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[1] 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 (25%) later developed 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 non-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 monochorionic and dichorionic twins in the four reports he cites is 107–229 g. To judge from the figures of Hales et al,[1] 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%.[2,3] This difference in rates is all the more striking if the twins were of different weights at birth, and if birthweight determined the chance of the subsequent development of diabetes. (Unfortunately, we do not know the birthweights of our twins with non-insulin dependent diabetes.)

Concordance 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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SIR,—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 monozygotic 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 monozygotic twins in matched-pair experiments, and the use of population-based twin registries to determine effects of monozygous or dizygous twinship on development of subsequent disease.[1]

Phillips' critique of classic twin studies found that birthweights in monochorionic (monozygotic) twins are 107 g to 229 g less than in dichorionic (predominantly dizygotic) twins. Part of this difference can be explained by maternal age. Mean birthweight increases in twins with maternal age (table). 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 dizygous twinning also increases with maternal age, reaching a peak twinning rate in the age range 35 to 39 years,[2] part of the difference in birthweight between monochorionic and dichorionic twins can be attributed to maternal age. Furthermore, a difference in mean birthweight between monozygotic 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.

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

Maternal age (yr)	No of births	Mean birthweight (g)
<20	7025	2154
20 to 24	20 829	2340
25 to 29	29 460	2434
30 to 34	22 825	2479
35 to 39	8549	2506
⩾40	1078	2488

*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 for diseases such as hypertension, 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 correlation, 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,[2] 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 is one cause of differences 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.

CASEWISE CONCORDANCE FOR DISEASES REPORTED BY AUSTRALIAN TWINS

Reported condition	Condordance per 100 (95% Pearson-Clopper confidence limits)		
	Monozygotic twins		Dizygotic twins same sex 446 pairs
	One placenta 767 pairs	Two placentas 112 pairs	
Asthma or wheezing	15·5 (6·5–29·5)	14·3 (0·4–57·9)	0·0 (0·0–13·0)
Hayfever	27·9 (21·6–34·8)	43·5 (23·2–65·5)	17·4 (10·8–25·9)
Hypertension	32·1 (24·4–40·6)	8·3 (0·2–38·5)	13·9 (7·8–22·2)
Myocardial infarction	14·3 (0·4–57·9)	..	0·0 (0·0–36·9)
Diabetes	20·0 (0·5–71·6)	..	0·0 (0·0–36·9)
Thyroid disease	13·3 (5·0–26·8)	12·5 (0·3–52·7)	0·04 (0·1–20·3)
Birthweight (Pearson r)	+0·75 (0·72–0·78)	+0·79 (0·71–0·85)	+0·67 (0·61–0·72)

As a test of Phillips' hypothesis, I re-examined data from questionnaire surveys of 3808 adult twin pairs.[3] These data included zygosity, reported birthweight, and occurrence of several common diseases. Single placenta MZ twins (of whom 75% will be monochorionic) did not differ significantly from DZ twins in prevalence of any of these diseases or in concordance between single and double placenta MZ twins (table). I conclude that effects such as those Phillips is concerned about are not large enough to alter the broad conclusions made in the classic twin design about genetic determination.

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SIR,—Dr Phillips says that twin studies may have misled us into believing a genetic origin of many diseases. His basic premise that the adverse prenatal environment of monozygotic twins relative to that of dizygotic twins will result in increased monozygotic concordance and hence to overestimates of genetic aetiology is fallacious, even by his own evidence.

Phillips notes that monozygotic twins have greater within-pair variability of birthweight than dizygotic twins—ie, they are more discordant. The relation of birthweight to later development in twins is complex and only where the intra-pair difference is extreme have differences in longer term outcome been detected.[1] In discussing the higher rates of congenital malformations he does not mention that the most recent data[2,3] show no difference in rates in monochorionic and dichorionic monozygotic twins, nor that discordance is the norm for congenital malformations in surviving twins, be they monozygotic or dizygotic.[1] Perinatal mortality also frequently results in the survival of a single infant;[1] such single survivors, who might be regarded as most at risk under Phillips' hypothesis, are rarely included in classic twin studies, and concordant pairs are never so. Overwhelmingly, differences in the prenatal environment of twins lead to discordance, and make monozygotic twins less alike. On present evidence, the classic twin study will not lead to erroneous overestimation of genetic influence on adult diseases in which prenatal factors are important in aetiology, but, if anything, to underestimation.

It is, as Phillips notes, difficult to determine whether prenatal factors affecting twins influence the development of adult disease. However, if this is the case, it follows that twins per se should have higher rates of the diseases in question than the general population. If monozygotic twins are more adversely affected than dizygotic twins, a disproportionate number of monozygotic pairs should be affected. Methodologically sound studies that address this issue in adult disorders are rare, but, for example, for psychiatric disorders[4] over-representation of twins is not generally the case. Schizophrenia, in single surviving twins may be the exception,[4] and some studies suggest that prenatal factors may be related to discordance for schizophrenia in monozygotic twins.[5]

Twin study methods have far wider application than the estimation of heritability.[6] The comparison of results obtained by various genetic epidemiological methods[7] enables information to be gathered about both the genetic and environmental influences on disease; proof of genetic aetiology is not what is being sought. There are other issues relating to classic twin studies of adult disease, such as ascertainment and investigator biases, and methods of analysis, which may have far greater impact on the validity of results and receive considerably less attention. Twins remain an important natural experimental model and the destructive divisions of the nature-nurture controversy are meaningless in modern medical research. The paradigm is no longer "nature or nurture?" but "how do genes and environment operate?". Twin studies continue to have much to offer in finding the answers.

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Sumatriptan and ischaemic heart disease

SIR,—Dr Ottervanger and colleagues report (April 3, p 861) the incidence of a transmural myocardial infarction after administration of 6 mg sumatriptan subcutaneously in a patient with cluster headache. They point out that the effect of sumatriptan on the human coronary vasculature has been reported to be mild, but offer no explanation of how this 5-hydroxytryptamine-like selective agonist could induce an acute coronary event severe enough to cause a myocardial infarction.

Data from our laboratory have also indicated that contractile effects mediated by 5-HT_1-like receptors are only weak in non-atherosclerotic human coronary arteries.[1] However, further studies demonstrated that the effect of serotonin, acting specifically at 5-HT_1-like receptors in healthy human coronary arteries, could be substantially enhanced in the presence of the thromboxane mimetic U46619.[2] We have been able to confirm that a similar interaction occurs between U46619 and sumatriptan in human isolated non-atherosclerotic coronary arteries (figure).

Dr Maclean and colleagues (April 24, p 1092) propose an explanation for the anomaly between the weak constrictor properties of sumatriptan in apparently normal coronary arteries and the occurrence of myocardial infarction. They suggest that basal release of nitric oxide in the healthy coronary artery is sufficient to inhibit the vessels' response to sumatriptan, but in smokers, in whom there is a loss of endothelial function, the effect of sumatriptan is unmasked.

We believe that stimulation of 5-HT_1-like receptors by serotonin, under certain conditions, may cause flow-limiting stenosis resulting in myocardial ischaemia and infarction. This could arise if the effect of selective 5-HT_1-like receptor agonists, such as sumatriptan, is enhanced by the presence of thromboxane-A_2 as well as conditions