SCOPE AND METHODOLOGY OF TWIN STUDIES

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The use of twins as a research tool is still proving its worth both by the number of scientists engaged in twin research and by the significance of their results. Old, familiar research designs are finding new applications, and new research designs are appearing. Of greatest current interest are the epidemiological studies made possible by the assembly and the aging of large numbers of twins in twin registries. As an outgrowth partly of the twin registries, partly of conceptual and mathematical progress, new methods have emerged for diagnosis of twin types and for analysis of twin data. One line of development started with the questionnaire method of zygosity diagnosis and has given rise most recently to zygosity diagnosis by principal component analysis. Another line started with probability calculations and has led to the use of generalized distance and noncentral chi-square. The appropriateness of these methods in different contexts needs to be critically considered. Also of importance are the psychologists' new methods of extracting genetic "factors". The greatest weakness of twin studies, long recognized, is their dependence on the assumption that DZ pairs provide an adequate control on the environmental differences within MZ pairs. This may be valid with respect to environmental influences that are highly self-selected. It is debatable for self-selected influences that differ among families, and clearly untenable for most influences imposed by the social environment peculiar to twins.

Twin research as proposed by Galton was the first scientific method of analyzing human heredity. But being the oldest method does not mean that it is now obsolete. The large number of scientists attending this congress evidently regard twin studies as important. However, the fact that we all regard our own research as important does not prove much. Therefore, my task is to provide an overview of research that uses twins as a tool, hopefully to show that this is a modern science, still changing and growing.

The criterion of a useful science is its product; in this case, the significance and quality of the conclusions derived from recent twin studies. No scientist has ever won a Nobel Prize for twin research. The only scientific break-through occurred a hundred years ago when it became known that some twins develop from a single egg. But ever since that genetic fact was recognized, twins have performed the important function of stimulating interest in human heredity; particularly in the area of psychology, where findings have been both impressive and controversial. Twin studies have also made some very solid contributions to science, and I would like to give you examples, but other speakers will do that.

The scope of twin research is limited in the sense that it is not a complete methodology; it is most useful as a primary test of hypotheses, or to yield approximate values of genetic parameters. But the scope is unlimited in terms of the diversity of applications and almost unlimited in diversity of research designs. In illustrating this diversity I shall not attempt to describe in detail all the methods or the research that I shall cite.

The older kinds of twin study are still going on. The oldest kind, detailed accounts of single twin pairs, now often appears in modern dress: e.g., medical reports of MZ pairs who differ from each other in some chromosomal anomaly (Aurias and Lejeune 1974). In another historic application,

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MZ twins are still being used to study the effects of pharmacologic agents (Vesell and Page 1968, Schwartz et al. 1973).

Another old kind of study is the small series of twins, assembled for a special objective. Recent examples include some traditional and often oversimplified studies of behavioral traits (Bakwin 1971) and some very original studies, like one on genetic factors in dental asymmetry (Staley and Green 1974). Twin samples collected because they have a particular disease are of course very numerous. The older research designs are easy to understand and relatively easy to execute, and so they attract many scientists in specialties outside of genetics. Geneticists sometimes try new methods because they know the limitations of the old ones. Conclusions derived from the older studies were rarely definitive, and depended upon interpretations. For example, MZ twins are almost certain to be more alike than DZ twins even in traits that do not depend on heredity, so the mere observation of an MZ-DZ difference does not prove inheritance. Yet the finding of no difference does not exclude inheritance; thus, no significant MZ-DZ difference appeared in the first twin study of urinary beta-amino-isobutyric acid despite strong genetic determination. The reason was that very few twin pairs had the abnormal genotype, and so most of the variance was due to measurement error (Sutton 1965).

More effective research strategies are numerous. Dencker (1958) provided a classic example of an effective use of twins in his study of differences between MZ twins that were discordant for head injury. That study revealed sequelae of injury that were too subtle to be detected by other methods. Equally revealing was Pollin and Stabenau's (1966) study of discordant schizophrenic twins. In a somewhat more complicated design applied to a review of literature, Rosenthal (1959) examined the clinical features of schizophrenia in concordart as contrasted with discordant MZ twins;the two groups have rather different forms of the disease. Several twin research designs are being used to cultivate the fertile field of infant behavior. For example, twins may be compared with their single sibs (Nichols and Broman 1974), and opposite-sex pairs are useful for studying early sex differences, whether inherited or not (Brooks and Lewis 1974). Twins often dramatize developmental timing, and comparison of age at disease onset in concordant MZ twins is valuable for analysis of the natural history of diseases (Gedda and Tatarelli 1971).

