Biometrical Genetics

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The study of continuous variation

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Preface to the first edition

The properties of continuous variation are basic to the theory of evolution and to the practice of plant and animal improvement. Yet the genetical study of continuous variation has lagged far behind that of discontinuous variation.

The reason for this situation is basically methodological. Mendel gave us not merely his principles of heredity, but also a method of experiment by which these principles could be tested over a wider range of living species, and extended into the elaborate genetical theory of today. The power of this tool is well attested by the speed with which genetics has grown. In less than fifty years, it has not only developed a theoretical structure which is unique in the biological sciences, but has established a union with nuclear cytology so close that the two have become virtually a single science offering us a new approach to problems so diverse as those of evolution, development, disease, cellular chemistry and human welfare. Much of this progress would have been impossible and all would have been slower without the Mendelian method of recognizing and using unit differences in the genetic materials.

These great achievements should not, however, blind us to the limitations inherent in the method itself. It depends for its success on the ability to assign the individuals to classes whose clear phenotypic distinctions reveal the underlying genetic differences. A certain amount of overlap of the phenotypic classes can be accommodated by the use of genetical devices; but where the variation in phenotype is fully continuous in its frequency distribution, so that no such classes can be defined, the method cannot be used. A different approach is required, one based on the use of measurement rather than frequency.

The first steps were taken nearly 40 years ago, when the theory of cumulative factors or multifactorial inheritance, as it was variously called, was formulated. The full implications of this theory have, however, only gradually become realized. In the same way the special types of experiment and statistical analysis necessary for the study of continuous variation have only gradually become available. Nevertheless, though slow, progress has been real and we are now in a position to see not merely how continuous variation can be explained genetically, but also how experiments can be conducted enabling

us to understand and to measure the special genetical quantities in terms of which continuous variation can be analysed and its behaviour in some measure predicted.

The present book does not aim at covering the whole literature of the subject. I have concentrated attention rather on trying 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 their new use, and to outline an analytical approach which can help us to understand our experimental results, particularly those which can be obtained from plant material. In doing so I have assumed some knowledge of genetics and statistics. To have done otherwise would have made the text unnecessarily long, for this information can be gained from a variety of other sources.

The data with which I have had to work have been limited by the paucity of experiments adequate in both scope and description and I have therefore been unable to try out the methods, which are described, in as wide a variety of circumstances as could have been wished. These methods are in no sense exclusive or final; indeed their limitations require no stressing. But improvements can be brought about only as more and better experiments are undertaken; and such experiments cannot be planned until we have explored the scope and limitations of those we already have. Improvement of experiment, refinement of analysis and development of theory must be simultaneous and progressive.

Among the experiments upon which I have been able to draw none has been more instructive than that on ear conformation in barley, hitherto unpublished. This experiment was made in collaboration with Dr Ursula Philip, now of the Department of Zoology, King's College, Newcastle-on-Tyne, and I wish to express my indebtedness to her for allowing its results to be published in this way.

April 1947 K. M.

Preface to the second edition

Much has happened in the genetical study of continuous variation since the Preface to the first edition of this book was written 23 years ago. Theory has been developed and extended to include, notably, interaction between non-allelic genes and also interaction between genotype and environment. New methods of genetical analysis have been introduced, among which special mention must be made of diallel crosses. Statistical techniques have been refined and extensive experimental programmes have been carried out. There is, of course, still much to do, but we are encouraged by representations from many people to feel that a new edition of *Biometrical Genetics* revised and extended to cover these new developments would meet a growing need.

We have based our treatment very largely on the approach set out in the first edition as extended particularly by the Department of Genetics in the University of Birmingham with which we have both been associated for so many years. We have not aimed at giving the more general mathematical treatments in all their complexity, even where these are available, or to cover such matters as selection procedures: accounts of these can be found elsewhere (as, for example, in Kempthorne's *An Introduction to Genetic Statistics* and Falconer's *Introduction to Quantitative Genetics*) and they are in any case extraneous to our theme which is, to quote from the Preface to the first edition, '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'. We shall be content if our readers feel we have gone some way to achieving this aim.

We are indebted to many colleagues, past and present, both for the encouragement they have given us in planning this new edition and their help in preparing it: We would mention especially Dr B. W. Barnes and Dr R. Killick for allowing us to use unpublished data, Dr J. M. Perkins for carrying out certain calculations for us, Dr Killick, Dr Perkins and Mr D. Hay for checking a number of the formulae, and Miss S. M. Evans for her help in the

preparation of the typescript. We hope that they will feel the trouble they took on our behalf not to have been fruitless.

