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NEW INSIGHTS INTO CONTINUOUS VARIATION

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Introduction

In the past, human genetic studies lay both at the foundation and the fringe of the main streams of genetic development. They lay at the foundation because our interest in individual humans leads to intensive study especially of rare pathologies and hence to the probability of discoveries of substantial importance, which however may well occur "before their time" as in the classical examples of Garrod's work. They also lay at the foundation because Galton began biometrical genetics with specific interest in human variables. They lay at the fringe because of the restrictions of experimental breeding, which necessitate the use of experimentally amenable organisms for the establishment of fundamental principles whose application to man may often be tested only in a derivative way.

In more recent years human genetics has become much more one of the main streams of genetical advance, because with the general development of biochemical genetics there are many more well established principles of fundamental genetic importance that can now be applied to or used for or advanced by the study of man, and because the development of population genetics has reached a stage when the unique value of our detailed censuses of human populations with specific labeling of each individual can be generally appreciated. In consequence, human genetic knowledge is in an explosive phase. Further, our knowledge of population genetics has, over the past ten years or so, brought genetical thought to a point where it becomes relevant to sociological studies, and this adds urgency to our desire to understand more of human microevolution.

There is however a vital gap in our knowledge, in a field where we are making little progress. Though we are now learning rapidly about the genetics of our own

species; though human biochemical genetics, cytogenetics, and population genetics are advancing apace and our knowledge of the heredity of clinical entities likewise, we are making little real progress in the understanding of continuous variation in man. This is because such studies derive from a branch of nonhuman genetics which has in some ways advanced little. The amount we know about population structure, what we can predict about evolutionary changes even in a simplified situation such as an artificial selection experiment, with respect to any continuous variable in any organism, even *Drosophila* or Maize, is strictly limited. What we know about the developmental or biochemical genetics of such characters is almost zero.

Because of this limitation for all organisms it is the more so for man. The theoretical genetics of continuous variables began with man in the hands of Galton because the really interesting variables are continuous. Subsequent developments of biometrical genetics, sophisticated though they are, leave us about as much in the dark as we were then.

Yet I would submit, we cannot pretend to have really begun to attack the most human problems of human genetics, we cannot lay the foundations for critical understanding of the genetic structure of human populations, and, hence, we cannot have much detailed understanding of their means of change in short-term, still less long-term, evolution, until we have some real knowledge of the genetics of some of the critical human variables that are continuous.

Major gene variables may be considered as of two kinds. The pathological, whose study is both of clinical importance and also of fundamental importance in the same way as study of major variables has been in all organisms in giving us the rules of heredity: and the polymorphic, where we have clear cut segregational polymorphisms such as in other organisms and more recently in man have thrown great light on the rules of population genetics.

But what we conventionally regard as major gene variables do not seem to me to include the most distinctively human variables whose understanding is vital to us. These are the psychological variables, which, though they may show some major mutants of more or less pathological kind, also always show continuous variation in what we call the *normal* section of the population. It is the genetic structure of populations with respect to this continuous variation within the normal range that we must understand, if we are to obtain real insight into those aspects of the genetic structure of human populations that matter most in relation to social structure and social change or evolution.

These questions, I would submit, are vital at the present time. There is hardly a question of importance in the sociology of human populations that does not depend upon answers to further questions to which sociologists perforce, as well as by predilection, usually assume unjustifiable answers. These further questions concern the distribution of psychological variables in and between populations, and the role of environment and genotype in determining these psychological variables; and hence the whole question of the structure of populations with respect to the distribution and flow within and between classes and races of genes affecting psychometric characters within the normal, nonpathological range of human beings.

All the experimental knowledge of natural populations that we have obtained over the last twenty years, including that of human populations, has pointed consistently toward the concept that there is far greater genetic variety among the normal members of such populations than we hitherto were inclined to believe. No matter what

the species or character, when appropriate critical investigation has been made it has regularly shown that there is wide genetic variety. This is even true of the most phenotypically stable characters such as scutellar bristle number in *Drosophila.* In fact we are now forced to a complete revision of our concept of the normal and with it to a complete rejection of typological thinking. It is far safer to think of each normal individual as genetically unique than to think of the abstract normal "type," necessary though that may be for some taxonomic purposes.

