and (b) genotypic effects small relative to $\sigma(=\sigma_P)$, the phenotypic standard deviation, (c) a constant normal distribution of environmental effects, which are

additive, and (d) the approximation (which cannot hold perfectly) that a mixture of normal distributions can be taken to be a normal distribution. Latter (1965) gives very useful ideas on part of the approximation process. It seems rather definite that Fisher thought one could get a reliable result by treating each locus singly and regarding all other loci as contributing noise, which would behave as random environment, and then by adding the results for the separate loci. This supposition pervades the literature of quantitative genetics (and of population genetics with fitnesses multiplicative over loci). Surely it should be questioned.

The Fisherian argument may be generalized to an arbitrary number of loci, with a similar approximative process, by taking the qualitative viability selective value of a genotype to be

$$s(\text{genotype}) = \frac{i}{\sigma}\,[\text{genotypic effect} - \text{mean}] \ .$$

This has been exploited by Griffing in a fine series of papers, for which the Felsenstein-Taylor bibliography may be consulted. Griffing considered only upper truncation selection, with genotypic expression not dependent on sex, and with random mating of the selected group. I cannot give here an appropriate review of this line of work. The requirement in the mathematics is that the selection be very weak, so that changes in population due to selection do not affect variance properties. I find it very remarkable, though some of the results can be derived from other considerations as I shall note later, that the parameters that characterize the successive means depend not only on the recombination probabilities, as they obviously should, but also on the parameters σ^2_A, σ^2_D, σ^2_{AA}, σ^2_{AD}, and so on, that I developed (Kempthorne, 1954). The upshot is then that one has a formula for the successive population means under weak upper truncation selection with random mating of the selected subpopulation.

To some extent, the results of Fisher and of Griffing are not at all unexpected. Suppose we have a large number of loci that are to some extent nonepistatic, then with random mating, we may

expect that the joint distribution of sire (S), dam (D) and offspring (O), for instance, with respect to the metric trait will be trivariate normal. This distribution is very special because conditional expectations of single variables are linear functions of the values of conditioning variables. Hence we have

$$O = \mu + \beta_{OS}(S-\mu) + \beta_{OD}(D-\mu) + e$$

with $E(e) = 0$ and with β_{OS}, β_{OD} determined from the variance matrix of S, D and O. And with random mating,

$$\beta_{OS} = \beta_{OD} = \frac{Cov(P,O)}{\sigma_P^2} .$$

Then we use the fact that

$$Cov(P,O) = \frac{1}{2}\sigma_A^2 + \frac{1}{4}\sigma_{AA}^2 + \ldots ,$$

in the case of no linkage, and we have part of Griffing's results. It is interesting that one can obtain some results without invoking Mendelism at all, but merely use purely statistical ideas of correlation and regression. One can go further, I believe. The whole area of selection can be approximated by purely statistical ideas of correlation and regression. The ideas of Mendelism merge with these ideas, as Fisher showed (more or less), and the fact that the theory does not need Mendelism in some respects, and one can almost say, does not use Mendelism intimately is, I think, a reason for it having a moderate degree of robustness in relation to assumptions. Apart from a difficulty I shall mention later, one could proceed as follows. Let there be a population; let rules of forming mating couples be defined in terms of metric traits of individuals and/or in terms of relationship; let there be selection of individuals on the basis of metric traits or metric traits of related individuals; and finally let the offspring be measured. Then without an atom of formal Mendelism and with a large data set, the joint distribution of offspring and parents can be determined. One can examine this distribution and determine a prediction

equation, which one can then apply for a few generations. The only flies in the ointment for this proposal are that every covariance would have to be determined from data and not inferred from, say, a coefficient of relationship and a heritability, and large data sets would be needed to control sampling error. So one could have a completely empirical selection procedure and a purely empirical process of obtaining a prediction of the result of continued selection. I suggest that this type of thinking should not be dismissed as a cranky idea. The reason that some predictions of the results of selection theory seem to work is that they are based on a process rather close to what I have sketched.

I should note before passing on that I do not have space to discuss the very important idea of reciprocal recurrent selection. A critical review of Comstock, Robinson and Harvey (1949) would be valuable.

