Twin studies in medical research

Sir,—Dr Phillips questions (April 17, p 1008) the value of twin studies in estimating the genetic component in the most common diseases of adult life. He points out that the intrauterine environment of twins, monozygous as well as dizygous, may be different and that this distinction may account for later differences in disease prevalence between co-twins. Thus, a greater concordance between monozygotic than dizygotic twins does not, Phillips says, necessarily indicate a genetic basis for a disease. We have long been studying diabetes, one of the adult diseases that Phillips mentions, and we offer our comments with respect to this disease.

Other workers have shown an association between low birthweight and the subsequent development of impaired glucose tolerance (IGT); of those with birthweights under 3400 g, 42 of 171 (24%) had IGT; of those over this weight at birth the figure was 24 of 199 (12%). But there was no difference in the frequency of diabetes in the two groups—14 (8%) versus 13 (7%). Thus no association of low birthweight and subsequent development of insulin-dependent diabetes was shown. It is true that there was a correlation between weight at one year and the later development of non-insulin dependent diabetes, although numbers were small, the total number of diabetics being only 27. Taken at face value, this finding suggests that failure to thrive between birth and one year, not low birthweight, is the significant factor leading to non-insulin dependent diabetes.

Phillips points out that twins can differ in birthweight. The mean difference between monozygotic and dizygotic twins in the four reports he cites is 107—229 g. To judge from the figures of Hales et al, this variation could account for only a very small difference in the prevalence of IGT. Likewise, the mean difference in birthweight of monozygotic and dizygotic twins that Phillips cites (167 g) could account for only a negligible difference in the prevalence of IGT, and none at all in that of non-insulin dependent diabetes. Yet the concordance rate for non-insulin dependent diabetes in monozygotic twins is 80–100%, and for dizygotic twins 0–17%. This difference in rates is all the more striking if the twins were of different weights at birth, and if birthweight determined the later development of non-insulin dependent diabetes. (Unfortunately, we do not know the birthweights of our twins with non-insulin dependent diabetes.)

Concordance rates between monozygotic twins may be due to shared environment as well as shared genes. Differences in concordance rates between monozygotic and dizygotic twins suggest a genetic component but do not exclude environmental factors. We do not regard the evidence of the effect of intrauterine environment on the aetiology of non-insulin dependent diabetes as convincing.

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MEAN BIRTHWEIGHT BY MATERNAL AGE IN TWIN BIRTHS, UNITED STATES, 1989*

<table>
<thead>
<tr>
<th>Maternal age (yr)</th>
<th>No of births</th>
<th>Mean birthweight (g)</th>
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<td>&lt;20</td>
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<td>20 to 24</td>
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<td>30 to 34</td>
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<td>&gt;39</td>
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*Previously unpublished tabulation from the National Center for Health Statistics. Centers for Disease Control and Prevention, USA.

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Sir,—In the classic twin study design, concordance for a trait is measured in monozygotic (MZ) and dizygotic (DZ) twin pairs reared together, and the overall contributions of shared genes and shared or unshared environment are estimated. The assumption is that MZ and DZ twins are acted upon by shared environments to the same extent, and it is usually this “equality of environments” assumption that is criticised as being unrealistic. Phillips argues that the increased intrauterine and perinatal morbidity of monochorionic twin pregnancies would lead to a breakdown of this assumption. He says that the results are “not specific to a particular disease such as diabetes mellitus and ischaemic heart disease. He selects these diseases because of evidence linking low birthweight with these conditions.

The fallacy in his argument is the assumption that alterations in mean birthweight reflect discordancies of birthweight within twin pairs. Monochorionic twins are actually less similar in birthweight than dichorionic MZ twins, 1 therefore, if birthweight is a risk factor for later disease, monochorionicity will actually decrease the MZ concordance in birthweight, and thereby decreasing estimates of disease heritability.