As I have said this is true of even so invariant a character as scutellar bristle number in *Drosophila,* where individuals with less or more than four bristles are rare, but it is possible to show that there are many genetically different, and hence physiologically different, ways of having four bristles. It is the more true of characters that show wide phenotypic variation with some heritability, such as the continuous variables, to which I am giving attention. We must suppose a very considerable range of genotypes affecting psychometric characters. In fact we may safely postulate each individual to be genetically unique in the constellation of genes that affected his psychology, as well as having been reared in a unique constellation of environment factors that affected his psychology. That sociological understanding, and hence social policy, must be hampered or misguided until geneticists can say much more about the genetics of these characters is self evident. To take but one example, of particular topicality in Britain: How can we assess education policy, without much more knowledge than at present of the relevant genetic variety?

Is the policy we have hitherto had of segregating the apparently more able in schools with higher academic attainment justified, or is our contemporary policy of imposing more uniformity of schooling justified? Ultimate answers to this question must depend in part on knowledge of the amount and *kind* of unalterable genetic differences, and when I say *kind* I have particularly in mind the nature of the genotype environment interactions there may be.

Now I am not suggesting that there is any prospect in the immediate future that geneticists might be able to contribute much toward answering such sophisticated questions. But I suggest the question as indicating the kind of direction genetic research should aim at. The direction is clearly toward knowledge of *specific* genes affecting psychological variables *within* the normal range, including knowledge of the interactions of such genes, and the interactions of their effects with those of relevant environmental variables. This is asking for knowledge of specific genes affecting continuous variables in human populations. It is in fact asking a lot.

Characters showing continuous variation within the normal range are what we have come to associate with the term polygenic variation, for which the techniques of biometric genetics have been developed. And the techniques of biometrical genetics, based as they are on an extension of the concept of multifactorial inheritance, do not aim primarily at revealing information about specific genes. Rather do they assume that there are many genes each of effect too small to isolate, and aim only at determining the average additive, dominance, epistatic, etc., effects of these genes.

But what we want, as I have said, is knowledge of genes. For example, with respect to the most easily measured psychological variable, IQ, we want answers to the questions: What genes are segregating in such and such a population? What are the specific effects, psychological, physiological, and biochemical, of each gene? How do they interact? What are the relative fitnesses of the various genotypes? Do the differ-

ences of fitness arise from the effects of the genes on the psychological variable itself, or from pleiotropic effects on other aspects of the organism? Which of the various loci involved are subject to stabilizing, disruptive, or directional selection? What are the environmental (including social) factors imposing this selection?

We can make no answer to these questions. Almost all that is known of the genetics of this variable IQ is that it has positive, probably rather high, heritability in the populations that have been studied.

New Light on the Study of Continuous Variation in Other Organisms

The characteristic techniques that have been used in the study of the genetics of continuous variables ever since Fisher's classic 1918 paper, and especially over the last twenty years, have been biometric analyses of variance and covariance. These techniques have developed to a level of sophistication beyond many of us and have given considerable powers of description and prediction in controllable experimental situations, and considerable insight into the nature of heritable components of variance. They have shown that continuous and discontinuous heritable variation have in common the properties of segregation, dominance, gene-interaction, linkage, and genotype-environment interaction, and established beyond doubt that the genes of biometrical genetics and the major genes of Mendelian genetics are subject to the same rules of inheritance for the same reasons—they are chromosomal.

However, though these techniques are most elegant and informative, the resulting understanding of continuous variables lacks a certain kind of precision that can only arise when we are able to say that such and such an individual contains such and such a gene. Only when we can say this can we begin to make precise attacks at the biochemical, physiological, and developmental levels; use our genetic knowledge to describe the character differences we observe in biochemically meaningful ways; and also study the fitness and evolutionary questions referred to above.

