A Defense of Path Analysis in Genetic Epidemiology

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SUMMARY

Contemporary models of multifactorial inheritance are described and justified from the perspective of their intended use in genetic epidemiology and their developmental sequence. Substantial empirical data and statistical theory support the practical adequacy of the assumptions of path analysis for most multifactorial traits that show vertical inheritance. The choice of scale for quantitative traits must be considered on an individual basis. From both biological and statistical perspectives, transformations of scale may be more appropriate for analysis than the measurements are themselves. Recent criticism of contemporary models and computational procedures is based on a caricature of path analysis rather than on the method as it is actually practiced. The utility of path analysis is primarily limited by an investigator’s biological insight and analytical skill, not by the method’s assumptions. Model-free descriptive statistics are inherently inadequate to characterize the stable and autonomous features of the underlying mechanisms that generate observable variation in multifactorial traits. In contrast, path analysis has led to remarkably stable estimates of structural parameters for a wide variety of important biological traits. While exploratory methods can be useful for preliminary data inspection, they cannot substitute for formal tests of hypotheses based on explicit, falsifiable models.

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INTRODUCTION

In science, both theory and analysis are invariably based on models that are simplifying approximations because hypotheses that are too vague or complex to be falsified are of no scientific value. In fact, the utility of a model is usually judged by the extent to which it simplifies and brings order out of an array of observations and suggests and guides further inquiry. An example that is especially notable for the early development of population genetics was Haldane’s use of “beanbag” models in which the simplifying assumption was made that individual genes acted independently [1].

During the past decade, the field of genetic epidemiology has produced methods for analysis of common traits with complex inheritance. Such complex familial transmission may involve the influence of many factors, including one or many genes, cultural inheritance, correlated home environments, and assortative mating, in addition to various ascertainment, age, and threshold effects [2–4]. The purpose has been to specify coherent quantitative models that facilitate explicit tests of alternative modes of inheritance, estimation of parameters of interest to geneticists, and predictions that can stimulate and guide further investigation. From a medical perspective, the prevention and treatment of common familial diseases is facilitated by such explicit disease models, which include both genetic and nongenetic risk factors. Extensions of general multifactorial inheritance were parameterized in terms of path analysis models [5–16].

Elsewhere in this issue [17], Samuel Karlin and his associates Cameron and Chakraborty (KCC) have criticized these methods. KCC warn of the “dangers” and “illusions” created by path analysis, whose assumptions are described as severely restrictive and arbitrary. However, they do not offer a more rigorous and realistic model. Instead, we are offered exploratory descriptive techniques that specify no explicit mathematical model and so evade the issue of the complexity of inheritance of common traits. Exploratory techniques can be useful tools for preliminary inspection and descriptive of data, but they cannot substitute for tests of hypotheses based on explicit models. For purposes of statistical inference in genetic epidemiology, available exploratory techniques are of limited utility because they have low sensitivity and specificity to distinguish alternative modes of inheritance and provide no formal tests of hypotheses, estimates of genetic or environmental parameters, or quantitative predictions [18]. In particular, they do not attempt to distinguish between genetic and cultural inheritance, which is a major goal of path analysis in genetic epidemiology.

The path analytic models of multifactorial inheritance that KCC criticize have become the standard by which newer approaches have been judged, in part because of their heuristic value. If this guidance is fundamentally misleading, as KCC claim, then we should seek more realistic solutions. Accordingly, it is important that we evaluate carefully the substantive criticisms of modeling in general and path analysis in particular that have led KCC to advocate exploratory methods despite their major shortcomings.

GOALS OF GENETIC EPIDEMIOLOGY

The overall goals and methods of genetic epidemiology must be understood before we can evaluate the possible uses and limitations of path analysis in that
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field. Genetic epidemiology is the scientific study of the etiology, distribution, and control of disease in groups of relatives and of inherited causes of disease in populations [19]. This involves a synthesis of methods from population genetics and epidemiology because its goals require the analysis of multiple genetic and environmental factors that simultaneously influence familial aggregation in non-experimental samples of natural populations [20]. The application of these methods is guided by information from a wide variety of disciplines, especially by the biological sciences ranging from molecular biology to clinical medicine.

The specific aims of genetic epidemiology include three interrelated activities: (1) specification of mode of inheritance, (2) characterization of genetic and environmental factors that influence risk of illness, and (3) quantitative predictions about morbid risks both in individuals and in distinct sets of families in order to guide and stimulate further research.

The first aim of specifying mode of inheritance requires consideration of possible chromosomal aberrations, the effect of individual environmental events, and genetic loci that have a large effect on risk for a trait, and other genetic and environmental background variables that individually have small effects. The major gene loci may be autosomal or X-linked, and their effect may show incomplete penetrance and variable expressivity. There may be multiple major loci that show epistasis, but, to the extent that their efforts are epistatic, they will not contribute much to vertical inheritance. Background variation within each relevant major gene locus may be nonfamilial or it may involve heritable genetic and/or cultural factors. Common traits are likely to have complex inheritance involving one or a few major genes with substantial heritable background variability. Consequently, models have been developed to test whether transmission is Mendelian and to allow for both major gene and multifactorial variability simultaneously [21–24]. Simple monogenic or polygenic models are obtained as special cases of these more general "mixed" models.

When a major gene locus is inferred by segregation analysis, linkage analysis may be carried out to confirm this and to map the site of the disease susceptibility locus [25, 26]. The possibility that the trait may be linked to a particular marker in some families and not in others may be considered [27]. When there is substantial multifactorial variation, it is useful to distinguish between the small effects of many gene loci and the effects of cultural inheritance and other nongenetic influences using path analytic techniques [5–16] or analysis of variance methods [28–34]. Such distinctions are important so that we may characterize relevant genetic and environmental variability well enough to plan intervention strategies and further etiologic research.

Segregation analyses in which allowance is made for both a major locus and its multifactorial background permit us to identify subsets of families in which the evidence for a segregating major gene is most clear [23]. These families may then be studied more intensely in order to understand the biological basis of the heritable defect. Furthermore, path analytic approaches may permit derivation of observable indices of the multifactorial background. Together this information about genetic and environmental variation can permit progressively sharper resolution of different factors in the etiologic process [16, 35].

