Does Inheritance Matter in Disease? The Use of Twin Studies in Medical Research

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The controversy about the relative importance of nature and nurture that goes on in fields such as psychology also goes on in medicine. The crucial question is: Do we go mad or develop heart disease because we inherit a special susceptibility to a disease from our parents, or are these diseases the result of a stressful environment throughout our lives? With most diseases, we cannot decide because patients almost always differ in both their nature, or genetic endowment, and their nurture, or environment, during the formative years of childhood, and of course, both can be important in particular diseases. Yet it is important to know whether in coronary heart disease, for example, it is worth persuading patients to alter their environment by stopping smoking. If they both smoke heavily and have heart disease because they have inherited an anxious, worrying temperament, then altering their smoking habits alone might have

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disappointingly little effect. For these reasons, medical research in this area has concentrated on the unique and unusual opportunities presented by the occurrence of disease in twins.

The idea for this approach came from the English biometrician Francis Galton in 1875. He pointed out that there are two kinds of twins, identical and nonidentical. Identical twins come from the same fertilized egg and therefore have the same set of genes, which determine their physical and mental characteristics. Nonidentical twins, like ordinary siblings born at different times, come from separate eggs and their gene patterns are no more (and no less) alike than those of ordinary brothers and sisters (see Figure 1). Both types of twins, however, usually share the same family environment during their childhood and are usually treated alike by their parents. If, then, one of the pair develops a disease that is transmitted through the genes, it is more likely to appear in a twin who is identical than in a twin who is genetically different. On the other hand, in diseases due to diet or some other aspect of family life that is not genetically determined in the strict sense, identical and nonidentical twin siblings of affected children are equally likely to develop the disease. Thus we can get some indication of the relative importance of heredity and environment in causing a specific disease by comparing the relative risk of a twin being affected when he or she is an identical twin to that risk when the twins are nonidentical. The difference in risk will be high in diseases where inheritance is important and low where it is not.

MEASURES OF DISEASE "CONCORDANCE"

Risks of the coincidence of disease appearing in both twins are measured in two ways. Both methods aim to assess the degree of *concordance,* or agreement, between the disease experience of identical and nonidentical twins. Table 1 shows a model population of six sets of identical twins. One measure of risk of both being affected is the "pair-wise concordance rate." In this

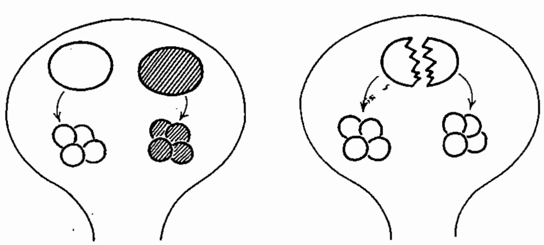

Figure 1 *Genes determining light hair are indicated by ○s and dark hair by ●s. Nonidentical twins come from separate eggs that carry different genetic elements that determine, for example, hair color in the two children. The color may or may not be different in the case of nonidentical twins. Identical twins result from the division of the same egg and so retain the same genetic element. Both children thus have the same hair color.*

Table 1 Concordance example

Pair Number	*First Twin*	*Second Twin*
1	⊙	⊙
2	⊙	⊙
3	⊙	⊙
4	⊙	⊙
5	⊙	○
6	⊙	○

(○ = unaffected; ⊙ = affected.)

example, in four out of the six pairs, both twins are affected, so the pair-wise concordance rate is $4/6 \times 100\%$ or $66\frac{2}{3}\%$. When neither twin has the disease the pair does not enter the table. The second measure depends on the relative frequency or risk of the twin of an affected person also suffering from the disease. This "proband concordance rate," or "affected concordance rate," in the example is given by the ratio of the number of twins affected as pairs (8) to the total number affected (10), that is, $8/10$ or 80%. The affected concordance rate is perhaps the more widely used rate in twin studies. (Knowing one of these measures, we can readily obtain the other, so no important choice is being made here; it is more a question of custom.)