April 1970

K. M.
J. L. J.

Preface to the third edition

The 11 years that have elapsed since the preface to the second edition was written have seen a continuing development in the genetical theory and analysis of continuous (or, as it is frequently termed, quantitative) variation. This is especially so in relation to genotype × environment interaction, the prediction of the range of true-breeding genotypes that can be extracted from a cross between two parental lines, the use of the triple test cross as a means of analysing the genetical variation, and in both the genetical and statistical planning of experiments, or, where experiments are impossible as in man, of the necessary observations.

These developments were foreshadowed in the previous edition, but we have now sought to bring out more clearly the ways in which the methods of Biometrical Genetics can be used to gain a greater understanding of the genetical properties of natural and quasi-natural populations, including those of man himself, and of the potentialities open to the plant breeder in the manipulation of his material. There is still, of course, much to do; but we hope that we are at least beginning to dispel the notion, still too widely held, that Biometrical Genetics is no more than an esoteric form of genetical endeavour having little but theoretical interest.

Not infrequently in the past the question has been asked, by reviewers and others, as to why we make what to some seems excessive use of our own experiments to provide illustrative material, rather than drawing on a wider range of data from the literature. There are several reasons for this. In some cases no similar experiment has been carried out elsewhere, and in any case if we are undertaking a novel type of analysis we may well need access to the original observations – which are available only from our own experiments. Perhaps, however, the chief reason is that we have been carrying out this kind of investigation with *Nicotiana rustica* and certain lines of *Drosophila melanogaster* for nearly 40 years. This has given us not only a close and comprehensive knowledge of our living material, but also series of linked observations each of which can, over time, aid in the interpretation of the rest, as is well illustrated by the frequent use we make of the cross between our lines 1 and 5 of *N. rustica*.

We have taken the opportunity of this edition, in general, to change the presentation of metrical data from inches to centimetres. We have, however, retained the use of inches in certain long-standing experiments.

Again we tender our thanks to those of our colleagues who have assisted in the preparations of this edition, and particularly to Dr P. D. S. Caligari, for allowing us access to certain of his original observations before his own account of them was published.

May 1981

K. M.
J. L. J.

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1. BIOMETRY AND GENETICS

The growth of genetical science as we know it today began with the rediscovery of Mendel's work in 1900. Nevertheless, at the time of that event there were already genetical investigations in active progress; investigations which, although contributing relatively little to the development of genetical theory, still have an importance of their own. These were begun by Francis Galton, who published a general account of his methods and findings in *Natural Inheritance* (1889), and were continued by Karl Pearson and his pupils. From them the application of statistical mathematics to biological problems received a great impetus, and if only for this reason they mark a significant step in the growth of quantitative biology.

The relative failure of this work in its avowed purpose, that of elucidating the relations of parent to offspring in heredity, stems from a variety of causes. Mendel himself regarded the failure of his predecessors as due to their experiments not making it possible 'to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their statistical relations'. While Galton's work can hardly be regarded as failing in the third respect, the nature of the material he chose rendered it impossible for him to succeed in the other two. His extensive use of human data, with its small families and genetically uncertain ancestries, introduced difficulties enough; but it was the choice of metrical or quantitative characters, like stature in man, that foredoomed the work from the point of view of the aws of inheritance. These characters show continuous gradations of expres- ion between wide extremes, the central expression being most common in any amily or population, and the frequency of occurrence falling away as we proceed towards either extreme (see Fig. 2). The distributions of frequencies of the various grades of expression sometimes as with stature in man, approximate closely to the Normal curve; but while retaining the same general shape they depart in other cases from this precise form, for example by being asymmetrical. The simple Mendelian ratios, with their clear implication of the particulate or discontinuous nature of hereditary constitution and transmis-

sion, depend on the use of characters by which individuals could be classed unambiguously into a few (usually two) distinct groups; they cannot come from continuous variation. Indeed, Mendel himself deliberately neglected such variation in his material, presumably with the clear recognition that it could only have a distracting influence in his analyses.