Apart from potential deficiencies of the theory discussed with respect to aspects such as epistacy, linkage and environment, there is one very critical aspect. This is that the population is infinite. What this means in simple upper truncation selection is that the population size is some very big number, say, N, from which the best $mN(0 < m < 1)$ members are chosen; these mN individuals are mated at random to produce a very large population, say of the same size N, as the base for the next cycle. This is surely a very artificial structure. It does, however, provide some basis for predicting gain from selection. Before turning to the role of finite population sizes, it may be useful to discuss some deficiencies of infinite population theory. I have already mentioned that our infinite theory does have the deep deficiency that it merely predicts the immediate gain from 1 cycle of selection. Just how many cycles of selection may be predicted reasonably is quite unknown. To get an idea of what is involved, consider a single segregating locus with $\underline{A}$ at frequency p, with no dominance and effect α for the substitution of $\underline{A}$ for $\underline{a}$. With weak selection,

usual simple assumptions,

$$\Delta p = \frac{i\, p(1-p)\alpha}{\sqrt{2p(1-p)\alpha^2 + \sigma^2}} \quad .$$

This equation can be iterated, of course, to obtain the whole selection response curve, and one can, of course, convert this, as Haldane did for qualitative selection, into a differential equation and solve. Even in this simple case, however, the only attributes determinable by conventional methods, it seems, are $2p(1-p)\alpha^2$ and σ^2. So even in this case we cannot determine $2(1-p)\alpha$ which is the total achievable gain. Perhaps under simple assumptions we can do this if we determine higher moments, a comment that recalls the thrust of the Fisher-Immer-Tedin (1932) paper, which seems to have had little impact, and perhaps justifiably. If now we consider the case of k loci we have

$$\Delta p_i = \frac{i\, p_i(1-p_i)\alpha_k}{\sqrt{2 \sum_j p_j(1-p_j)\alpha_j^2 + \sigma^2}} \quad , \; i = 1,2,\ldots,k \; .$$

In this case, if we are given a set of pairs $\{(p_j, \alpha_j)\}$, where p_j, α_j are the initial frequencies and loci effects, we can compute easily by recursion the progress over cycles of each p_j and of the population mean. I have not been successful so far in my attempts to see how any set of observations on the initial population of the usual type enables a determination of the nature of the response curve over cycles to selection and of the limit that would be achieved. The same problem arises, of course, with finite populations.

There are, I think, some points of interest in this arena. We may note, for instance, that the change in mean under the very ideal circumstances is $\Delta\mu = i\sigma_A^2/(\sigma_A^2 + \sigma^2)$, where $\sigma_A^2 = 2p(1-p)\alpha^2$. It is clear, then, that a priori, there is no logical requirement that the response curve be concave, i.e., have decreasing 'slope.' It seems to be rare for the response in a second cycle to be greater that that in the first cycle of selection for attributes of usual

interest in economic species; though, of course, one could get such a curve by transformation of attribute. On the question of limits, it is interesting that at the present conference we saw cases in which, apparently, one can make progress indefinitely (apart from natural limits such as 0%, 100%). The matter of being able to make a prediction of the genetic potential in different genetic populations is most obscure. For instance, we may have 6 inbred lines from which we generate 15 F_1 and then 15 F_2 populations. How are we to form a judgment on which population we should attack by quantitative selection? If the F_2 populations are equally variable, we should, presumably, take the population with the higher mean, but it seems obvious that we should examine a large sample of each F_2 population to aid the judgment. Should we take, for instance, the F_2 with the largest σ_A^2 (assumed measurable)? This one will give the largest immediate response, but will it give the highest mean after a number of cycles of selection? We do not know. The fact is, I believe, that we have no idea of the limits to selection in infinite (i.e., very large) populations with infinite (i.e., very many) observations on covariances of relatives. We cannot tell whether lizards can become dinosaurs or not under selection for size. At a more useful level, can we develop 300-bushels-per-acre corn, or hens that lay three eggs in two days? Is it important in theory to be able to do something about the questions I have raised? I think so, but perhaps we have to accept unanswerability.

