Twinning and anencephalus occurrence in relation to fetus-fetus interaction

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Elwood, J. M. (1976). *British Journal of Preventive and Social Medicine*, **30**, 29-31. **Twinning and anencephalus occurrence in relation to fetus-fetus interaction.** The hypothesis proposed by Knox (1970) that an anencephalic fetus arises from a fetus-fetus interaction between two dizygous twins predicts that the twinning rate, the population incidence of anencephalus, and the female proportion of anencephalics in a population should be positively interrelated. These associations were tested using Canadian data during a long period of time and over a large geographical area. The results did not support the hypothesis.

Anencephalus is a common and severe abnormality of which the aetiology remains unknown despite much clinical, experimental, and epidemiological research. Hypotheses relating to infectious disease, drugs, simple genetic mechanisms, and several dietary factors have been suggested but not substantiated. Knox (1970) proposed a quite different hypothesis: that anencephalics arise from a fetus-fetus interaction between a pair of dizygous twins. This hypothesis predicts several epidemiological associations, which are tested in this paper.

THE HYPOTHESIS

The fetus-fetus interaction hypothesis claims that to produce a single anencephalic fetus several conditions must be met simultaneously:

1. a pair of dizygous twins is formed,
2. each twin differs in its genetic constitution with respect to a diallelic gene system on the X chromosome, giving the potential for a fetus-fetus interaction,
3. an environmental 'trigger' factor operates which allows the interaction to occur.

In a population, the anencephalus incidence rate will, therefore, depend on the dizygous twinning rate, the frequencies of the relevant genes, and the

frequency of the environmental trigger. The hypothesis further states that the proportion of the anencephalics which is female will be positively related to the trigger frequency. Thus if the gene frequency can be regarded as constant, differences in anencephalus incidence between population groups defined by, for example, place of residence, time, social class, or maternal age should be associated with differences in dizygous twinning rates, or in the sex distribution of the anencephalics, or both. Study of such differences in British data has shown results consistent with the hypothesis (Knox, 1974). In this paper the predictions will be tested using Canadian data covering a large geographical area and during a long period of time. Two further assumptions must be made. First, the changes in the total twinning rate are taken to reflect changes in dizygotic rates; although data are not available in Canada, in other countries secular changes have been restricted to dizygotic rates (James, 1972; Jeanneret and MacMahon, 1962), and international differences in monozygotic rates are very small compared with the large differences in dizygotic rates (Bulmer, 1970). Secondly, it is assumed that differences in the prevalence of anencephalus at birth reflect differences in the incidence of anencephalus in early pregnancy rather than differences in fetal losses. The comparisons of anencephalus rates and twinning rates will use crude rather than age or parity standardized rates, because

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the increase of both twinning and anencephalus rates with maternal age and parity is not considered as a confounding factor, to be controlled, but as a direct consequence of the hypothesis (Knox, 1974).

METHODS

Information on anencephalus mortality and on twinning rates was obtained from Statistics Canada; the sources have been described previously (Elwood, 1973, 1974). Anencephalus rates are expressed as stillbirths plus infant deaths from anencephalus per 1000 total births, and twinning rates as twin pairs per 1000 total confinements; 'total' including livebirths and stillbirths from 28 weeks' gestation. Anencephalus mortality rates are very close estimates of the prevalence of anencephalus at birth (Elwood, 1974).

RESULTS

GEOGRAPHICAL VARIATIONS

Very large interprovincial differences in the mortality rates from anencephalus in Canada have been observed (Elwood, 1974). The geographical pattern was different during the two periods 1943-54 and 1955-69, and these periods are shown separately in Fig. 1, where the nine provinces are arranged from west to east. Also shown are the twinning rates and the female proportion of anencephalics. During the period 1943-54, the highest anencephalus mortality rates were in Ontario

and Prince Edward Island, which did not show high twinning rates or high female proportions as predicted by the hypothesis. The prairie provinces (Alberta, Saskatchewan, Manitoba) had higher twinning rates than the rest of Canada and also slightly higher female proportions than eastern Canada, but had low anencephalus rates. During the period 1955-69, the eastern provinces showed high anencephalus mortality, but did not show high twinning rates or high female proportions.

