DEATH-DISCORDANT TWINS

A New Method to Evaluate Genetic Factors in Chronic Diseases

ULF DE FAIRE, TORBJORN LUNDMAN
The Serafimerlasarettet Medical Clinic, Stockholm, Sweden

One of the most important lines of research on unselected large scale twin registries are mortality follow-ups. Death-specific concordance rates have been calculated using different measures of concordance. These estimates are of great importance but they only reflect an "all or-none" classification of the genetic effect. It is suggested that mortality studies could be extended to, and include studies on, death-discordant twins. Such studies combine the advantages from mortality follow-ups on total twin populations with the detailed clinical investigation on subsamples. By examining the surviving cotwins with respect to various traits and supposed risk factors, an opportunity has been provided to study the genetic determination on the development of disease. This approach has been used in a study of ischaemic heart disease (IHD) and its risk factors in a representative subsample from the Swedish Twin Registry.

Ever since the days of Galton, twins have been studied with regard to the genetic influence on chronic diseases. Several models have been suggested for testing specific hypotheses among twins. The most common technique is probably the classical twin method, described by several authors (Dahlberg 1926, von Verschuer 1958, Gedda 1961, Harvald and Hauge 1965). Here the rate of concordance for some specific trait is compared between MZ and DZ twin pairs. A significantly higher degree of concordance in the MZ pairs speaks in favour of genetic factors being responsible for the difference. Various measures of concordance rate have been applied, depending on the mode and level of ascertainment. With the use of the proband concordance rate (Allen et al. 1967) the individual is considered the unit of ascertainment and concordant pairs therefore are counted twice. Other measures of concordance are the pairwise and the total concordance rate (Allen et al. 1967, Smith 1972). However, concordance rates are unlikely to determine the mode of inheritance of a particular trait, but if multifactorial inheritance is assumed, the relation of concordance rate to the underlying correlation in liability between twins is useful because the correlation does not depend on the frequency of the trait (Smith 1972).

One of the most important lines of research on unselected twin registries, like the registries in Denmark, the U.S., and Sweden, are mortality follow-ups. By the use of the twin proband method (Allen et al. 1967), concordance rates for death in myocardial infarction have been calculated on the Danish twins (Harvald and Hauge 1970). This method makes it possible to estimate the morbidity risk or life time expectancy of disease for MZ and DZ cotwins of affected persons. After adjustment for age, this risk can be compared with risk figures for other groups of relatives or for the general population (Allen et al. 1967).

Concordance rates for total mortality have been worked out on the U.S. and Swedish twin registries (Hrubec et al. 1974). The measure of genetic effect (heritability, h^2) chosen for this analysis was based upon a model presented by Falconer in 1965 and later refined by Edwards (1969) and Smith (1970 and 1972). The model can be applied not only to family studies but also to studies on twins. It assumes, however, that there is a normal distribution of total liability to a condition (death, for example)

CODEN: AGMGAK 25 114 (1976) — ISSN: 0001-5660
Acta Genet. Med. Gemellol. (Roma) 25: 114-116

that consists of a combination of genetic predisposition and environmental influences. This means that the method is not valid if there is a major single gene contributing to the causation of the disease. According to Slack (1974) it is important to consider the practical measures that can be taken from genetic information with respect to prevention of ischaemic heart disease (IHD). For this purpose one should find out the proportion of genetic liability to IHD that can be attributed to single gene effects compared with the contribution of the polygenically determined liability.

Data in form of specific death concordance rates are important, but they only reflect an " all-or-none " classification of the genetic effect. There are, of course, individuals affected by the disease who die from other causes.

Significant differences in concordance rates may also be discernible only with rather large samples. It therefore seems justifiable to seek for and include individuals with other degrees of severity of the disease. The most appropriate approach ought to be regular clinical surveys of unselected twin populations, but performing such surveys of total number of twins probably would meet too great practical and economical difficulties. To meet the need for information on symptoms and attitudes of large twin populations, mailed questionnaires have been used, whereas more complex clinical and laboratory methods have to be applied on representative subsamples as already done on the Swedish Twin Registry (Lundman 1966, Liljefors 1970).