Finiteness of Populations

There has been a huge intellectual effort in the past 20 years by workers, in works far too numerous to list, directed towards the role of the sampling variability that occurs with finite sampling from finite or infinite Mendelian populations. The logic of the game is fairly straightforward in terms of stochastic processes, but the mathematics are rather complex, even in simple cases, and very difficult with anything but the case of a single segregating locus. Just how this very extensive theory is relevant to

theory of quantitative genetics merits lengthy presentation. I hope someone will give a definitive discussion of the question.

One aspect of this whole endeavor has been used by A. Robertson (1960) in his well-known theory of limits. Because this theory is relevant to quantitative genetic selection, it is perhaps useful to give a very elementary exposition. Consider a particle that moves over a set of states, which we index by $1,2,\ldots,S, S+1, S+2, \ldots, S+k$, where states $S+1, S+2, \ldots, S+k$ are absorbing in the sense that once the particle reaches any one of the states it does not move. The first S states are not absorbing in that there is a nonzero probability of leaving any of them. Let u_i be the probability that the particle will reach state $S+1$, say, eventually, given that it is initially in state i. Let T_{ij} be the probability that the particle goes from state i to state j in one step. Then, clearly

$$u_i = \sum_{j=1}^{S} T_{ij}u_j + T_{i,S+1}$$

or, in matrix terms, with obvious definitions,

$$u = Tu + v .$$

Hence

$$(I-T)u = v, \text{ and } u = (I-T)^{-1}v.$$

One may be able sometimes to work from this base.

One interesting case is considered in this volume (Bailey). Suppose we have a selfing species; we start with an individual, obtain M offspring by selfing; we measure each offspring and select the best to begin a new cycle. If we have a single locus with 2 alleles A, a, then the states are Aa, AA and aa, where AA and aa are absorbing states. Then let

p_2 = Prob{Aa gives a selected offspring which is AA},

p_1 = Prob{Aa gives a selected offspring which is Aa},

and

p_0 = Prob{Aa gives a selected offspring which is aa}.

If u = Prob{a line starting from Aa reaches the state AA}, then

$$u = p_2 + p_1 u ,$$

or

$$u = \frac{p_2}{1-p_1} = \frac{p_2}{p_2 + p_0} .$$

So to determine the probability u, we need only to obtain the ratio p_2/p_0 for a single cycle of selection, this being, however, not a small task.

If we have a population with gene frequency p, and if the state of the population at the beginning of any cycle of selection is given by the gene frequency, with p = 1 or 0 being absorbing states, and u(p) is the probability that a population starting from the state p eventually reaches the state 1, then

$$u(p) = \sum_{p'} T_{pp'} u(p') ,$$

where $T_{pp'}$ is the probability that in any one cycle the gene frequency changes from p to p', assumed to be the same for all cycles. This equation can be solved with a small number of states when one has obtained $T_{pp'}$ for all p, p', this indeed being no small task in general without highly heuristic arguments. Also direct attack with most partly realistic models involves a large number of states and $\{T_{pp'}\}$ depends on one or more parameters.

The special case used by Robertson is that of a diploid population with a single diallelic locus of size N, characterizable by gene frequency, which will be of the form i/2N, where i is the number of, say, A genes. Then

$$u(i) = \sum_{i'} t_{ii'} u(i') .$$

We may use the Euler summation formula

$$\sum_{x=1}^{X} f(x) = \int_{1}^{X} f(w)dw + \frac{1}{2} F(X) + R ,$$

or some variant, with remainder R small. This process gives us the integral equation

$$u(p) = \int T(p,p+x)\, u(p+x)dx \ ,$$

where $T(p,p+x)$ is the probability of a shift from p to p+x in one cycle. Then by expanding $u(p+x)$ and ignoring remainders, we obtain the standard differential equation and, e.g., the solution for the case of no dominance, as

$$u(p) = \frac{1 - e^{-2NSp}}{1 - e^{-2Ns}} \ .$$

Work by several has shown that this remarkably simple formula gives very good approximation for the case of a single locus. A critical review of the voluminous literature would be valuable but is impossible here.

Attack primarily by W. G. Hill and A. Robertson on the case of 2 or more loci is extremely difficult and, with suggestions for parameterization from diffusion approximation, has depended on very extensive use of simulation and computers.