Some of the most important innovations in twin research are connected with the use of very large twin registries. These registries have greatly facilitated systematic twin studies of rare diseases, and have also made possible the analysis of the common diseases that depend mainly on environment. The large size of twin registries has made new methods necessary. First and incidentally, the registries are managed, and in some cases assembled, with the help of computers, and much of the analysis is done by machine.

Partly to meet the demands of twin registries, two principal methods of zygosity diagnosis have become differentiated. For small twin samples, often subsets of a twin registry, the preferred practice is to depend entirely on genetic markers, which can detect about 97% of DZ pairs. Any errors are known to be of only one type: the inclusion of DZ pairs in the MZ population. Dermatoglyphics, pigmentation, and metric traits are now used less for zygosity diagnosis and more as topics of study (Vrydagh-Laoureux and Defrise-Gussenhoven 1971, Kloepfer and Parisi, 1974). The oldest criterion of zygosity, the fetal membranes, has been almost forgotten because the information is so difficult to obtain. This is regrettable, because the membranes seem to indicate several important differences among MZ twins (Lutz 1974, Boklage 1974).

For any large number of twins the use of genetic markers is too expensive and in some other circumstances blood is hard to obtain. The questioning of close relatives in order to diagnose zygosity was tried by Essen-Möller (1941), but remained under a cloud until Cederlöf et al. (1961) had the courage to say that a questionnarie completed by the twins was sufficiently reliable for many purposes. Questionnaires have now been developed also for use with parents of young twins (Cohen et al. 1973). Such zygosity questionnaires have usually been validated on a subset of the twins by use of genetic markers. The genetic markers conflict with the questionnaire in less than 10% of same-sex pairs (Jablon et al. 1967). However, another 5 to 15% are usually unclassified. It should be remembered that assignment of some twins to a residual, undecided group is not entirely satistactory. Even if

the definite classifications are all correct, conclusions of a study can be biased by omission of very similar DZ pairs or dissimilar MZ pairs. Bias will result whenever similarity as perceived socially is correlated with similarity in the trait being studied.

When a questionnaire is used there may be a problem of how to evaluate incomplete or inconsistent responses. In one study this problem was solved by discriminant function analysis (Cohen et al. 1973). A series of twins were classified by both blood groups and questionnaire; weights were then assigned to the several questions according to how often they aggreed with the blood-group results. This procedure gives a sharp dividing line, and if the formula is applied rigidly to all pairs there is no undiagnosed residue. Some twins will, of course, be misclassified. In the sample studied, the formula made only 2% errors, but there would be more errors if the formula were applied to another sample, instead of the sample from which the weights were calculated.

The same authors have now taken a further step (Cohen et al. 1975). Using the same questionnaire with a sample of twins who had not been blood typed, they applied principal component analysis to the answers. They assumed that the first principal component, the main source of variance, was the difference between MZ and DZ pairs. The resulting weights correlated closely with those obtained for the discriminant function. The method may, however, have little practical value. It does not provide an objective dividing line between the groups, and discriminant functions may soon be available for questionnaires that have been validated by bloodtyping.

The questionnaire methods must be used with caution. The object of a twin study is usually to compare the similarity of MZ twins with the similarity of DZ twins in some important trait. Errors of zygosity classification tend to reduce the difference between the two groups of twins. But if the classification is based on perceived similarity, any correlation between similarity as perceived and similarity in the trait under study will tend to exaggerate the difference between the groups. When the correlation is strong, the second tendency may outweigh the first, so that errors of classification increase the contrast between MZ and DZ groups and give an overestimate of the genetic influence. This risk may, however, be small (Nichols and Bilbro 1966).

Another line of development began with calculation of the probability that a blood-type-concordant pair of twins might be DZ. Three rather similar methods have been proposed for combining observations on several genetic markers, all based on relative likelihoods and Bayes' theorem (Essen-Möller 1941, Smith and Penrose 1955, Sutton et al. 1955, Wilson 1970).