If some effect of chorionicity other than birthweight and prematurity is responsible for differences between MZ and DZ twins, 7 then several predictions can be made. 1—If the processes involved in monochorionic pregnancy are important in the genesis of disease, an increase in the prevalence of a trait should be observed in MZ twins. This is the case for a number of developmental malformations, but has not been noted for other diseases. 2—Since the second-born twin is more likely to have perinatal hypoxia and trauma, prevalence of conditions in which these mechanisms are important will be affected by birth order. 3—If monochorionic placentas lead to greater sharing of maternal or placental effects, this will cause a bias in the variance of a trait between MZ and DZ twin groups, which, for continuous traits, can be tested by a simple variance ratio. A further prediction is that classic twin studies will reach conclusions inconsistent with those of other genetically informative types of study. In a number of the diseases Phillips mentions, molecular genetic evidence now exists to confirm the conclusions reached by the twin method.

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3. Newman B, Selby JV, King M-C, Slemenda C, Fabsitz R, Friedman GD. Birthweight and the subsequent development of impaired glucose tolerance (IGT); of those with birthweights under 3400 g, 42 of 171 (24%) had IGT; of those over this weight at birth the figure was 24 of 199 (12%). But there was no difference in the frequency of diabetes in the two groups—14 (8%) versus 13 (7%). Thus no association of low birthweight and subsequent development of insulin-dependent diabetes was shown. It is true that there was a correlation between weight at one year and the later development of non-insulin dependent diabetes, although numbers were small, the total number of diabetics being only 27. Taken at face value, this finding suggests that failure to thrive between birth and one year, not low birthweight, is the significant factor leading to non-insulin dependent diabetes.

4. Phillips points out that twins can differ in birthweight. The mean difference between monozygotic and dizygotic twins in the four reports he cites is 107—229 g. To judge from the figures of Hales et al, this variation could account for only a very small difference in the prevalence of IGT. Likewise, the mean difference in birthweight of monozygotic and dizygotic twins that Phillips cites (167 g) could account for only a negligible difference in the prevalence of IGT, and none at all in that of non-insulin dependent diabetes. Yet the concordance rate for non-insulin dependent diabetes in monozygotic twins is 80–100%, and for dizygotic twins 0–17%. This difference in rates is all the more striking if the twins were of different weights at birth, and if birthweight determined the later development of non-insulin dependent diabetes. (Unfortunately, we do not know the birthweights of our twins with non-insulin dependent diabetes.)

The 352 g range in mean birthweight according to maternal age is more than twice the average of the mean differences between monochorionic and dichorionic birthweights in the studies Phillips cites. Because dizygotic twinning also increases with maternal age, reaching a peak twinning rate in the age range 35 to 39 years, part of the difference in birthweight between monochorionic and dichorionic twins can be attributed to maternal age. Furthermore, a difference in mean birthweight between monochorionic and dizygotic twins does not represent an irremediable flaw of classic twin studies: confounding variables such as birthweight and its associated prenatal environment can be controlled by stratification in the analysis.

5. Sin—We have a different perspective on twin studies than that presented by Dr Phillips. He does not make the important distinction between classic twin studies (which compare disease concordance in monochorionic and dizygotic twins) and other twin study designs. The problems of classic twin studies may not apply to other designs that are less likely to be affected by prenatal factors. Examples of such designs include comparing characteristics within twin pairs raised together with variations within those raised apart, randomisation of monochorionic twins in matched-pair experiments, and the use of population-based twin registries to determine effects of shared or unshared environment on the aetiology of non-insulin dependent diabetes as convincing.
A bookkeeping of the frequency of diseases in twins and their experience with effects ascribed to selective serotonin receptor agonists (5-HT1B-like agonists) has been made as a natural experimental model. A paradigm is no longer “nature or nurture?” but “how do genes and environment operate?” Twin studies continue to have far wider application than the broad conclusions made in the classic twin design about genetic determination. 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