Apart from the great complexity of results obtained and the problems of extension to a large number of loci, for which see Robertson (1970), the utility of this approach to applied quantitative genetics is quite obscure to me. The behavior of an infinite population under quantitative selection depends, even with additive gene action, on gene frequencies, on gene effects and on recombination values. I was interested, but not surprised, that in the present conference the old questions of number of loci and size of effects were being raised again, and appeal was being made to an estimation procedure, Castle-Wright, that had been discarded (except by the Birmingham School) as requiring too many assumptions. In the case of a single locus with two alleles and AA-aa = α, say, we need to determine p and α, as in the case of the infinite population theory, to determine the fixation probability.

The foregoing also brings sharply into focus a point that should have been obvious to us all decades ago, but was not. The step from a finite population π_1 to a finite population π_2, involving selection or not is, because of Mendelian processes and environmental variation, a random variable of very complicated structure. The result of a single line of successive populations is then a very complex vector random variable. A single "replicate" of a selection experiment is then a random variable of unknown properties, and is nearly useless, except that it indicates, surely, one possibility that occurred. Extensive verbal theorizing from one such line is obviously unjustified. Under a simple model, some theory applicable to observations on individuals in a single selected "line" has been developed by W. G. Hill (1970). The complexities of inference from a realization of a stochastic process have yet to be dealt with.

How To Design a Quantitative Genetic Study?

All the preceding, and considerations not mentioned, raise for the quantitative geneticist the very basic question of how to design an experimental quantitative genetic study, with, say, a laboratory species, such as Drosophila or mice or Tribolium. Obviously, one can conduct an upper truncation selection experiment for a metric trait. Obviously, too, such an experiment must be replicated, or one will be lost in a cloud of mere speculation, which may well be about random features of a particular realization. Every process that one applies must be replicated. The simplest replication is to make a number of independent starts from the base population. In this case, however, the successive results from a given start are obviously correlated in a serial way. If one introduces, say, relaxed selection or selection in an opposite direction at some point in time, this must be replicated. Exactly the same considerations hold in an observational study, whether with a quantitative genetics or population genetics orientation. A single time series realization may easily be worth little more "than the paper

it is written on." These considerations have the consequence that even a naive exploratory experiment involves a massive effort.

Suppose one takes cognizance of the need for replication of Mendelian sampling as well as of environmental variability, to what scientific directions should a quantitative genetics experiment be oriented? I believe that this question has not been addressed seriously. I have commented on the simple experiments of "biometrical genetics." They do little more than enable estimation of some simple covariances of relatives. The same seems true of diallel cross experiments. What do general and specific combining ability experiments tell us, apart from indicating which of a set of lines "combines well" with the whole set of lines? It is critically necessary that the questions posed here are addressed seriously and in a questioning way.

The basic dilemma is that an experiment design must be based on a hypothesized theory, even a naive one. Insofar as theory of quantitative genetics is deficient, good ideas for quantitative genetic experiments do not arise.

The Matter of Reproductive Fitness

The mathematics of the theory of quantitative genetics discussed clearly uses intimately in the modelling the assumption that there is no genotypic variability in fecundity or viability. All covariances of relatives are based on this assumption. In the naive selection theory we have, it is assumed that there is no "natural selection;" all selected individuals have only variability in fecundity and viability represented by purely random error, which may then be essentially ignored in almost all the basic mathematical computations. The blending of "natural selection" with directed selection via metric attributes is an outstanding theoretical and experimental problem. This is potentially a topic on which ideas of population genetics and quantitative genetics may merge with fruitful results. Is the conflict between natural selection and humanly directed selection at the root of the

well-known difficulties in poultry breeding for egg production? Is natural selection the explanation for the inability to maintain some lines in some species under intense inbreeding? How should one attempt to examine the possibilities?