The nature of continuous variation makes the study of specific genes difficult, because we have more or less large environmental components of variance, and multifactorial inheritance together. So much has this seemed to complicate the task that it has become almost a dogma that continuous variables, even in *Drosophila* or Maize, can *only* be studied by biometric methods, so that most of us begin with the view that attempts to discover relevant specific genetic loci would be defeated before they were begun. Especially is this defeatist view likely to be prevalent in human genetics. If the task be deemed impossible even in experimentally amenable organisms like *Drosophila* what hope is there with man?

However, over the last nine years, my colleagues and I have had considerable success in attempts to handle specific components of polygenic systems in *Drosophila,* and recently others have had success with other organisms of less obvious merit. We do not yet know how generally applicable our results will be, but are now inclined to take a wholly new (or in fact very old) attitude to the genetics of continuous variables, because so far whenever serious attempts have been made to study polygenic variation in terms of specific genes, a few handleable genes have proved to mediate a large part of the genetic variance under study.

This new attitude is to assume that it will in fact be possible as well as profitable to isolate some of the relevant genes and study their individual effects. I will therefore

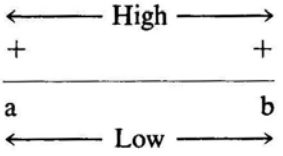
briefly review our work and its conclusions, and discuss the essential principles of techniques which hold out hope of success and then ask which of these techniques might be practicable as supplements or complements to biometrical techniques in attack on such important variables as IQ in man.

The Drosophila *Result*

The general technique we have used with *Drosophila* is described in Thoday [1961]. It has involved marker genes and extensive progeny testing of marker recombinant and nonrecombinant chromosomes, using the lack of crossing over in the male as a tool to permit multiplication of chromosomes to categorize their status, largely independently of the uncontrollable environmental variables, and thus to permit treatment of continuous variates as if they were continuous. I would stress at this point that we have tried to locate the genes quite precisely in the known linkage groups, that more simple techniques may be used for simpler aims, and that the aims may have to be simpler with man. But it is easier *first* to describe the principles in terms of the more precise aims.

The essential principles of the marker technique are as follows. Suppose we start with a stock with an unusually high mean value of the metric understudy, then we mate it to a stock of normal mean marked in each chromosome and determine which chromosome or chromosomes are most relevant. We then concentrate on the chromosomes singly, mating them to other stocks with two or more markers in the one chromosome.

Heterozygous females are thus produced which may be designated



These are mated to low *a b*-marked stock males and equal numbers of the four marker recombinant classes of male progeny are scored for the metric understudy. The ideal result is as follows:

Marker class	+ +	*a* +	+ *b*	*a b*
Mean	High	Medium	Medium	Low

Three simple hypotheses and (several more complex) will explain this result.

First is the hypothesis that there is one locus between the markers. On this hypothesis the heterozygous female is $+ H +/\mathrm{a}\ L\ \mathrm{b}$, ($H$ and L being the alleles affecting our metric), and each of the marker recombinant progeny comprise two genetic classes, e.g., $a +$ are $a H +$ and $a L +$ mixed.

Second is the hypothesis that there are two loci outside the markers. On this hypothesis the heterozygous female is $H + + H/L$ a b L and the marker recombinants each comprise only one class, e.g., $L\ a + H$.

Third is the hypothesis that there are two loci within the markers. On this hypothesis the heterozygous female is $+ H H +/\mathrm{a}\ L L\ \mathrm{b}$ and the marker recombinants each comprise three classes, e.g., $a H H +$, $a L H +$, and $a L L +$. (If there were three loci there would be four classes and so on).

All that remains is to progeny test sufficiently to determine whether the marker recombinants fall into one, two, three, or more recognizable classes.