This specification also permits efficient quantitative predictions of recurrence...
risks and suggests further research to test these predictions. The method of progress is an iterative one in which multiple methods are used to gain additional biological insight; these insights are formulated explicitly as progressively more realistic models, and then retested by a variety of techniques. Thus, the major goal of path analysis in genetic epidemiology is not the estimation of heritability as KCC state. Rather, heritability estimates are a by-product of the process of delineating the mechanisms that underlie the genetic epidemiology of a trait. Moreover, path analysis is not used in isolation from information from other genetic and biosocial studies. Path analysis is one of several modeling approaches used to evaluate the consistency and validity of our biological insights about the mechanism of transmission of multifactorial traits.

Since the major goal of genetic epidemiology is to characterize the inherited causes of disease, we have a medical imperative to identify risk factors and mechanisms that can make a practical difference in the prevention and treatment of disease. Perhaps we could be content to "slowly inch" forward, as KCC suggest, if our subject was purely theoretical, but our subject urgently requires us to apply practical biostatistical techniques that can help us integrate and evaluate data about the biosocial risk factors that lead to disease. There can be no excuse for neglecting practical methods that can help us uncover stable features of disease transmission and make useful predictions.

In the next section, we will evaluate the justification for the assumptions of path analysis in relation to its intended use in genetic epidemiology. Elsewhere in this issue [36], Sewall Wright comments on the significance of KCC's comments for path analysis more generally.

THE FUNDAMENTAL ASSUMPTIONS OF PATH ANALYSIS

The theory and application of path analysis has been developed and described in detail by Wright [37]. It is useful to summarize the basic method here because KCC imply that the rules are arbitrary.

Let us consider a finite number of standardized random variables arranged in a historical or logical sequence distinguishing antecedent, contemporary, and subsequent (dependent) variables. Wright has shown that three assumptions are sufficient to justify the basic equation of path analysis: (1) unitary factors—all variables are treated as unitary factors, so that one part of a composite variable is not more significant in one relation than another; (2) linearity—the relationships among these unitary factors are linear so that equal changes in an antecedent variable in different parts of its range are associated with equal changes in its dependent effects; (3) complete additivity—each dependent variable is completely determined by the sum of the effects of proximate antecedent variables. That is.

\[ X_i = p_{i1}X_1 + p_{i2}X_2 + \cdots + p_{ik}X_k = \sum_{k=1}^{K} p_{ik}X_k. \]  \hspace{1cm} (1)

In equation (1), the \( p_{ik} \) are called path coefficients, which are standardized partial linear regression coefficients. They are represented in diagrams as a single-headed
arrow pointing from the antecedent variable $X_k$ toward the dependent variable $X_j$ ($X_j \leftarrow X_k$). The $X_j$ antecedents, where $k = \{1, 2, \ldots, K\}$, may include a hypothetical residual variable, so that determination is formally complete.

The correlation between $X_j$ and any other variable $X_i$ is defined as the expectation of the product of standardized variables, so

$$r_{ij} = E(X_j X_i) = E(X_j \sum_{k=1}^{K} p_{ik} X_k) = \sum_{k=1}^{K} p_{ik} r_{jk}.$$  \hspace{1cm} (2)

Equation (2) is Wright’s fundamental equation and shows that any correlation $r_{ij}$ may be decomposed as the sum of products of paths to $X_i$ and correlations $r_{jk}$ among the antecedents $X_k$ and the variable $X_j$. This derivation depends only on additivity and linearity, not on the assumption of normality or the nature of the correlations. The variables need not be causally related. It applies to the case of reciprocal interaction as well as to fully recursive systems.

Further distributional assumptions were introduced for purposes of estimation of correlations and formal hypothesis testing. Our empirical experience suggests that the additional assumption of normality is not especially restrictive. Given the prior assumptions of additivity and linearity, the DeMoivre-Laplace theorem and more generally the central limit theorem suggest that the distribution of multifactorial traits will tend toward normality at least as a first-order approximation \cite{37, 38}. This will be discussed further in the next section in which the plausibility of all these assumptions is examined for common traits that are presumed to have a complex developmental pathway from genotype to phenotype.

JUSTIFICATION OF THE FUNDAMENTAL ASSUMPTIONS

What is the experimental and theoretical basis for the fundamental assumptions of path analysis that justifies their application in genetic epidemiology? What is the biological justification for transformations of scale often used to satisfy the assumed statistical properties? How can the underlying assumptions be tested empirically in particular applications if they do not hold generally? To what types of traits can path analysis be usefully applied? We will examine these crucial questions separately for additivity/linearity and for normality because the assumptions enter at different levels of the modeling and computation. Even though we do not believe that nature acts strictly according to any single set of mathematical assumptions, substantial empirical data and theoretical considerations indicate that the assumptions of path analysis are reasonable first-order approximations for many multifactorial traits that show substantial vertical inheritance.

Additivity and Linearity

It is well established that the effects of any individual gene replacement may vary depending on the whole complex of genetic and environmental background factors with which it is combined \cite{37, 39}. Thus, gene action is not additive in general. Presumably, this was the basis of Mayr’s opinion that “beanbag genetics” was meaningless from both a physiological and evolutionary perspective \cite{1}. 

Nevertheless, the additivity assumption does not require strictly additive gene action, but only that the additive genetic variance be the chief determinant of the observable genetic properties of a population. Considerable data from quantitative genetics does provide empirical evidence that additive genetic variance is usually the chief component of resemblance between relatives and the response to selection [37, 40, 41].

It is likely that the causal basis of this empirical finding is the nature of the distribution of gene effects: loci with large effects are few in number and have rare abnormal alleles whereas loci with small and additive effects are common and polymorphic [42]. In other words, gene action is certainly not strictly additive in general, but the stable feature of the action of genes that have a small effect on most traits that show substantial vertical inheritance is additive to a first-order approximation. Traits that do not show much vertical heritability are more likely to involve nonlinear interactions and more often require other approaches.