Related, perhaps, to this is the view that may be advanced by some that yield in a species like maize, or egg production in poultry, is very much like an attribute of "natural fitness." I think this analogy can easily be very overworked and may be strongly misleading. I say this because the economically superior populations generated would, I believe, have no future in a "natural" millieu. It is well-established, it seems, that a very good double cross maize hybrid will degenerate very rapidly under "natural" conditions. It follows, I believe, that any attempt to relate the hybrid vigor that we find, e.g. in maize, to what one might expect under natural evolutionary processes is most unlikely to be fruitful. Any appeal to equilibrium arguments for naturally evolving populations is unlikely, I opine, to be effective in the situation where man is making huge changes both genetically and environmentally. In the area of man-directed selection and modification of environment, we have obviously not reached equilibrium, or we would fail to make progress and cease our efforts. Indeed, the justified concern of the globally oriented ecologist is that we are not at equilibrium, but on a "primrose path" that will lead to the destruction of natural life as we now see it. It should be noted that I use the adjective "justified." I do not wish to imply that the concern should lead to a complete return to purely natural processes, which could lead to the death by starvation of billions of existing humans.

The Theory of Applied Quantitative Genetics

This topic, like many others I have mentioned, merits deeply critical examination, and I regret being able to make only a few remarks. The general approach as exposited excellently by Falconer (1960), for instance, uses the idea that genes act essentially additively, and recourse is then made to a concept that I find

rather obscure--that of breeding value, which is presumably the mean of an infinite offspring array.

The general structure of the logic may be presented rather succinctly as follows. Suppose we have a random variable Z', which equals (Y',X'), where $Y' = (Y_1, Y_2, \ldots, Y_p)$ and $X' = (X_1, X_2, \ldots, X_q)$, the whole variable Z having a (p+q)-variate probability distribution. Consider then estimating or predicting a variable a'Y by means of b'X, with the criterion that $E[(a'Y - b'X)^2]$ shall be a minimum. Here the vector a is given, and b is to be determined. Let the variables have zero means and variance-covariance matrices as follows:

$$E(XX') = F, \quad E(XY') = G, \quad E(YY') = H .$$

Then we wish to find the vector b which minimizes

$$Q = a'Ha - 2b'Ga + b'Fb.$$

Differentiation gives the equation

$$Fb = Ga .$$

If we write, taking F to be invertible, as it will be,

$$b = F^{-1}Ga + \delta ,$$

we have

$$Q = a'Ha - a'GF^{-1}Ga + \delta'F\delta .$$

This is minimized, clearly, with δ as the null vector; thus we have the fully proved formal solution, given for a particular frequently occurring situation expressed by the well-known equation Pb = Ga. The general procedure was given by Fairfield Smith (1936), though it goes back for decades in psychological testing. The situation stated is very general in that $X_1, X_2, \ldots, X_q$ are observations on individuals, and $Y_1, Y_2, \ldots, Y_p$ are so-called breeding values. It may be that there is just one Y, or that there is a Y associated with each X. The basic formulae given by Lush, which have found such wide use in animal breeding, may be derived from this

standard basis. Some of the more recent work by Henderson (e.g., this volume) is derivable by the same route with a model

$$Y = Z\beta + \text{error}$$

with the vector $Z\beta$ representing fixed effects, the same minimization, but with the additional restriction that $a'Z = \emptyset$ (the null vector), or with an additional assumed model

$$X = A\beta + \text{error},$$

again with $A\beta$ representing fixed effects.

To say this is not to imply, however, that the overall problem is solved. One may readily adjoin ideas of restricted selection indices (Kempthorne and Nordskog, 1959). There are very difficult questions of statistics. There are very difficult questions resulting from the existence of selection in the "X" data, e.g., selection oi bulls by daughter records. Also, underlying application to large animals are very difficult questions relating to the overlapping of generations which are discussed by Hill and Pollak in this volume.

It seems that, at root, the same formalization holds for selection in a plant population, though complexities arise at a basic level because of the use of intense inbreeding, which is avoided in animal populations.

Concluding Remarks

To develop a fully adequate theory of quantitative genetics is a fantastically difficult task. One has only to contemplate Mendelian processes, which while very simple for a single segregating locus, are simply not workable for, say, 1000 linked loci. Even in the case of a single segregating locus, there are simply formulated theoretical questions that we have been unable to answer. Attack on the field requires, we see, almost the whole panoply of mathematics, and particularly ideas of stochastic processes, an area of the 20th century. The field of quantitative genetics uses also a considerable portion of the available statistical theory,

which is a 20th century creation. We are involved in applied mathematics rather different from the conventional physical science type and much more difficult. That the problems are huge is obvious because the aim is, in some respects, to explain quantitative variation in the whole biological world.