These descriptions of the general principles will suffice, though the breeding programs may have to be more complex when for instance the markers affecting the metric, or recessive genes are involved. Using the same principles we [Thoday, Gibson, & Spickett, 1964; Spickett & Thoday, 1966; Gibson & Thoday, 1962; Wolstenholme & Thoday, 1963] have analyzed a number of high sternopleural chaeta number lines of *Drosophila melanogaster* with some success. There is no need to go into detail here, as the work is fully published, but I will summarize the most striking results, which were obtained from a high sternopleural chaeta number line produced by Thoday [1961] with 100 generations of selection. This line (vg6) had, when analyzed, 40 chaetae per fly which is a very high mean indeed, and was compared to a standard inbred line (Oregon) with 20 chaetae per fly.

The high line gives the results expected of a polygenic difference in F1 and F2 of a cross with a line of normal chaeta number. We are dealing with a continuous variable. Nevertheless it proved that we were able quite clearly to demonstrate that the high line and Oregon differed in five loci which with their interactions accounted for 87.5 per cent of the difference of mean. There were two loci in chromosome III, which were equal and additive in effect. There was one locus in chromosome II which had pronounced positive interaction with one of those in chromosome III, and there were two loci, one near each end of chromosome I which also interacted with chromosome III [Spickett & Thoday, 1966].

Having isolated these genes, and in consequence obtained stocks possessing them in known combinations, we were able to study the effects of some of these genes in new ways [Spickett, 1963]. This further study involved considerations of chaeta pattern and other aspects of development of the sternopleurite, and its results are summarized in Fig. 1.

Three conclusions follow from these results. First, the demonstration that variation is continuous is no indication that the number of genes segregating need be large. On the contrary the bulk of the genetic variance may be mediated by very few quite effective loci. Second, the different genes of a polygenic system may have quite specific and quite different effects on the character and if we will but make serious attempts to isolate relevant genes these specific effects and their modes of interaction are open to study and might thereafter be used as diagnostic criteria of the genes, permitting them to be studied by the normal techniques used in the study of discontinuous variation. Third, the technique of genetic analysis of continuous variables may be used as a powerful tool for the developmental analysis of complex character differences with the aim of determining the unitary genetic components which may thus be opened to physiological and biochemical study. I need hardly stress how valuable this approach might be in behavior genetics, whether of mice or man.

The General Principles of Technique for Identifying Specific Genes Affecting Continuous Variables

Difficulties in the identification of specific genes affecting a continuous variable arise from one or both of two reasons. Heritability may be limited and the number of genes may be inconveniently large. Successful techniques must therefore depend