KCC claim that transmission of traits of importance in genetic epidemiology, such as human serum cholesterol levels, involve nonadditive gene action and gene-environment interaction. They offer no data to support their claim, and available data actually contradict their opinion in the important case of serum cholesterol, a major risk factor for coronary vascular disease [42]. Serum cholesterol levels show substantial vertical inheritance, and estimates of the contributions of shared polygenic factors and home environment to familial aggregation for the natural logarithm of serum cholesterol levels are remarkably similar in samples of Japanese-Americans studied in Honolulu by path analysis [43], Caucasians studied in Cincinnati by path analysis [15], and in Tecumseh, Michigan, by variance component modeling [31]. In addition, Sing et al. studied 12 unlinked polymorphic genetic markers for their association with serum cholesterol levels, after extraneous influences of age, sex, and socioeconomic factors were taken into account [30]. At least four of these genetic markers were predictors of cholesterol variation. They accounted for about 1% of the variability in cholesterol values, suggesting that the total number of relevant genetic factors may be quite large in view of the small proportion of the genome that was sampled. Moreover, the contributions of these four markers were approximately additive (fig. 1). Further analyses, using age as an index of a number of relevant environmental factors that may change over the lifetime of an individual (diet, activity, stress) revealed no changes in the contributions of these factors with age; that is, there was no evidence of nonlinear gene-environment interaction [42].

Falconer’s data for two-way selection for body weight at age 6 weeks in mice provides another instructive example (fig. 2). It should be noted that linear regression lines fitted to the population means provide a good account of the response to selection (the data on the first generation should be disregarded because the method of selection was different). The difference between the two lines at the end of selection was 16 times the original genetic standard deviation, in accord with the hypothesis of many genes contributing to variation in weight [44]. Figure 2 suggests that the response to selection was asymmetrical with realized heritability being three times as great in the downward direction as in the upward. This asymmetry initially suggested the presence of directional dom-
FIG. 1.—Human serum cholesterol levels and no. genetic markers predictive of an increase in mean cholesterol (mg % ± SE adjusted for age and sex). The high-risk markers were ABO (non-0), haptoglobin (22), Gm (a-), and nonsecretor (se se). Based on 3,737 individuals in Tecumseh, Michigan, described by Orr et al. [42].

inference as a component of genetic variability [44]. However, later experiments showed asymmetry in some of six replicates, but none in the average of the six replicates, indicating that the asymmetry was most likely due to random drift in the unreplicated small populations that were selected ([40], pp. 189–194; and D. S. Falconer, personal communication, 1982). This shows that apparent deviations from linearity are often not replicable in other samples. In other words, deviations from linearity often do not have the property of stability or invariance that we seek in structural models of practical value.

Another facet of the additivity assumption is illustrated by the data of Harrison and Owen on the inheritance of skin color in matings between blacks and Caucasians [45]. This has been clearly summarized by Cavalli-Sforza and Bodmer [46]. They studied the percentages of light reflected at different wavelengths (the reflectance) by the skin of black, Caucasian, hybrid, and backcross groups. Different results

FIG. 2.—Two-way selection for 6-wk weight in mice. On the left, the responses of the two lines are shown separately. On the right, the "divergence" is shown (i.e., the difference between the upward- and downward-selected lines). Reprinted with permission from Falconer [40].
regarding number and additivity of genes was implied depending on which measurement was used. The offspring of blacks and Caucasians had reflectance values nearer the mid-parent value at 545 μm than at either 425 μm or 685 μm. They found that the reflectance at 545 μm and the antilog of reflectance at 685 μm gave results consistent with a simple linear model. This shows that apparent deviations from linearity may often depend on the scale of measurement.

These examples underscore the fact that there is no a priori way to determine whether a particular scale of phenotypic measurement adequately reflects the influence of a latent variable, such as underlying gene action. The false issue in much of the discussion of KCC is whether all quantitative phenotypes considered in genetic epidemiology are suitable for path analysis. The real issue is whether an investigator can specify a scale of measurement for a particular phenotype that will satisfy the expectations of additivity and linearity approximately and provide useful results [47]. Quantitative predictions about measurements can be made so that hypotheses can be tested and potentially falsified. Then the types and scales of measurement that prove useful (in the sense of yielding confirmable predictions and stable parameter estimates in different samples and across populations of interest) are those we later come to regard as “natural”—no one can know this a priori. This approach to scaling in biology is fundamentally different from the a priori definitions to which some are accustomed. The same trait may require different scales of measurement in different analyses. Therefore, it is not the results of path analysis that are illusory, as KCC claim, but rather as Falconer concludes, “the idea that every character must have its ‘natural’ and correct scale is largely illusory” ([40], p. 262).

**Normality**

The assumptions of additivity and normality are closely related. According to the central limit theorem, many factors (with any individual distributions having finite variance) that contribute not too unequally and that are largely independent in occurrence and additive in their effects tend to a compound distribution that is normal [37, 38]. The compound distribution of factors with nonadditive interaction within each of many independent groups also tend toward normality. Thus, provided that factors or groups of factors have additive effects, there is a tendency toward normality of the frequency distributions of quantitative traits from which heterogeneity from such covariates as age and sex has been removed. In any case, the assumption of normality appears justifiable as a first-order approximation for many multifactorial traits.

However, some physiological traits show substantial skewness. This is expected for the distribution of a variable to which each of many factors contributes a percentage increment rather than an absolute increment. For example, factors that influence growth variables such as weight, and homeostatically-regulated physiological traits such as blood pressure or lipid levels, often show continually greater effects as the base to which they are applied increases. For such variables, logarithmic or, more generally, power transformations may be more appropriate for path analysis than the measurements are themselves. This biological rationale for logarithmic transformation was noted as long ago as 1879 by Galton [37, 40].
As a result, transformations are often carried out prior to path analysis of such physiological variables.

Although the compound distribution of many additive factors will tend to a normal distribution, this does not guarantee that the joint distribution of several such compound variables will tend to be multivariate normal; that is, the joint distribution of several variables is not necessarily multivariate normal even if all their marginal distributions are normal or are individually transformed to a normal distribution. However, we do not necessarily require strict multivariate normality of all the latent variables in our models. We do assume that many genetic and environmental factors contribute additively to each phenotype and that the joint distribution of the phenotypes of relatives are approximately multivariate normal. We also assume that certain partial correlations, noted later, are zero. Multivariate normality of all the variables in our models is sufficient, but not necessary, to assure these conditions. Empirical experience with biological applications suggests that it is unusual to have marginal normality of each of several variables without their joint distribution being approximately normal.

Careful attention to scaling of measurements is important from both biological and statistical perspectives. Scales of measurement may be so chosen that individual marginal distributions of observed variables are normal. This is necessary, but not sufficient, to insure multivariate normality, and a practical alternative to the criterion of marginal normality has not been proposed.