SOME RESULTS FROM THE DANISH TWIN REGISTRY

Table 2 compares the affected concordance rates for identical and nonidentical pairs of Danish twins of whom at least one is affected by one of the diseases listed. The high rates in identical twins versus the lower ones for nonidentical twins for tuberculosis (54 versus 27), rheumatoid arthritis (50 versus 5), bronchial asthma (63 versus 38), and epilepsy (54 versus 24) suggest a strong genetic element in these diseases. On the other hand, death from acute infections other than tuberculosis and rheumatic fever (14 versus 11) shows no such disparity between the identical and nonidentical pairs of twins. Chance exposure to

Table 2 Occurrence of selected somatic diseases in the Danish Twin Register based on a survey of 4,368 same-sexed pairs

	Affected Concordance Rates (%)			
Disease	*Identical Rate*	*No.**	*Nonidentical Rate*	*No.**
Cerebral apoplexy	36	120	19	164
Coronary occlusion	33	122	27	179
Tuberculosis	54	185	27	309
Rheumatic fever	33	178	10	238
Rheumatoid arthritis	50	63	5	73
Death from acute infection	14	137	11	235
Bronchial asthma	63	94	38	125
Epilepsy	54	37	24	49

*Numbers refer to number of affected individuals, not pairs.

infection, perhaps outside the home, seems therefore, to be much more important than any inherited susceptibility.

THE UNUSUALNESS OF TWINS

These examples have shown the potential of this method of distinguishing between genetic and environmental factors in different diseases. A word of caution is needed, however, about the risks of generalizing from twins to the population as a whole, for twins are unusual in more senses than one. They are unusual in that multiple births occur relatively infrequently. In 1964 only 1 delivery in 96 was of twins. (Triplets and quadruplets occurred once in 9,977 and once in 663,470 deliveries—compared with the ratios of 1 in 9,216 and 1 in 884,730 expected on the basis of the Helin-Zeleny hypothesis; that is, if twins occur once in 96 deliveries, triplets and quadruplets will occur once in 96 × 96 deliveries and 96 × 96 × 96 deliveries, respectively. This hypothesis does not concern us here.)

Most important from the medical point of view is the fact that twins are more likely to be born to black than to white Americans and especially to older mothers who have already had several children. In a condition like mongolism, which is particularly common in children born to older women who have had large families, twins are thus likely to be more often affected than are singletons. Because twins have to depend on nutrients designed for a single child in the womb, they start at a disadvantage and are more likely to be born prematurely and to have difficult births. It is hardly surprising that their death rate in infancy and early childhood is higher than average. As they grow older, their disadvantage lessens, and in respect to the diseases of adult life, their experience is probably close to that of singletons. Thus assessments based on observing disease in middle-aged twins are likely to be reasonably applicable to people in general.

PRACTICAL ASPECTS OF TWIN STUDIES

Sampling Populations of Twins. Early studies of disease in twins were often based on a patient with an unusual disease who came to the hospital and was found to have a twin suffering from the same condtion. As in clinical medicine in general, the apparently unusual tends to be noted and published. Series of such coincidences in twins have thus been given prominence in the medical literature. But, because of the haphazard method of collection, such series are unlikely to give a true picture of the incidence of disease in the population of twins as a whole. Volunteer series, recruited perhaps by appeals in the media, are also likely to be biased. The ideal is to collect information either on all twins born in a generation or at least on a randomly selected, and thus truly representative, sample of them. Particularly in Scandinavia where vital records have long been accurate and complete, national twin registers have been established on this basis to serve medical and social research.

Some results from the Danish Twin Register have already been given. This Register comprised all twins born in Denmark during a defined period (1870–1910). Of the 37,914 twin births that occurred during that time, over half of the pairs had been broken by the death of one or both twins before their sixth birthday; these were not followed up. About 40% of the pairs were of different sex and not so useful for investigating diseases occurring in one sex more than another. Of the remainder, some 60% were nonidentical twins of the same sex and 40% were identical and so like-sexed pairs. (In other words, the elimination of mixed-sex pairs from the surviving sets of twins changed the identical-nonidentical ratio of twin births from the usual 20:80 to 40:60.)

Establishing Type of Twins. Having identified and traced the twins through the population registers and other means, a problem arises in establishing their type by methods that can be widely and simply applied. In studies of small numbers, refined techniques can be used to compare inherited characteristics such as blood groups or blood-protein patterns to see whether in all such respects the twins are truly identical. Fingerprints, voice sounds, and other physical traits can also be used. For large-scale surveys, in which subjects cannot be examined but only interrogated by postal questionnaires, simpler methods are needed. It is fortunate, therefore, that the reply to one question is surprisingly effective in distinguishing identical from nonidentical pairs of twins. That question may take the form of "Were you as like as two peas in a pod?" and it is encouraging to note that when this question was asked, over 95% of pairs in which both answered yes proved, on blood and other examination, to be identical, and when both answered no, over 95% were fraternal; finally, 2% disagreed.