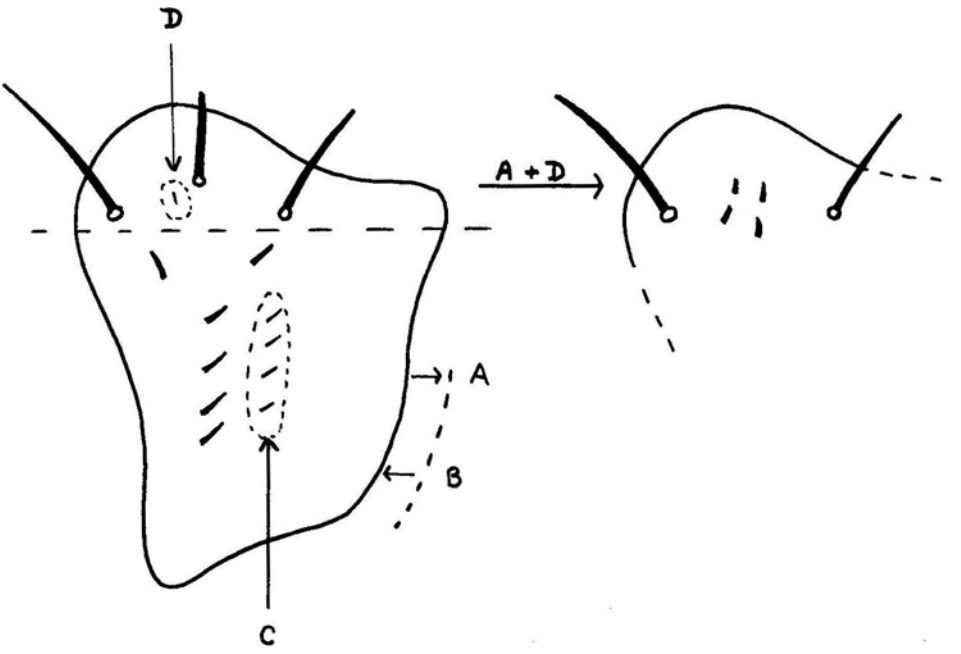


FIG. 1. The effects of four genes isolated from a high sternopleural hair number line of *Drosophila. The left hand figure shows the pattern of hairs on the sternopleurite of wild-type Oregon inbred and, enclosed in dotted line, the effects of the individual genes. The right-hand figure shows the effect of the genes A and D together.*

A increases cell number and hair number in all regions.

B decreases cell size, compensating for the fly size effect of A without influencing hair number.

C has a local effect on hair number tending to give a double row of microchaetes.

D has a very local effect adding one hair near the middle macrochaete. With A it replaces this machrochaete by several microchaetes. It works by delaying differentiation of the middle macrochaete initial.

either on maximizing effective heritability, as we have done with *Drosophila* by progeny testing, or by limiting the number of genes whose effects are being studied together, or both. Biometric techniques evade these difficulties at the price of specific genes, but it is my thesis that we must and can avoid this price [Thoday, 1966a & b]. We will avoid the price only by converting the continuous into a discontinuous variable, or into a number of discontinuous variables that we can treat separately, by one or both procedures mentioned above.

There are several ways in which we may maximize heritability with experimental organisms. We may make relevant environmental factors as uniform as possible. We may choose populations in which heritability is unusually high or we may use statistical analyses to abstract from the complex variable under study components that show higher heritability.

There are likewise several ways in which we can attempt to limit the genes under study at any one time. Markers may be used to isolate single chromosomes as we have done with *Drosophila,* and Law [1966] has done using cytological markers in successful location of development time polygenes in wheat. A backcrossing and inbreeding program can be used as Wehrhahn and Allard [1965] have done with

wheat. Or we may use multivariate analysis, or developmental, physiological and biochemical analysis to identify separable components of our complex character whose inheritance may be studied as separate more or less discontinuous variables. And markers may be used to study linkage relations in programs that effectively ignore background genotype as we have done successfully in many of our breeding programs with *Drosophila.*

Some of these techniques may be and others may not be possible with man. We can do little to maximize heritability except by choosing component characters with high heritability. We cannot use controlled environments, and we cannot use deliberately contrived progeny testing programs. We cannot put single chromosomes on controlled backgrounds or use backcross and inbreeding programs. We may however, use character analyses to simplify our problem, and we have, thanks to the extensive work being done on biochemical and other polymorphisms, quite a lot of suitable markers if we can use them properly.

The limitation to the use of markers, as always with human genetics, is that we have to use the markers as we find them segregating in our population: we cannot control the matings as we can with mice or flies. However, once we accept the idea that a continuous variable like IQ may not in fact be mediated by many genes each of small effect, but that much of the genetic variance may be brought about by a few genes of large effect, the use of markers as we find them begins to seem feasible, in two ways.