INADEQUACY OF MODEL-FREE STATISTICS

If structural models are only approximations, why not abandon modeling in favor of model-free statistics as suggested by KCC? We have already noted that available model-free techniques are of limited utility because they have low sensitivity and specificity to distinguish among the effects of multiple types of genetic and environmental determinants. Furthermore, the limitations of model-free methods in genetic epidemiology are related to a severe and fundamental defect that cannot be remedied by increasing the number or sophistication of the descriptive statistics to be used.

The advantage of structural modeling over model-free approaches can be illustrated by comparison of structural analysis to regression analysis in which no causal model with unobserved or uncontrolled variables is specified. A structural equation is an attempt to represent the unique functional relationship between a set of causal variables and their effect. In contrast, a regression equation represents only an empirical association, specifically the conditional mean of a dependent variable as a function of explanatory variables. KCC apparently fail to appreciate this distinction or its significance. This is shown by their questioning our distinction between structural equations and other regression equations, such as we used for marital relationships and reverse paths. It is shown by their preference for a purely statistical approach to modeling, using the best observable linear predictors in a particular population rather than using additional biological insights.

In general, regression coefficients are mixtures of the structural parameters, so that if one structural parameter changes, all the regression coefficients may change [47, 48]. A useful or valid structural model has parameters that remain
stable or vary individually over the set of populations in which we are interested, such as samples of different types of individuals (singletons, twins, adoptees), ethnic groups, or locales. These properties of autonomy and invariance of structural parameters are what make them preferable to the best-linear predictor approach that neglects unobserved variables [49] and, more generally, to model-free descriptive statistics [47, 49, 51].

The stability and autonomy of structural parameters must be evaluated by empirical studies of many different population samples. Thus, the utility and validity of a structural model is shown by the similarity of parameter estimates in different populations. This stability of estimates across diverse populations is illustrated by results obtained by modeling of the familial transmission of many traits including serum cholesterol levels [9, 15, 29, 43], other lipids and lipoproteins [9, 15], fasting blood glucose [51, 52], plasma uric acid levels [53, 54], immunoglobulin E levels [55, 56], and blood pressure [57, 58]. The stability of these results strongly supports the validity of our general model of multifactorial inheritance for common traits of interest in genetic epidemiology.

This has been possible in genetic epidemiology to a greater extent than in other disciplines that have used path analysis because we have relatively strong general theories on which to base our structural models, compared to the fields of psychology, sociology, and economics, where the direction of effects is more often uncertain. The importance of extra statistical considerations in causal interpretation has been emphasized since path analysis was first introduced. The need to evaluate the effects of multiple unobserved and uncontrolled variables in nonexperimental data requires the use of structural models, rather than model-free statistics, in order to evaluate these theories.

Because such interpretive methods require both statistical and extrastatistical information, they do not permit conclusions with unconditional certainty about the true state of nature. Some tentative modeling assumptions may seem mathematically arbitrary but are crucial to the hypothetico-deductive process of identifying the mechanisms underlying the transmission of diseases. Moreover, explicit comprehensive models are needed to test the adequacy and internal consistency of interpretations made from any set of descriptive statistics.

DEVELOPMENTAL SEQUENCE OF THE PATH MODELS

KCC presented the different models of multifactorial inheritance in stasis as if they were arbitrary alternatives. Actually, they reflect a historical sequence of progressive refinement based on extensions of theory and experience with earlier applications. It is useful to recognize this sequence and the motivation for the changes in order to avoid several mistakes made by KCC.

In 1974, Morton [5] and Rao et al. [6] introduced a path model that concentrated on resemblance of sibs, half-sibs, and twins. This model simplified the treatment of parent-offspring pairs. Realizing that such models were oversimplifications, and partly motivated by development elsewhere [59], in 1976 Rao et al. [7] introduced another path model describing cultural and biological inheritance in the presence of assortative mating. This model allowed for polygenic inheritance, a single environmental variable common to each member of a sibship and influenced
by each parent, and intergenerational differences in the polygenic and cultural heritabilities (for a special case of the model, see KCC [17], fig. 1). Assortative mating was due to social homogamy; dominance and gene-environment interactions were excluded. One major feature of these methods was use of an observable but imperfect index of home environment that made the model identified using nuclear family data only [7]. Another was the assumption of normality for estimation of correlations and hypothesis testing, introducing Fisher’s $z$-transform to hasten the asymptotic approach of the correlations to normality [6, 9].

For the analysis of physiological data, specific maternal effects were introduced in 1978 [8]. Rao and Morton tested their linear model in the presence of nonlinear gene-environment interaction, using data generated by Cavalli-Sforza and Feldman, and observed that neither genetic nor cultural inheritance was exaggerated [60]. Their model was also applied to many physiological traits and American IQ data. The high estimates of heritability for IQ (about 70% in children and 30% in adults) sparked constructive scrutiny by Goldberger and others, but no fundamental flaws or changes in parameter estimates [61, 62]. In Goldberger’s own words, “They build upon the remarkable work of Sewall Wright, and proceed from an explicit, logically tenable, and internally consistent, causal model” ([63], p. 196).

In 1979, Cloninger et al. [11] introduced the BETA model in which cultural inheritance was extended to allow transmission of environmental factors from parents to each child separately and to allow residual environmental variability to be correlated among siblings. The home index was permitted to be influenced by both genetic and environmental factors, but intergenerational differences were not considered. Assortative mating was due to direct phenotypic preference (see KCC, fig. 3). The introduction of reverse paths and the assumption of zero partial correlation of mates in the absence of direct phenotypic preference allowed extension of the model beyond nuclear families to any pair of vertical or collateral relatives. Conceptual and statistical aspects of the BETA model and its extensions and special cases are described elsewhere [10–12, 64]. Application to the same American IQ data analyzed by Rao and Morton [8] suggested much lower estimates of genetic heritability (about 30%) and cast doubt on the assumption that SES or Burk’s culture index were simple indices of the cultural determinants of IQ.