Quantitative traits like head measurements are less amenable to such calculations for four reasons. First, most such traits are affected by the environment, prenatal or postnatal, and this obscures the difference between the two types of twins. Second, such traits are often correlated with one another, requiring correction for redundant information, for example by the method of generalized distance (Defrise-Gussenhoven 1967). Third, most quantitative traits depend on age in growing children, and on sex in adults also. This variation may be reduced by standardization within age and sex groups before combining such groups, but only if a large reference population is available. Moreover, variation of a trait may not be physiologically equivalent at different ages (Bulmer 1970). In that case, the groups cannot properly be combined. The trouble is that one does not know when it is or is not proper to combine different groups.

A fourth and rather curious problem connected with quantitative traits is that if in some measurement a pair of twins is far from the population mean, a large difference between those twins in more likely than between twins who are near the center of the distribution. Defrise-Gussenhoven (1968) reported that the noncentral chi-square distribution coincides with these probabilities, and permits a more accurate comparison of MZ and DZ twins. This clearly has application to other situations beside zygosity diagnosis.

Some other new statistical methods bear no relation to zygosity diagnosis. First, I would mention the statistical treatment of diseases and other qualitative traits. Findings of this type are usually reported as concordance rates. The pairwise concordance rate suffers marked distorsion under incomplete ascertainment (Hrubec 1973) and corrections have been proposed (Allen 1955, Selvin 1970). It is now generally known that the distortions are completely avoided by use of proband concordance

rates (Bulmer 1970, Smith 1974); that is, by giving the numbers of individuals ascertained as index cases in concordant and discordant pairs, not the numbers of pairs.

There are alternatives to the concordance rate for analysing discontinuous traits in twins. Complete ascertainment of a twin population, as in a twin registry, makes it possible to count the twin pairs in which neither member is affected. There are then two concordant classes and one discordant class, and their relations can be expressed either as the coincidence rate (World Health Organization 1966) or as the discordance rate suggested by Feinleib (Schwartz and Feinleib 1974). Or, the numbers can be substituted into a formula for the standard normal deviate, Z, which permits a direct test of significance of the MZ-DZ difference (Schwartz and Feinleib 1974).

The use of concordance rates, as such, to estimate heritability has no good theoretical basis (Smith 1974). By assuming different genetic models one may deduce either a high or a low degree of genetic determination from the same data. Given a discontinuous trait with reduced penetrance and a low rate of familial recurrence, the simplest explanation assumes one susceptible genotype that results from multiple, interacting Mendelian factors, but this model rarely fits a real trait (Bulmer 1970). Methods for treating threshold characters, borrowed from animal genetics (Edwards 1960, Falconer 1965) translate discontinuous variation into information about a continuous variable, liability. This permits diseases with all-or-none expression to be explained and analyzed in terms of additive, polygenic effects. The original methods have been modified to make optimal use of twin data (Bulmer 1970, Smith 1974).

Turning again to quantitative traits, Holzinger's classical formula for heritability, based on variances, seems to have a sentimental value for many gemellologists. It is indeed pleasantly simple and does not, as has sometimes been stated, underestimate the importance of genetic factors by a half. However, it probably never yields the true degree of genetic determination. Another objection to all variations of Holzinger's formula and even to the variance ratio, V_{DZ}/V_{MZ}, is that they do not use the information derived from variation between pairs.

There are several better methods of analyzing twin data especially if other relatives can be brought into the analysis (Cattell et al. 1955, Bulmer 1970, Christian et al. 1974). I believe the most versatile and complete methodology is that of the biometrical genetics group in Birmingham (Jinks and Fulker 1970). The main advantage of their method seems to be its capability of testing assumptions and fitting a model with the same data. It can also test the significance of any estimates obtained. A few years ago the biometrical genetics group stressed that they could separate dominant and additive components of the genetic variance. This feature may remain important in the formal mathematics, but probably nothing more. They have now calculated the number of twin pairs required for genetic analysis, and one conclusion is that to estimate both dominant and additive genetic components in human data would require impossibly large numbers of twins (Eaves 1972). The same calculations yielded other bad news. A strong genetic influence might sometimes be detected with as few as 100 pairs of twins and siblings, but much larger numbers are needed to detect low heritability or to estimate the magnitude of even a high heritability.