Let us consider what, on this assumption, we might expect to find. First, it should be stressed that our interest cannot be in the genetics of IQ as a "character"; it can only be in the genetic variation in IQ that is to be found in the population under study. Hence, we are only interested in loci that are segregating frequently in the population and these will be at intermediate gene frequencies. Likewise the markers to be useful must be at intermediate gene frequencies: they will be the polymorphisms with which we are growing very familiar. Suppose then that there is in our population such a locus affecting IQ linked to a marker locus such as MN, which I choose since it has the advantage that we can recognize the heterozygote. To simplify the situation I postulate that the IQ locus has only two alleles of equal frequency, is completely linked to MN but is in linkage phase equilibrium. Then it should follow that MM, MN, and NN genotypes should have similar IQ means and variances, but there should be differences of within- and between-family means and correlations of IQ according to MN status. The matings MN $\times$ MN provide the revealing families. Within these, if we compare IQ's of sib pairs with a system similar to Penrose's [1935] sib pair linkage test, we find the essential point. It is made in Table 1. We should expect a higher variance within and a lower variance between families in the MN than the M or N individuals of such progenies. Likewise the within-sib pair correlations should be lower for MN pairs than for M pairs, or N pairs. M and N pairs should be like MN pairs. Pleiotropic effects of the marker locus itself would of course show up as differences of mean IQ distinguishing the M N classes and spread over families rather than confined to particular families, and the search for pleiotropically effective marker genes is another way of attacking the problem.

I am no mathematician and am not competent to develop and elaborate on methods for such analysis of human variables. I merely put this example forward to show the sort of lines along which a start might be made in the use of markers (genetic and cytological) for the identification of genes of continuous variation in man. If,

TABLE 1. USE OF HETEROZYGOUS MARKER MATINGS TO DETECT LINKED POLYGENES

Mother	Progeny	Father			
		MA/NA	MA/Na	Ma/NA	Ma/Na
MA/NA	MM	AA	AA	Aa	Aa
	MN	AA	AA or Aa	AA or Aa	Aa
	NN	AA	Aa	AA	Aa
MA/Na	MM	AA	AA	Aa	Aa
	MN	AA or Aa	Aa	AA or Aa	Aa or aa
	NN	Aa	aa	Aa	aa
Ma/NA	MM	Aa	Aa	aa	aa
	MN	AA or Aa	AA or aa	Aa	Aa or aa
	NN	AA	Aa	AA	Aa
Ma/Na	MM	Aa	Aa	aa	aa
	MN	Aa	Aa or aa	Aa or aa	aa
	NN	Aa	aa	Aa	aa

10/16 Matings give genetic variance among MN
$\therefore$ within family variance MN > M or N

Progeny of MN × MN Matings
($pA = q_a$) (No dominance)

Genetic Values AA = 1, Aa = 0, aa = −1

	M	MN	N	M and N
Mean	0	0	0	
Variance within sibships	0	¼	0	
Variance between sibships	½	¼	½	
r sib-pairs	1	½	1	½

however, such means are tried and prove successful, it should be possible to identify families possessing different genes and seek their cooperation in physiological studies of the effects of the differing loci contributing to IQ variance.

The approach then would be to study IQ and other metric characters in samples of families segregating for as many marker genes as can be handled, and to determine which marker loci and which metric characters show the associations we predict on the assumption that a significant part of the genetic variance of the metrics is determined by a few loci.

This assumption is not of course incompatible with the concept that very many loci will be involved. It is, however, incompatible with the concept that the loci are all of roughly equal effect. Our immediate task would be confined to identifying the more effective loci and studying these. That there are such loci I feel sure, and I find support from the fact that it is often possible to explain published results on the basis of rather few loci even though critical proof that such explanations are correct is lacking (see review on *Behavioral Genetics* by McClearn and Meredith [1966] for some relevant examples).

This marker approach will undoubtedly have to be combined with character analysis. It can readily be seen from the results of the pattern analysis of chaeta number (Fig. 1) how forms of character analysis may help, not only in choosing component characters of high heritability but also in identifying differing genetic causes of high or low IQ. Though these chaeta pattern analyses were obtained after genetic

analysis, we can now see that pattern analysis might have assisted the genetic analysis had they been done in conjunction. In addition, however, my colleagues [Spickett, Shire, & Stewart, 1966] in their work on mice have come up with a beautiful example which shows how analysis of the character under study, and concentration on some component of it, can make it possible to obtain evidence of a single locus