Such discrepancies in the IQ analyses led to a careful evaluation of similarities and dissimilarities of the two models. A major source of difference appeared to be assortative mating. Whereas the “Hawaii group” assumed social homogamy, the “St. Louis group” assumed phenotypic homogamy. Motivated by this, Morton and Rao [65], Rao et al. [13], and Cloninger [66] generalized assortative mating to mixed homogamy with social homogamy and phenotypic homogamy as two special cases. The associated statistical issues will be discussed later. This led to the most recent model, which includes both the generalizations of cultural inheritance of the BETA model and mixed homogamy (see KCC, fig. 2). Using this, we could then systematically evaluate the nature of the model-dependence of the parameter estimates of the earlier models. This has recently been done for American IQ data [14]. The general model confirms a moderate genetic heritability (about 30%–40%) of IQ with the more general treatment of cultural inheritance,
regardless of assumptions about assortative mating or intergenerational differences. Also, the estimates of genetic and cultural heritability are essentially the same whether estimated with indices or using IQ data in multiple classes of relatives with indices excluded.

The more elaborate models were applied to cognitive and behavioral traits, whereas simpler models have proved adequate for less complex physiological traits. Overall, it should be clear that these models represent simplifying approximations that have developed in progressive stages in response to the needs of genetic epidemiology for data analysis and interpretation.

**INTERNAL CONSISTENCY OF MULTIFACTORIAL MODELS**

The basic structural model of combined polygenic and cultural inheritance has been found to be coherent and internally consistent by many investigators besides ourselves (e.g., [63]). This has been described in terms of explicit structural equations, distributional assumptions, and associated constraints on the size of parameters described in detail elsewhere [11]. The questions raised by KCC about the coherent specification of covariance relationships in path models used in genetic epidemiology primarily involve the treatment of assortative mating. They raise questions about the sign of intrinsic correlations represented by double-headed arrows (↔) and the distributional assumptions underlying path reversal and copaths.

KCC falsely assume that a double-headed arrow must be nonnegative (≥ 0). For example, they assume that under social homogamy the correlation \( u \) between the cultural value of mates must be nonnegative. Unfortunately, this misimpression is not clarified in the diagrams of Rao and Morton in which \( \sqrt{u} \) was used for the path to each spouse for the special case of positive assortative mating. However, more generally, the correlation \( u \) was not constrained to be nonnegative in the computer programs. This should have been especially clear to KCC, who labeled the negative estimates of \( u \) reported in [9] as counterintuitive!

The structural relationship with the most restricted chain properties is the correlation due to a common antecedent, whether specified (← X →) or implied (↔). In the absence of copaths, only one such correlation may appear in a chain. Of course, a common antecedent may lead to either positive or negative correlations depending on whether its effects have the same or opposite signs, respectively. Following Wright, it is customary to use a two-headed arrow to represent any ambiguous correlation, that is, any correlation whose cause need not be explained for the purpose of the analysis. This is convenient because it requires the most restricted possible treatment of this relationship in deriving other correlations. If less restriction is assumed, the choice of another symbol must be justified. An explicit example is the correlation between \( C_F \) and \( G_F \) under path reversal in figure 4.2 of KCC: The correlation \( a - \gamma \phi \) arises from correlations among the residuals of \( C_F \) and \( G_F \) induced by path reversal, as we have shown elsewhere [62], and may be either positive or negative in sign. The constraints on parameters due to assumptions of nonnegativity suggested by KCC are unnecessary.

Similarly, KCC's claim that we failed to incorporate a genic-cultural (G-C) correlation for children, thus leading to inconsistency in the treatments of parents
and children, is entirely false. Such a correlation has been derived for a child in terms of parental variables and equated to the G-C correlation in parents \((\alpha)\), as expected at equilibrium \([8, 11, 13]\).

Path reversal was introduced in the BETA model in 1979 for the treatment of phenotypic assortment in order to avoid duplication of variables. To extend the treatment of phenotypic assortment beyond nuclear families, reverse paths were used also with representation of marital correlations by unidirectional paths. We cautioned that these representations were not causal relationships (as defined earlier), but merely representation of our assumption that certain partial correlations were zero \([11]\). Specifically, we assumed zero partial correlation between the antecedents of each individual phenotype and the phenotype (and antecedents) of his mate, holding the influence of the intermediate phenotype constant \([11], p. 194\). This assumption is not distribution specific and yet is sufficient to justify our treatment of both reverse paths and unidirectional marital paths \([67, 68]\). We explicitly assumed multivariate normality in our derivations \([11], p. 179\), but this was for other reasons (specifically, interest in multifactorial traits). Under multivariate normality, zero partial correlation is equivalent to the concept of conditional independence, but not necessarily with other distributions. Thus, contrary to the statements of KCC, the assumptions of neither multinormality nor conditional independence are required for path reversal.

Unidirectional marital correlations still did not permit derivation of correlations between the paternal and maternal antecedents within a classical path analytic framework. This required introduction of a coefficient with a bidirectional influence on covariance structure, represented by a headless bar \([66]\). Cloninger called this coefficient a copath and suggested relaxation of the classical assumption of complete determination of all correlations by antecedents. This in turn led to a distinction between intrinsic and extrinsic structural relations.

Natural causation is the prototype of intrinsic structural relations with particular properties including a specific direction in time and space, such as transfers of genes along pedigree lines. In contrast, extrinsic relations or adventitious associations involve only nonrandom pairing of factors such as in phenotypic assortative mating. Our early application of this distinction was to phenotypic assortative mating in which phenotypic preferences of mates induced an adventitious association between otherwise independent sets of intrinsically related variables (i.e., the phenotypes and their antecedent causes). We agree with KCC that copaths may be validly applied in such situations with otherwise independent sets of factors (e.g., KCC's figure 5.1). However, later work has shown that introduction of an adventitious association between two variables with a common cause, as in KCC's figure 5.2, may involve selection (in the sense of a change in the variances) as well as changes in covariances. As a result the properties of copaths originally given by Cloninger may not apply in some complex systems with both common antecedents and adventitious associations, as discussed in section 6 of Cloninger \([66]\) and in figure 5.2 of KCC. Van Eerdewegh has recently used the work of Aitken \([69]\) to provide an extension of path analysis to allow for selection in such complex systems \([70]\). However, it should be emphasized that the treatment of either phenotypic assortment or social homogamy with copaths requires no
introduction of selective mating functions. Similarly, mixed homogamy may be modeled as assortment for two correlated phenotypes simultaneously [66] without introducing selective mating functions. Thus, our treatments of mixed homogamy and its two special cases are coherent and logically consistent [70].