Yet this continuous variation could not be completely overlooked. Darwin himself had emphasized the importance of small cumulative steps in evolutionary change, and observation on any living species, especially the most familiar of all, man, showed how much of the variation between individuals was of this kind. The genetical problem of continuous variation remained, therefore, a challenge to geneticists; the more so as biometrically, Galton and Pearson had clearly shown such variation to be at least in part hereditary, even though they had failed to discover the mode of transmission. Neither the Galtonian nor the Mendelian method was of itself capable of supplying the solution. The understanding of continuous variation awaited a fusion of the two methods of approach, the genetical and the biometrical, for each supplied what the other lacked. The one gave us the principles on which the analysis must be based; the other showed the way in which to handle continuous variation, the way of representing it in a form which made fruitful analysis possible.

Fusion was, however, delayed by a rivalry which arose between Biometricians and Mendelians as soon as Mendel's work was rediscovered. This was aggravated by divergent opinions on the importance of continuous and discontinuous variation in evolutionary change, and exacerbated by the polemics of the protagonists. In time, attempts to reconcile the two views became welcome to neither party. The original discordance seems to have arisen because neither side understood the full implications of Mendel's fundamental separation of determinant and effect, of genotype and phenotype. The Biometricians seem to have regarded continuous somatic variation as implying continuous genetic variation, and the Mendelians seem to have considered discontinuous genetic variation as incompatible with anything but obviously discontinuous somatic variation. Indeed, de Vries took continuity of variation in the phenotype as a criterion of its non-heritability.

Two important steps had to be taken, therefore, before the biometrical and genetical methods could be brought together. In 1909 Johannsen published his *Elemente der exakten Erblichkeitslehre*. In it he described the experiments with beans which led him to formulate his pure line theory. In particular he showed that heritable and non-heritable agencies were jointly responsible for the variation in seed weight with which he was concerned; that their effects were of the same order of magnitude; and that there was no means, other than the breeding test, of distinguishing between their contributions to the variation. The relations between genotype and phenotype were thus becoming clearer. The effects of discontinuity of the genotype could be smoothed out and con-

tinuous variation realized in the phenotype by the action of the environment.

In the same year a second Scandinavian geneticist, Nilsson-Ehle, took the other step. He found that in wheat and oats there existed hereditary factors whose actions were very similar, if not exactly alike. There were, for example, three such factors for red versus white grain in wheat. Any one of them, when segregating alone, gave an F_2 ratio of 3 red:1 white. Two of them segregating together gave 15:1 for red:white, and all three together gave a 63:1 ratio. That the red-grained plants in these F_2's were of various genetical constitutions could be shown by growing F_3 families. Some of these gave 3 red:1 white, others 15:1, others 63:1 and still others all red. Yet there were no detectable differences in colour between plants owing their redness to the different factors. There were certainly some differences in redness, but these appeared to be associated more with the number of factors than with the particular factors present. The first degree of redness would be given equally by the three genotypes Aabbcc, aaBbcc and aabbCc; the second by the six genotypes AAbbcc, aaBBcc, aabbCC, AaBbcc, AabbCc and aaBbCc; and so on. It thus appeared that different factors could have similar actions, and actions which were, at least in some measure, cumulative.

These factors in wheat and oats had effects sufficiently large for Mendelian analysis to be possible; but it was realized by Nilsson-Ehle, and also independently by East, that similar factors of smaller individual action could account for continuous quantitative variation if enough of them were segregating . Each factor would be inherited in the Mendelian way, and its changes would be discontinuous or qualitative. Yet with a number of such factors, having similar and cumulative action, many different dosages would be possible, of which the intermediate ones would be the most common (Fig. 1). With phenotypic expression proportional to factor dosage, variation would be quantitative, would follow Galton's frequency curves and would be nearly continuous. Continuity would be completed by the blurring effect of non-heritable agencies, which would of course make the phenotypic ranges of the various genotypes overlap.

During the next 10 years this multiple factor hypothesis, as it was called, was applied to data from a variety of organisms, notably by East and his collaborators, and by Fisher. The former showed that the inheritance of a number of continuously variable characters in tobacco and maize could be fully accounted for on this view (e.g. East, 1915; Emerson and East, 1913). Fisher carried the integration of biometry and genetics still further. He demonstrated that the results of the Biometricians themselves, particularly the correlations which they had found between human relatives, must follow on the new view (Fisher, 1918). From the Biometricians' own data he was able to produce evidence of dominance of the multiple factors, and he attempted the first partition of continuous variation into the components which the multiple factor hypothesis led him to expect.