SECULAR VARIATIONS

The inconsistency of these observations with the hypothesis could be due to variations in the frequency of the relevant genes, as the ethnic composition of the Canadian population varies between different provinces. However, there has been little ethnic variation in time within regions of Canada. In Canada as a whole, the annual anencephalus mortality rates and twinning rates have decreased in recent years and there has been a small fall in the female proportion of anencephalus (Elwood, 1973, 1974) which is consistent with the hypothesis. However, the trends in anencephalus mortality differ in different regions so it is interesting to see if the other factors change in consistent ways. Fig. 2 shows the anencephalus mortality rates from 1943 to 1970 in the five main regions of Canada. It can be seen that the secular changes in anencephalus mortality in Quebec, Ontario, and the prairies have been much more marked than those in the maritimes or in British Columbia, shown below

FIG. 1. Twinning rates (twin pairs per 1000 confinements, T), female proportion of anencephalics (F), and anencephalus mortality rates per 1000 total births (A), during two periods of time for nine provinces of Canada, shown in west (left) to east (right) order.

BC = British Columbia; A = Alberta; S = Saskatchewan; M = Manitoba; O = Ontario; Q = Quebec; NB = New Brunswick; NS = Nova Scotia; PEI = Prince Edward Island

FIG. 2. Anencephalus mortality rate per 1000 total births, twinning rate (pairs per 1000 confinements), and female proportion of anencephalics, for five regions of Canada during four-year periods from 1943 to 1970.

Q = Quebec; O = Ontario; P = prairies (Alberta, Saskatchewan, Manitoba); BC = British Columbia; M = maritimes (New Brunswick, Nova Scotia, Prince Edward Island)

but on the same scale. However, the secular trends in twinning rates have been very similar in all regions since 1952, and the regional differences before this do not match the anencephalus rates—for example, the twinning rate in Ontario rose from 1943 to 1952 while the anencephalus rate fell. The hypothesis would predict that in the provinces where the twinning rate fell without a large change in the anencephalus rate, the trigger frequency, reflected by the female proportion, would rise; there is little evidence that this occurred.

The most likely explanation of the trends shown in these data is that some factor or factors are causing twinning rates to decline in all regions of Canada, and that other factors are responsible for declining anencephalus rates in Quebec, Ontario, and the prairies. The lack of consistent trends in the female proportion does not support the hypothesis.

The interaction between the three factors was also examined by a regression model of anencephalus rate on twinning rate and female proportion, using logarithmic transformations. The model represented is that the probability of an anencephalic birth depends on the product of the probabilities of a twin conception and of the action of an environmental trigger. The results were equivalent to those derived from inspection of the data; the coefficients of the twinning and/or female proportion factors were significant and positive, as predicted by the hypothesis, in relation to the 28 years' annual data for Quebec, Ontario, and the prairies only; in the annual data for the other regions, and in the geographical variation within periods of time, the two coefficients were non-significant or negative and the multiple regression coefficient was small.

DISCUSSION

The results reported here do not support the hypothesis that fetus-fetus interaction is the major aetiological mechanism for anencephalus. Associations between population rates cannot of course test aetiological factors of which the effect may be a small contribution to the total incidence of the disease; however, in the present context this method can be

defended on the grounds that the hypothesis is based largely on these types of epidemiological data. Available Canadian data did not allow testing of other predictions of the hypothesis, except that of the associations with maternal age. A comparison of twinning rates, anencephalus rates, and the female proportion of anencephalics by maternal age showed no positive associations; the twinning rate rises steadily with age while the anencephalus rate shows a u-shaped pattern with minimum rates at 20–29 years; there is no trend in the female proportion. In view of the difference between the present findings and those of Knox (1974) in British data, it is important to test other predictions of the hypothesis such as those concerning social class, the sex distribution of previous siblings, and the birth interval before the affected pregnancy, in another independent source of data.

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