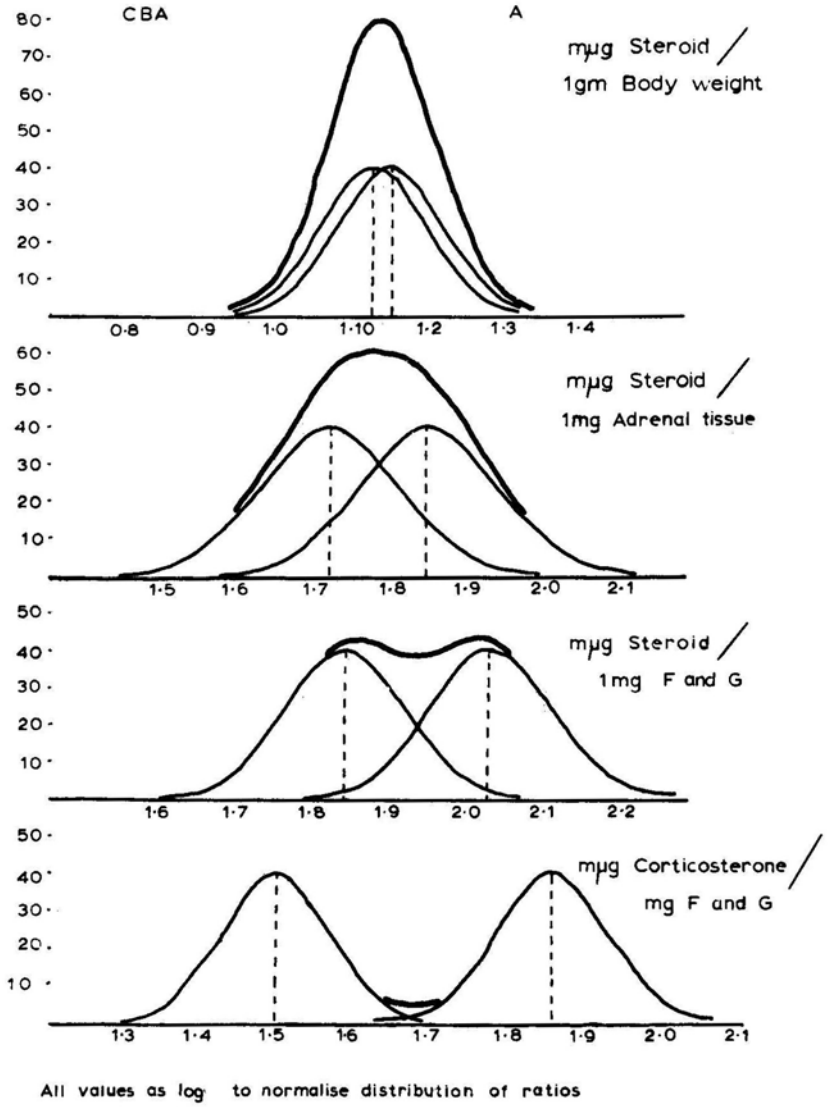


FIG. 2. *Distinction between the mouse strains CBA and A. Curves are drawn on the basis of observed means and variance. Distributions are given for the strains jointly and separately. The quantities of hormone are obtained in* in vitro *synthesis by adrenals.*
Upper graph: quantity of corticosteroid hormone per unit body weight.
Upper middle: quantity of steroid hormone per unit weight of adrenal.
Lower middle: quantity of steroid hormone per unit weight of hormone-producing tissue.
Lower graph: quantity of particular hormone (substance B) per unit weight of hormone-producing tissue. [*Spickett, Shire, & Stewart, 1966*].