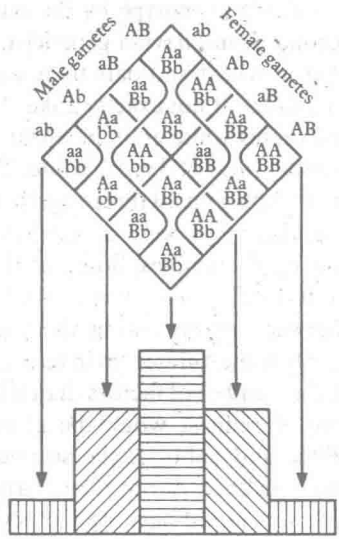

Figure 1 The polygenic or multiple factor theory. The distribution of phenotypes obtained in an F_2 with two genes of equal and additive effect but without dominance, neglecting non-heritable variation. The phenotypic expression is proportional to the number of capital letters in the genotype. There would be seven phenotypic classes with three such genes, nine classes with four genes and $2k + 1$ classes with k genes.

2. POLYGENIC SEGREGATION AND LINKAGE

The essential features of the multiple factor hypothesis are two: that the governing factors or genes are inherited in the Mendelian fashion; and that they have effects on the character under observation similar to one another, supplementing each other and sufficiently small in relation to the non-heritable variation, or at least in relation to the total variation, for discontinuities to become indiscernible in the phenotypic distribution. In this way smooth, continuous variation of the phenotype could arise from discontinuous, quantal variation of the genotype.

There is an obvious danger in postulating these multifactorial or polygenic systems. The constituent genes are so alike in their effects and so readily mimicked by non-heritable agencies, that they cannot easily be identified individually within the systems. Since such genes obviously cannot be followed by the simple Mendelian technique, how may we be sure that they are in truth borne on the chromosomes and so subject to Mendelian inheritance?

On the negative side there is the evidence of reciprocal crosses. Though these sometimes differ a little in respect of continuously variable characters, presumed to be under polygenic control, they do so no more often than is the case with discontinuously variable characters. The two parents therefore

generally contribute equally to the genotype of the offspring in the way expected of nuclear heredity, and not unequally as might be expected if inheritance was of some other kind.

More positive evidence is, however, available. The properties characteristic of nuclear-borne genes are two, namely segregation and linkage. Although neither segregation nor linkage of the genes under discussion can be observed by the usual methods, the necessary tests can be made in other ways.

If we take two different inbred and therefore very nearly true-breeding strains, both they and their F_1 will show variation virtually only in so far as non-heritable agencies are at work. But genetical segregation of the nuclear genes which differentiate the parents will occur in F_2, and the heritable variation to which it leads will be added to the non-heritable. The F_2 should therefore be more variable than the parents and the F_1: its frequency distribution will be broader and flatter. Furthermore, as Mendel showed, the genes at each locus are homozygous in half the F_2 individuals. Segregation will still occur in F_3 families, but it will be for only half the gene pairs on average. The average variation of F_3 families will therefore lie between that of F_2 on the one hand, and parents and F_1 on the other; but the F_3 families will differ among themselves, some having variances approaching one extreme, some the other and most being intermediate. At the same time the homozygous genes by which the F_2 individuals differed will give rise to differences between the mean phenotypes of the F_3 families, and these means will be correlated with the phenotypes of the F_2 parents. Even where the parental strains are not nearly true breeding the F_2 will generally (though not inevitably) show greater variation than either F_1 or parents.

Thus the necessary test of segregation is to be found in the relative variation of the different generations following crossing. It is sufficient to say that whenever a critical test has been made, and a very large number have now been made, the results have accorded with the expectation based on nuclear inheritance. A characteristic case is shown in Fig. 2.

Tests of linkage, the second property of nuclear genes, may be of two kinds. We may seek for linkage of the quantitative genes (or polygenes if we name them after the polygenic variation they determine) with genes of major effect, capable of being followed by Mendelian methods. Or we may seek for linkage between polygenes themselves.

The first case of apparent linkage between polygenes and a major gene was reported by Sax (1923). He crossed a strain of *Phaseolus vulgaris*, having large coloured seeds, with another whose seeds were small and white. Seed size showed itself to be a continuously variable character, but pigmentation proved to be due to a single gene difference, the F_2 giving a ratio of 3 coloured-: 1 white-seeded plant. By means of F_3 progenies the coloured F_2 plants were further classified into homozygotes and heterozygotes. On weighing the beans from the three classes of F_2 plant, PP, Pp and pp (P giving pigment and p no pigment), the average bean weights shown in Table 1 were obtained.