Our treatments of assortative mating represent only the consequences of unspecified processes on the joint distribution of mates. Our models do not specify a causal model for the marital process. On the other hand, the nonlinear selective mating function proposed by Karlin [71] is unrealistic for traits with both high marital correlations and high reproductive fitness. For example, the phenotypic variance of married individuals must be less than $\frac{1}{2}$ of the variance of the total population in order to achieve a marital correlation of 0.5 under Karlin's [71] selective mating system (see his equation 2.13). Such high selection seems implausible for most traits of interest in genetic epidemiology. In other words, selective mating seems plausible only when its effects are not appreciable within a few generations.

VALIDITY OF STATISTICAL AND COMPUTATIONAL PROCEDURES

Distribution of Correlation Estimates

Even when the joint distribution of a pair of variables is bivariate normal, the distribution of the correlation estimate is skewed rather than symmetrical unless the true value is zero. Fisher showed that the distribution of a sample correlation coefficient, $r$, based on a sample from a bivariate normal population, approaches normality as the sample size ($n$) increases [72]. He proposed a transformation of $r$, calculated as $z = \frac{1}{2} \ln \left[ \frac{(1 + r)/(1 - r)}{2} \right]$, that is almost normally distributed with constant variance $1/(n - 3)$. One of the methods of analysis we proposed, method-1 given by equation (3) below, is based on this property.

The joint distribution of several correlation estimates was recently investigated by Fang and Krishnaiah using Edgeworth expansions [73]. The asymptotic distribution contains two leading terms: one term is the multivariate normal density, and a minor term involves partial derivatives of the multivariate normal density with $\sqrt{n}$ in the denominator. Adequate approximations are usually obtained by the first term alone in samples of reasonable size. This justifies the basic assumption in our second method given below by equation (4).

More recently, through simulation studies, Wette et al. [74] investigated the distributions of correlation estimates and their $z$-transforms when the family size is variable [74]. It was shown that the $z$ transformation of a sample correlation, computed simply as $z = \frac{1}{2} \ln \left[ \frac{(1 + r)/(1 - r)}{2} \right]$, is almost normal even in samples as low as 50 families. Even the correlation estimates are normally distributed for somewhat larger sample sizes. In addition, the empirical variance of a $z$-transform, determined using 1,000 replications, closely corresponds to the asymptotic minimum bound, thus demonstrating nearly full efficiency of correlation estimates [74].

Estimation of Path Coefficients

These distributional properties of correlations and their $z$-transforms have been taken into account in three methods we have suggested for estimation of parameters
\( \theta \) of path models and for tests of hypotheses. Consider \( m \) estimates of correlations \( r_i \), their \( z \)-transforms \( z_i \), based on sample sizes \( n_i, i = 1, 2, \ldots, m \).

In method-1, assuming the \( z_i \) are independent, the log likelihood is approximated as
\[
Q = \sum_{i=1}^{m} n_i [z_i - \bar{z}_i(\theta)]^2
\]
and \( \bar{z}_i(\theta) \) are the \( z \)-transforms of the true correlations \( \rho_i(\theta) \), which are functions of \( \theta \). If the samples of \( n_i \) pairs are independent, then \( Q \) is asymptotically distributed as \( \chi^2 \).

On the other hand, if the sample correlations are determined from a single sample, they are not independent. For this reason, method-2 was proposed as an alternative, where all the relevant correlations and variances are first estimated simultaneously under the assumption of multivariate normality of the family data. After convergence of the iterative process, an empirical information matrix \( K \) is obtained with its elements computed by double differentiating the log-likelihood function of the family data with respect to the estimated correlations [75]. This estimate of \( K \) is a consistent estimator of the corresponding population matrix; that is, with increasing sample size, it will tend to the true matrix. Then, \( Q \) may be approximated as
\[
Q = \sum_{i=1}^{m} \sum_{j=1}^{m} [r_i - \rho_i(\theta)]K_{ij}[r_j - \rho_j(\theta)] ,
\]
where \( K \) is the empirical information matrix of \( r_i \), not dependent on the parameters \( \theta \). This second method was originally described with a slightly different method of computing the \( K \) matrix [9]. Unfortunately, KCC incorrectly represent our formula for method-2 by replacing the empirical sample information matrix \( K \) by \( K(\theta) \), the unobserved population information matrix, which is a function of unknown parameters. Their error led to the false charge that we had incorrectly omitted the log determinant of \( K^{-1}(\theta) \). However, the log determinant of the empirical covariance matrix \( K^{-1} \) is a constant, and their discussion is irrelevant to our method.

Assuming the joint distribution of the sample correlations is approximately multinormal [73], then in method-2 [equation (4)], the asymptotic distribution of \( Q \) may be approximated by \( \chi^2 \).

We are aware that a full likelihood approach involves writing down the density of the family data assuming multivariate normality. Numerical optimization methods can then be used to maximize the full likelihood directly for estimating \( \theta \), as described in method-3 elsewhere [75]. A primary limitation of this method is the enormous computational time involved: each hypothesis fitting uses all the family data, and fitting a few hypotheses can amount to several hours of computer time, even for family studies of moderate size. Therefore, a more useful alternative would be to consider the joint distribution of \( r_i \), which depends on \( \rho_i(\theta) \), and estimate \( \theta \) from the full likelihood based on \( r_i \). This method depends on knowledge
of the exact distribution of \( r_i \). In some sense, this is better than using the likelihood based directly on all the family data.

There are other alternatives, as discussed above (methods-1 and -2), to simplify computations, and which, we believe, are as efficient as the full maximum likelihood estimates. One may treat equation (3) as a distance between \( z = (z_1, \ldots, z_m) \) and \( \tilde{z} = [z_1(\theta), \ldots, z_m(\theta)] \). However, when the \( z_i \) are not independent, there is no theoretical justification for treating the Q obtained by method-1 as a \( \chi^2 \). Another alternative is method-2 [equation (4) above]. In suggesting this approach, our motivation was similar to that of the method of modified \( \chi^2 \) introduced in statistics by Neyman and extensively used by Berkson. The advantages are that computations are simple, and a large sample test is available for goodness of fit through a \( \chi^2 \) statistic.

KCC suggest using the asymptotic normal distribution of \( r_i \) to derive maximum likelihood estimates. As observed by us, the correct method is to use the exact distribution of \( r_i \). In the absence of this, the method suggested by KCC has the same ad hoc nature as our method-2. It is not known whether the estimators so obtained would be better than ours. Computationally, they are more complicated than ours. Method-2 provides best asymptotically normal (BAN) estimators, similar to those obtained by the method of modified \( \chi^2 \). This property, together with the goodness-of-fit test it provides, justifies its use in practical work.