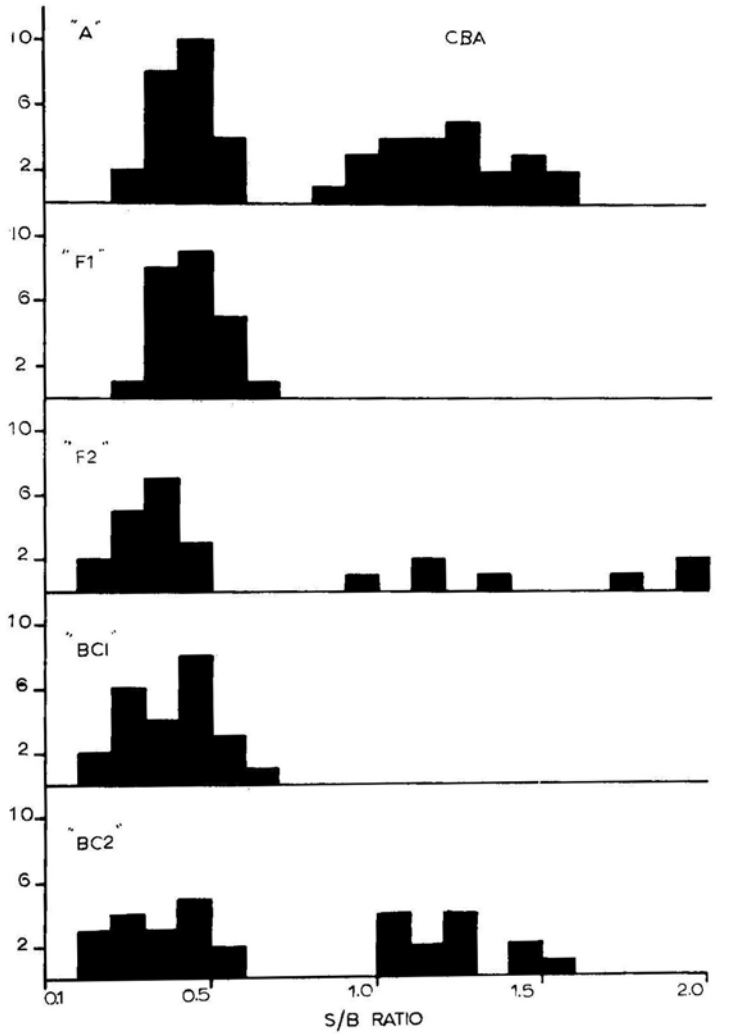


FIG. 3. *Discontinuous segregation of a character closely related to that defined in Fig. 2. BC1 is the backcross to strain A, BC2 that to strain CBA.* [*Spickett, Shire, & Stewart, 1966*]. *The ratios in F2 and BC2 fit a one-locus hypothesis. The histograms showing the frequency distribution of the S/B ratio in the strains A and CBA and crosses between them.*

segregation. The effect on the data for P1 of redefining the character they were studying is shown in Fig. 2. Figure 3 shows the segregation of the redefined character in F2. A single gene is defined by precise definition of the character used to track it. It matters not whether we now regard this as a major gene or as a component of a polygenic system: all genes must ultimately be responsible for discontinuous variation if we can get sufficiently near to the biochemical gene action level. What matters is that we should be able to abstract handleable variables from the complexes we start with.

The types of character analysis may be various. Multivariate analyses may help us to pick out of complex metrics, components of relatively high heritability and

components linked to the markers we use in a marker analysis. The variables brought into the multivariate analyses may be of any kind, from ordinary partitioned components of test batteries, to sets of randomly chosen postulated correlates, biochemical or physiological. Preferably of course they would not be randomly chosen, but would be variables which parallel work on the experimentally more amenable mouse indicated were likely to be involved.

I hope I have said enough to indicate that it is now in principle possible in other organisms for us to do the formal, developmental, biochemical and population genetics of some of the loci concerned with the continuous variables that are really important from the evolutionary point of view. I do not see why we should now wait before we try seriously in man, and hope again I have said enough to persuade some human geneticists that it will be possible.

The genes that are segregating in our populations and affect continuous psychological variables are the most important genes we can study whether from the sociological or the evolutionary point of view. Some of them I am sure could be handled with real precision. The sooner we identify them the better.

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