As stated before, a study of mortality is of great importance. Valuable extensions of mortality studies could be studies on death-discordant pairs, i.e., pairs in which one of the partners has died. Such a study combines the advantages from a mortality follow-up on a total population with the detailed clinical examination of a subsample. This approach has been used in a study of IHD and its risk factors in 205 male and female death-discordant pairs from the Swedish Twin Registry (de Faire 1974). The basic prerequisites for this study was a continuous information on deceased twins through a regular matching of the Swedish Twin Registry against a total death registry for Sweden. Since 1971 this was done once a month. The matching gave access to the death certificates which in turn indicated whether or not the deceased twin had been treated in a hospital. The cause of death was established from all collected information as hospital records, autopsy protocols, etc. The surviving cotwins could then be examined on average 5 months after the death of the partner.

To be able to evaluate the genetic contribution to the development of the disease under study, it seems important to examine the surviving cotwins reasonably soon after the occurrence of death discordance. An increasing biological homogeneity with growing age may otherwise distort our conclusions to be drawn from the results.

The surviving cotwins may be examined with respect to various traits or manifestations of the disease in question. If an important genetic influence exists, silent and manifest forms would appear significantly more often in MZ cotwins whose partners have died from the disease under study as compared to DZ cotwins. The comparison should also be extended to surviving cotwins whose partners have died from other causes, thus permitting a stepwise comparison between surviving cotwins with different genetic predisposition. In the Swedish study on IHD in death-discordant twins, various clinical traits and ECG findings were successively included in the criteria suggesting IHD, thus giving a cumulative increase of prevalences in the different zygosity groups.

According to Falconer (1965) we may suppose an underlying gradation of affectedness, normally distributed, and thus find all individuals above a certain value or threshold to exhibit the disease. The definition of the threshold provides a fixed point by which to compare different zygosity groups with different prevalences. With the same assumption of normality in mind we may calculate the heritability not only for manifest disease but also for preclinical conditions. It has been proposed by Epstein (1964) that if one could identify and measure all of the predisposing traits as underlying biologic disturbances in terms of metabolic or other defects, then it would probably emerge that they are more common than the prevalence of the disease would suggest and show more clear-cut distributions among family members.

With a mortality follow-up of the examined cotwins, the predictive value of measured risk factors

may then be established and by the use of the twin proband method (Allen et al. 1967) it is also possible to estimate the mortality risk or lifetime expectancy for the disease in the different zygosity groups.

REFERENCES

Allen G., Harvald B., Shields J. 1967. Measure of twin concordance. Acta Genet. (Basel), 17: 475.

Dahlberg G. 1926. Twin Births and Twins from a Hereditary Point of View. Stockholm.

de Faire U. 1974. Ischemic heart disease in death discordant twins. A study on 205 male and female pairs with special reference to hereditary factors. Proc. 1st Int. Congr. Twin Studies, Rome. Acta Genet. Med. Gemellol. (Roma), 25: 271-275.

Edwards J.H. 1969. Familial predisposition in man. Br. Med. Bull., 25: 58.

Epstein F.H. 1964. Hereditary aspects of coronary hearth disease. Am. Heart J., 67: 445.

Falconer D.S. 1965. The inheritance of liability to certain diseases, estimated from incidence among relatives. Ann. Hum. Genet. 29: 51.

Gedda L. 1961. Twins in History and Science. Springfield: Charles C. Thomas.

Harvald B., Hauge M. 1965. Hereditary Factors Elucidated by Twin Studies. Genetics and the Epidemiology of Chronic Disease. Washington: U.S. Department of Health, Education and Welfare.

Hrubec Z., Lorich U., de Faire U., Lundman T. 1974. Twin concordances in Sweden for mortality and their variation with zygosity. Presented at the 1st Int. Congr. Twin Studies, Rome.

Liljefors I. 1970. Coronary heart disease in male twins. Hereditary and environmental factors in concordant and discordant pairs. Acta Med. Scand. [Suppl.], 511.

Lundman T. 1966. Smoking in relation to coronary heart disease and lung function in twins. A co-twin control study. Acta Med. Scand. [Suppl.], 455.

Slack J. 1974. Genetic differences in liability to atherosclerotic heart disease. J.R. Coll. Physicians London, 8: 115.

Smith C. 1970. Heritability of liability and concordance in monozygous twins. Ann. Hum. Genet., 34: 85.

Smith C. 1972. Correlation in liability among relatives and concordance in twins. Hum. Hered., 22: 97.

Verschuer O. von 1958. Die Zwillingsforschung in Dienste der Inneren Medizin. Verh. Dtsch. Ges. Inn. Med., 64: 262.

Ulf de Faire, M.D., Serafimerlasarettet, Fack 12700, 11283 Stockholm, Sweden.