A large number of traits were analyzed by both methods with similar results [9, 76–79]. This empirical experience led us to favor method-1 [equation (3)] even though we realize it involves the simplifying assumption that the \( z_i \) are independent. An evaluation of the three methods through computer simulation suggests that the empirical distribution of Q in method-1 deviates appreciably from \( \chi^2 \) when the family resemblance is strong, but still yields accurate parameter estimates [78].

In methods-1 and -2, only the means are functions of unknown parameters, not the covariance matrices, as falsely claimed by KCC. In the third method, only the covariance matrix is a function of the unknown parameters, not the means. Therefore, the standard method of maximum likelihood is valid for these methods. All three methods are discussed in greater detail elsewhere [75].

**Hypothesis Testing**

Two types of \( \chi^2 \) tests are used in evaluating hypotheses in multifactorial path models: goodness-of-fit tests (GFT) and likelihood-ratio tests (LRT). An LRT is used to test only the fit of a more restricted model relative to a less restricted model. In contrast, a GFT is used to test the overall adequacy of the model. Clearly in equations (3) and (4), Q provides a GFT since it measures the extent to which expected correlations predicted by a given model correspond to the observed ones. On the other hand, an LRT for testing a specific null hypothesis (a more restricted model) is given by twice the absolute difference between the log likelihoods under the general model and the null hypothesis. In the present case, using methods-1 and -2, this simplifies to differences between the Qs under the two models. Therefore, Q provides a GFT, and the difference between two appropriate Qs provides an LRT. If Q is small, we can conclude that we cannot
falsify the general model. This does not guarantee that every assumption specified in the model is exactly valid, only that the consequences of any violations do not lead to an appreciable deviation between observed and expected values of the correlations [68]. Even though this GFT may not be highly sensitive to all our underlying assumptions, it is unclear how one model (e.g., a nonlinear model) can be preferred over a more parsimonious model (e.g., a linear model) that cannot be falsified empirically.

**Numerical Analysis**

A model does not provide an automatic algorithm for data analysis; rather, it is a tool that must be applied with clinical and etiological insight as well as analytical skill in order to yield meaningful results. Even when a model is theoretically valid, a data analyst must remain alert to technical problems in numerical analysis.

Let us illustrate this by reconsideration of the numerical example presented by KCC in their table 4. Since their equations (4) and (6) do not correspond to any of our methods, we will first only consider their equation (3), which is the same as our equation (3), or method-1. The 16 sample correlations generated by the 10 true parameter values chosen by KCC were analyzed by us using a FORTRAN computer program called BPATHMIX developed on a HARRIS 100 computer system [80]. BPATHMIX, and its univariate version PATHMIX [15, 16], were both developed based on identical logic using GEMINI [81]. KCC presented two cases, each based on a separate set of initial values for the parameters. In neither case did they obtain solutions in the vicinity of the true parameter values, by any of the three methods they considered. On the other hand, our table 1 presents five sets of initial values, including the two sets considered by KCC. In every case, we recovered the true parameter values without encountering boundary points in the search. Since this was accomplished using equation (3), we cannot reconcile this with the KCC assertion that "it is most unlikely that the maximization of equation (3) . . . will yield anything akin to a maximum likelihood estimate."

Moreover, we considered many sets of starting values between the two extremes of our cases (4) and (5) in table 1, and in every case we recovered the correct values. Only when we started all parameters at .8 or greater, sometimes one or two parameters went to a bound. However, when we restarted at the boundary solution as initial values by changing the one or two boundary values slightly (changing 1 to .9 and 0 to .1), we obtained correct parameter values again. In table 1 we give not only our solutions starting from their initial values (for cases 1 and 2), but we also give our solutions starting from KCC's final solutions (by changing boundary values of 1 and 0 to .9 and .1, respectively, as we commonly do with real data) in which we recovered the true values.

To facilitate evaluation of the results presented, table 1 also includes three summary measures for each final solution. The residual $\chi^2$ using equation (3) is zero for all of our solutions as it should be, but not for either of the two KCC solutions. The quadratic form $u'k^{-1}u$, measuring departure of a final solution from a maximum, is again zero for all of our solutions but grossly nonzero for KCC's solutions. The third measure, $V(C_r) = f_F^2 + f_M^2 + 2u_f f_M$, represents
### TABLE 1

**Effect of Initial Estimates of Parameters on the Final Estimates in Path Analysis Applications:**

**Comparison of Our Results with Those of KCC [17]**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True value</td>
<td>Initial value</td>
<td>KCC final</td>
<td>Our final</td>
<td>KCC final</td>
</tr>
<tr>
<td>c</td>
<td>.30</td>
<td>.10</td>
<td>.305</td>
<td>.300</td>
<td>.300</td>
</tr>
<tr>
<td>y</td>
<td>.80</td>
<td>.10</td>
<td>.589</td>
<td>.800</td>
<td>.800</td>
</tr>
<tr>
<td>h</td>
<td>.70</td>
<td>.10</td>
<td>.680</td>
<td>.700</td>
<td>.700</td>
</tr>
<tr>
<td>z</td>
<td>.90</td>
<td>.10</td>
<td>1.000</td>
<td>.900</td>
<td>.900</td>
</tr>
<tr>
<td>u</td>
<td>.50</td>
<td>.10</td>
<td>.732</td>
<td>.500</td>
<td>.500</td>
</tr>
<tr>
<td>f_s</td>
<td>.50</td>
<td>.10</td>
<td>1.000</td>
<td>.501</td>
<td>.500</td>
</tr>
<tr>
<td>f_m</td>
<td>.50</td>
<td>.10</td>
<td>.045</td>
<td>.500</td>
<td>.500</td>
</tr>
<tr>
<td>t</td>
<td>.75</td>
<td>.10</td>
<td>.751</td>
<td>.750</td>
<td>.750</td>
</tr>
<tr>
<td>i</td>
<td>.60</td>
<td>.50</td>
<td>.433</td>
<td>.600</td>
<td>.600</td>
</tr>
<tr>
<td>i_M</td>
<td>.60</td>
<td>.50</td>
<td>.585</td>
<td>.600</td>
<td>.600</td>
</tr>
</tbody>
</table>