Of great interest for this audience is the great value assigned by the Birmingham studies to MZ twins, both raised together and raised apart. For some purposes, separated siblings can be substituted for separated MZ twins, but I believe that this depends on what I shall call the twin-environment assumption: the assumption that DZ twins share the same environment as much as do MZ twins. To be sure, MZ twins are not absolutely necessary for human quantitative genetics. Their children, equivalent to half-sibs raised in different families, may prove even more useful (Nance 1974).

Of several other broad genetic problems currently being attacked with the help of twins, one seems to hold special promise for the future. Psychologists would like to identify and separate genetic factors that affect behavior, but simple genetic factors rarely correspond with normal phenotypic traits. The first attempt to analyze the genetic variance in two human traits was, I believe, a study of tooth size in twins (Osborne et al. 1958). The method of "cross-twin analysis" gave evidence in MZ twins for genetic factors that exercized common control over adjacent teeth, while DZ twins revealed another set of genetic factors controlling adjacent teeth independently.

This early attempt at multivariate genetic analysis took two characters and sought evidence for two genetic factors. It is much more difficult to analyze data on more than two variables in search of two *or more* discrete genetic factors. (In this usage, a genetic factor may be one locus or a polygenic set of loci with similar effects.) Separating genetic factors from each other and disentangling them from the environment formerly required two stages, and did not work very well (Cattell et al. 1955, Loehlin 1965).

Vandenberg (1965) first proposed a departure from conventional factor analysis that would accomplish the two objectives in one process. He applied matrix methods which I do not understand and, in effect, extracted several genetic factors, each in the form of a discriminant function for distinguishing MZ from DZ twins. At least two other methods are now available for extracting genetic factors from twin data (Partanen et al. 1966, Loehlin and Vandenberg 1968, Eaves 1973). They all require large samples and complicated mathematics.

Before closing I want to face quarely the greatest weakness in most twin studies, particularly the psychological studies. This is their dependence on the twin-environment assumption. MZ twins raised in dissimilar homes are ideal subjects for genetic study, but they are hard to find. Most studies use MZ twins raised together, and control on the shared environment by comparing them with DZ twins raised together. But this is a valid control only if MZ and DZ environments are really comparable.

The twin-environment assumption can be challenged and, to some extent defended, at three levels. First, some elements of the environment may be universal, and so strongly self-selected that they would be nearly constant for one genotype in any family of a given society. For example, nearly all children are exposed to music, but some pay more attention than others. If this variation were mainly genetic, we could say that the musical environment is more similar for MZ than for DZ twins, and yet for statistical purposes we could treat the difference as genetic variation. Actually, variation in musical ability is much more complicated (Stafford 1970).

Second, some environmental factors are self-selected but dependent on the options available. This is generally true for foods, friends and amusements. MZ twins raised together would have very similar exposure to these influences, but MZ twins raised apart would not. DZ twins raised together, having some different preferences on a genetic basis, would to that degree have dissimilar exposure to these influences. Most practitioners of twin research recognize this kind of environmental difference between MZ and DZ twins. Some of them argue that it will not invalidate their conclusions. One piece of evidence is encouraging. R. C. Nichols (1965) analyzed achievement test scores in a large number of twins. He determined which twin pairs had a history of marked differences of experience. He found such a history in more DZ pairs than MZ pairs, but in such a relation to the mean intrapair variances that the estimate of heritability was the same, whether dissimilar pairs were included or excluded.

At the third level the twin-environment assumption is most vulnerable. Some elements of the environment of twins are not at all self-selected, and result from the social condition of twins. Some experiences are shared by twins because they are so often together, or because they imitate each other, or because their family and friends react to them usually as a pair instead of as individuals. It seems that these similarities must be greater for MZ twins, and this cannot be treated as an expression of their genotypes.

Research is being conducted on these questions, and a few conclusions are emerging. First, the label that parents attach to their twins, MZ or DZ, does not seem to matter; in most respects parents treat twins similarly if the twins are similar (Scarr 1968). With respect to clothing, however, parents treat DZ twins alike about as often as they do MZ twins (Cohen et al. 1975). Finally, MZ twins imitate each other a little more often than do DZ twins (Wilde 1970).

After much more research, the twin-environment assumption will probably be sustained within certain limits. It will then perhaps be possible to persuade the skeptics that, within these limits, inferences from twin studies are valid.

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