That we see great deficiencies in our presently available theory should not be a surprise. It seems likely, however, that the mere following of the routes of the past will not be really effective. There is deep need for that very rare human attribute, creativity, which our human society does not support as much as it should. Instead, support is given for "polishing the apples of past thought," and a dedicated creative effort that is unsuccessful receives short shrift. The importance of quantitative genetics to human affairs merits much greater support of free, unfettered, and potentially unsuccessful effort than it has heretofore received. Obviously, much larger selection experiments must be made to suggest testable hypotheses. A somewhat natural reaction to selection experiments of the past is "Interesting, but so what?". Obviously mathematical and statistical research of difficult order is needed. Obviously, because the "gestalt" is so complicated, the mathematical and statistical problems must be approached by the computer, the fastest that exists, with large financial support, because an hour or two can merely generate a cloud of noise.

In recent years we have heard, via Camus, of "The Myth of Sisyphus," who it may be recalled spends eternity rolling a boulder to the top of a hill only to have it roll to the bottom again. I believe this myth has relevance to all science. We develop a naive theory, and we are momentarily very pleased with it, but then we see that our progress has generated even more difficult problems. Having rolled our boulder to the top of the hill, we find nearly the same boulder at the bottom of an even steeper hill. We see this in physics and chemistry and in evolutionary genetics, as described by Lewontin (1974) for instance, which I see as a tale full of creative effort, but ending not with a "bang" but with a

"whimper." We see it, of course, also in qualitative genetics. Our triumphs of yesterday lead to our anxieties of today. There should be very little "mutual back-slapping" for the progress. But also we should not write polemics attempting to pin-point our failures.

On the contrary, we should perhaps feel somewhat gratified that we do have some theory with some predictive power, as was shown by several contributors to our conference. It seems quite unarguable that applied quantitative geneticists have made huge genetic improvements in some economic species, and part of that progress is a result of use of our admittedly very naive quantitative genetic theory.

* * * * * * * * *

It is critical to note that this review of the status of quantitative genetic theory does not treat all subareas with appropriate attention and depth. To do so was quite impossible. Furthermore, the bibliography below is very incomplete. I can only say that most of the writings of the founders, Fisher, Haldane, Wright, of every contributor to the conference, and of many individuals mentioned without reference are important in the area. The prime source is the bibliography of Felsenstein and Taylor (1973), a huge proportion of which is relevant.

BIBLIOGRAPHY

(1) Anderson, V. L. and Kempthorne, O. (1954). A model for the study of quantitative inheritance. Genetics 39, 883-898.

(2) Cockerham, C. C. (1954). An extension of the concept of partitioning hereditary variance for analysis of covariance among relatives when epistasis is present. Genetics 39, 859-884.

(3) Comstock, R. E., Robinson, H. F. and Harvey, P. H. (1949). A breeding procedure designed to make maximum use of both general and specific combining ability. Agronomy Journal 41, 360-367.

(4) Comstock, R. E., Robinson, H. F., and Cockerham, C. C. (1958). Quantitative Genetics Project Report 1947-1957. Institute of Statistics Mimeo Series Number 167, North Carolina State University.

(5) Falconer, D. S. (1960). Introduction to Quantitative Genetics. New York: Ronald Press Co.

(6) Falconer, D. S. (1972). Review of Biometrical Genetics. Heredity 28, 415-417.

(7) Felsenstein, J. and Taylor, B. (1973). A Bibliography of Theoretical Population Genetics. National Technical Information Service, U.S. Dept. Commerce, Springfield, Va.

(8) Fisher, R. A. (1918). The correlation between relatives on the supposition of Mendelian inheritance. Transactions of the Royal Society of Edinburgh 52, 399-433.

(9) Fisher, R. A. (1930). The Genetical Theory of Natural Selection. Oxford: Clarendon Press. Reprint, (1958), New York: Dover Inc.

(10) Fisher, R. A. (1941). Average excess and average effect of a gene substitution. Annals of Eugenics, London 11, 53-63.