Residual $\chi^2$: 0.000 ... 3.870 0.000 0.000 ... 3.759 0.000 0.000 ... 0.000 ... 0.000 ... 0.000

$u'k^{-1}u$: 0.000 ... 523.029 0.000 0.000 ... 548.287 0.000 0.000 ... 0.000 ... 0.000 ... 0.000

$V(C_v)$: 0.750 0.022 1.068 0.751 0.751 0.156 1.000 0.750 0.750 0.750 0.752 1.666 0.749 0.005 0.751

**Note:**
1. "KCC final" corresponds to the KCC solution using their formula (3), given in their table 4. Cases 1 and 2 are the two cases discussed by KCC in their table 4.
2. "Our final" was obtained using BPATHMIX, which uses GEMINI [80, 81].
3. "Our-KCC" was obtained using BPATHMIX, starting from the "KCC final" values (boundary values 1 and 0 were changed to .9 and .1, respectively).
4. Residual $\chi^2$ was computed as per formula (3) of KCC.
5. $u'k^{-1}u = \sum u_i u_j k_{ij}$,
6. $V(C_v) = f_s^2 + f_m^2 + 2u_i f_s f_m$. 

This table compares the initial and final parameter estimates for different cases, along with the residual $\chi^2$ values and $V(C_v)$ for each case.
the variance of child's familial environment apart from a residual component. Therefore \( V(C_r) \) is constrained above by 1. Its true value is .75, which was recovered in all our solutions, but not in KCC's solutions. In fact, one of the KCC's solutions exceeded the constraint, rendering that solution inadmissible. We also programmed the other two KCC's methods, given by their equations (4) and (6), taking \( K(\theta) \) to be diagonal just as they did. In all five cases presented in table 1, we recovered the true parameter values by both these methods as well, again without encountering boundary points. Therefore, we fail to understand how KCC obtained the results they presented in their table 4. In any case, their failure to recover the true parameter values cannot be attributed to path models, our methods of analysis, or GEMINI.

Nevertheless, in general, there is no guarantee of obtaining an interior maximum likelihood solution or the global maximum from a particular starting point. An investigator must be alert to technical problems and to results that cast doubt on the validity of a model. Mathematical sophistication is no substitute for careful analysis.

DISCUSSION

Substantial empirical data in quantitative genetics support the practical adequacy of the assumptions of additivity, linearity, and normality in the path analysis of most multifactorial traits. The choice of scale for quantitative traits must be considered on an individual basis, and transformations of scale may be more appropriate for analysis than the measurements are themselves. The computational procedures used in contemporary applications of path analysis are reasonably well justified by the statistical properties of functions of correlations among variables in such linear systems. If any particular model is to be proven invalid, either the underlying assumptions must be demonstrably wrong or it must be falsifiable by some kind of goodness-of-fit test.

Surprisingly, KCC seem not to appreciate the biological and statistical motivations for scaling of variables prior to analysis that have been well established since the work of Galton over a century ago. They have not clearly recognized the importance for a biologist of the distinction between the unique structural form of a model and other convenient ways of representing such relations by means of various regression and correlation coefficients. They have overlooked the developmental sequence of our models, distorting their relationship by depicting them as arbitrary alternatives in stasis.

However, the critique of path analysis by KCC is primarily based on some unfounded concerns and their errors. Specifically, they falsely assume that correlations represented by double-headed arrows must be nonnegative, and then complain that we have not considered the resulting factitious constraints. They erroneously suggest that path reversal requires the assumption of multivariate normality as a result of their confusing the requirements for zero partial correlation with the requirements for conditional independence. They confirm the validity of copaths under the conditions we have used them in our treatment of assortative mating, but criticize an extension to some more complex systems without making clear that this is irrelevant to any of our current models. They misstate the criterion
we use in estimation of path coefficients, and then point out the problems associated with their estimator, which is irrelevant to our work. They ignore our use of goodness-of-fit tests to assess the adequacy of our models, possibly because their acknowledgment would largely vitiate their own criticism. Finally, they criticize our methods of numerical analysis based on their misuse of the generalized minimization program GEMINI. The results they ascribe to path models, our methods of analysis, and GEMINI are not reproducible and must be due to errors in their application. We were able to recover the true parameter values not only for the two cases KCC considered but also for all cases we have considered. Despite these limitations, the critique of KCC is useful because it underscores the need for investigators to consider their analytical methods with care.

In actual applications to traits of importance, such as human lipoproteins and blood pressure, path analysis has led to identification of the causal features of familial transmission that are stable across highly diverse populations of interest. In effect, KCC criticized a caricature of path analysis, rather than path analysis as it is actually practiced. We conclude that the utility of path analysis to resolve genetic and cultural inheritance is limited primarily by the biological insight and numerical skill of its users, not by the method’s assumptions.

The critique of path analysis and related parametric methods by KCC seems intended to justify their advocacy that exploratory methods replace statistical inference. We take the position that, while exploratory methods can be useful for preliminary data inspection, they cannot substitute for formal tests of hypotheses based on explicit models. By our use of modeling in general and path analysis in particular, we make no pretense of knowing the “clear, precise, and final solutions to the complex problems raised by genetic epidemiology.” We only hope to provide empirical tests of our biological insights and statistical assumptions and to refine our models in light of the results [68].

In assessing the utility of such models in genetic epidemiology, Edmund Murphy noted that “the next best thing to uttering the truth is to say something so sufficiently definite that it can be constructively disagreed with” [82]. The critique of KCC does confirm our success in having been sufficiently explicit that others can disagree with us and potentially reject our hypotheses. Accordingly, genetic epidemiology will be better served by practical applications of path analysis and related parametric methods than by the quixotic quest to explore data without specifying an explicit mathematical model. Model-free methods have not played an important role in the progress of any science, and there is no reason that genetic epidemiology should prove to be an exception.

Genetic epidemiology is greatly indebted to Sewall Wright for developing the remarkable technique of path analysis for the interpretation of multivariate linear systems in a consistent quantitative manner. We take pleasure in dedicating this defense of path analysis to Sewall Wright on the occasions of his ninety-third birthday and the sixty-fifth anniversary of his conception of path analysis. His rare combination of biological and statistical insight has provided genetic epidemiology with a truly sound foundation.
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