Once the pairs of twins have been classified, their disease experience must be ascertained. This can be done by collecting hospital records or death certificates over a period of years or by asking questions directly about either past illnesses or the presence of symptoms of chronic diseases such as coronary heart disease or rheumatism.

Other Applications of Twin Studies. Twin studies also may help to detect the effects of environmental factors in disease. Cigarette smoking, for example, is believed to cause other lung diseases as well as lung cancer. As in the case of lung cancer, it could be argued that an individual inherits both a liability to take up smoking and a specific susceptibility to lung diseases such as chronic bronchitis. If this were true, the apparent association between cigarette smoking and the presence of bronchitis could be dismissed as an effect arising at least in part from other causes rather than as proof that smoking caused bronchitis.

Surveys of smoking habits in identical and nonidentical twins have shown that there is indeed some evidence of a genetic element that affects the smoking habit. Regarding smoking as a disease, we can, as before, compare the affected-concordance rate in identical twins with that in nonidentical twins. This shows that, if one twin smokes, his or her twin is more likely also to be a smoker if they are identical twins than if they are fraternal (and thus no more closely related than an ordinary brother or sister).

Table 3 Prevalence of cough among smokers and nonsmokers in smoking discordant twin pairs

	Cough Prevalence (%)		*Total Number of Cases*
	Smokers	*Nonsmokers*	
Identical twins			
Men	14.6	7.7	274
Women	13.6	7.6	264
Nonidentical twins			
Men	12.3	5.5	733
Women	14.5	5.7	653

Because of this genetic element in smoking, the independent effect of smoking on bronchitis has to be assessed by comparing the frequency of bronchitis in identical twins who share the same genetic endowment but smoke different amounts. A survey based on the Swedish National Twin Study has done just this and the results for both types of twins are given in Table 3. These are set out simply in the form of prevalence rates that give the percentage of people in each group who have chronic coughs. Clearly, within each group of identical twins, smokers have higher prevalence rates for chronic cough than nonsmokers. In other words, even when the genetic background is identical, smoking appears to be associated with more bronchitis and thus is likely to be its cause.

Related Ideas. The use of twins is not confined to studies of medicine or biology; they have been used in studies of reading, for example. The idea of using identical twins as a control in the smoking investigation is a special case of the important statistical idea of using homogeneous "blocks" to test different effects. First, keeping close to the twin idea, in agricultural experiments, littermates are sometimes assigned to different treatments such as feeding regimes to improve the precision of the resulting average weight gains under the different diets. Of course, many litters may need to be used, but fewer individuals will be needed because of the "matching" provided by the litters.

Future International Collaboration. The results from the Scandinavian Twin Registries show how useful such data can be. Unfortunately, for less common diseases even large national registries may not uncover enough cases of a specific disease (as in different forms of heart disorder) to make detailed statistical analysis possible. The World Health Organization has therefore set up a "registry of registries" to collect data in a uniform fashion in many countries and assemble and analyze them centrally. In this way we hope to reap the full benefit of the unique research opportunities that studies of twins in sickness and health can provide.

PROBLEMS

1. Why are volunteer series in twin studies likely to be biased? (*Hint:* Refer to the essay by Meier.)
2. By comparing the risk of an identical twin being affected to that of a nonidentical twin, an experimenter would eliminate any ________________ factors, and thus any observed differences between the two kinds of twins could be attributed to ________________ factors.
3. In the data of Table 3, only those pairs of twins are considered for which:
   a. Either both are smokers or nonsmokers.
   b. One twin is a smoker and the other a nonsmoker.
   c. Either both or one or none are smokers.

   Which answer is correct?
4. Refer to Table 3. Can you convert the data of cough prevalence from percentage into incidence (number of cases)? Carry out this conversion for the identical twins if you can; explain what other information you need if you can't.
5. Explain how one should use twins in studies to detect:
   a. The effect of genetic factors in disease.
   b. The effect of environmental factors in disease.

REFERENCES

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