(11) Fisher, R. A., Immer, F. R. and Tedin, O. (1932). The genetical interpretation of statistics of the third degree in the study of quantitative inheritance. Genetics 17, 107-124.

(12) Gillois, M. (1964). La relation d'identité en génétique. Unpublished thesis. Faculty of Sciences. University of Paris.

(13) Harris, D. L. (1964). Genotypic covariances between inbred relatives. Genetics 50, 1319-1348.

(14) Heber, R., Gaber, H., Harrington, S., Hoffman, C. and Falender, C. (1972). Rehabilitation of Families at Risk for Mental Retardation. Rehabilitation Research and Training Center in Mental Retardation. Madison: University of Wisconsin.

(15) Hill, W. G. (1970). Theory of limits to selection with line crossing. Mathematic Topics in Population Genetics. (Ed., K. Kojima). 210-245. New York: Springer-Verlag.

(16) Kempthorne, O. (1954). The correlations between relatives in a random mating population. Proceedings of the Royal Society of London, B, 143, 103-113.

(17) Kempthorne, O. (1957). An Introduction to Genetic Statistics. New York: J. Wiley and Sons. Reprinted (1969) Ames: Iowa State University Press.

(18) Kempthorne, O. (1960). The biometrical relations between relatives and selection theory. Biometrical Genetics. (Ed., O. Kempthorne) 12-23. New York: Pergamon Press.

(19) Kempthorne, O. (1974). Review of collected papers of R. A. Fisher. Social Biology 21, 98-101.

(20) Kempthorne, O. and Nordskog, A. W. (1959). Restricted selection indices. Biometrics 15, 10-19.

(21) Latter, B. D. H. (1965). The response to artificial selection due to autosomal genes of large effect. I. Changes in gene frequency at an additive locus. Australian Journal of Biological Sciences 18, 585-598.

(22) Lewontin, R. C. (1974). The Genetic Basis of Evolutionary Change. New York: Columbia University Press.

(23) Malécot, G. (1948). Les mathématiques de l'hérédité. Masson et Cie, Paris. Eng. trans. (D. M. Yermanos). The Mathematics of Heredity. San Francisco: Freeman and Co.

(24) Mather, K. (1949). Biometrical Genetics. 1st Ed. London: Methuen.

(25) Mather, K. and Jinks, J. L. (1971). Biometrical Genetics. 2nd Ed. Ithaca, New York: Cornell University Press.

(26) Norton, B. and Pearson, E. S. (1976). A note on the background to, and refereeing of, R. A. Fisher's 1918 paper 'On the correlation between relatives on the supposition of Mendelian inheritance.' Notes and Records of the Royal Society of London 31, 151-162.

(27) Robertson, A. (1960). A theory of limits in artificial selection. Proceedings of the Royal Society of London, B. 153, 234-249.

(28) Robertson, A. (1970). A theory of limits in artificial selection with many linked loci. Mathematical Topics in Population Genetics. (Ed. K. Kojima) 246-288. New York: Springer-Verlag.

(29) Schnell, F. W. (1961). Some general formulations of linkage effects in inbreeding. Genetics 46, 947-957.

(30) Schnell, F. W. (1963). The covariance between relatives in the presence of linkage. Statistical Genetics and Plant Breeding. (Eds., W. D. Hanson and H. F. Robinson). 468-483. Washington, D. C.: National Academy of Sciences - National Research Council Publication No. 982.

(31) Smith, H. F. (1936). A discriminant function for plant selection. Annals of Eugenics 7, 240-250.

(32) van Aarde, I. M. R. (1975). The covariance of relatives derived from a random mating population. Theoretical Population Biology 8, 166-183.

(33) Willham, R. L. (1963). The covariance between relatives for characters composed of components contributed by related individuals. Biometrics 19, 18-27.

(34) Wright, S. (1921). System of mating. Genetics 6, 111-178.

(35) Wright, S. (1963). Discussion - Plant and animal improvement in the presence of multiple selective peaks. Statistical Genetics and Plant Breeding. (Eds., W. D. Hanson and H. F. Robinson) 116-122. Washington, D. C.: National Academy of Sciences - National Research Council Publication No. 982.