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Survival of Nieces and Nephews of Schizophrenic Patients

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Summary. Evidence was found against the hypothesis that heterozygous carriers of a schizophrenic gene have a reproductive advantage through enhanced fertility. In consequence an investigation was made of the possibility that an advantage is gained through diminished early mortality among the offspring of carriers. The results were equivocal. While an observed deficit of infant deaths was attributable to under-reporting, the possibility of a true advantage could not be ruled out, because of the statistical unreliability of the findings in a sample of the size available. A plea is made for a collaborative effort to settle the issue.

Introduction

The single gene theory of schizophrenia is difficult to reconcile with the diminished fertility of schizophrenics and the stable incidence of the disease unless one postulates a biological advantage among heterozygotes.

We have previously reported evidence that the fertility of sisters of schizophrenic patients is not higher than that of the general population (Buck *et al*, 1975). However, a biological advantage could be conferred upon the heterozygote through diminished mortality in infancy and childhood. We have examined this possibility by collecting data on the survival of children born to the brothers and sisters of the patients in our study.

We are aware of only one other study of mortality among nieces and nephews of schizophrenics. In Sweden, Kay and Lindelius (1970) found that the observed mortality was considerably less than that expected from general population mortality rates. (Observed deaths were 58 per cent of expected deaths among nephews from birth to age 4, 50 per cent among nephews from ages 5 to 14, 47 per cent among nieces from birth to age 4, and 73 per cent among nieces from ages 5 to 14.) These investigators expressed doubts about the validity of their observations. The expected mortality was derived from the national population in which urban and illegitimate births were likely to have been more frequent than in the study population. Also, they suspected that some deaths might have been unrecorded, although it is not clear why this should have been so, given the fact that the deaths were ascertained from parish records.

Data Collection and Analysis

Information was sought about the offspring of 690 brothers and sisters who were known to have married. Although 969 married sibs had been identified at the beginning of the study, not all could be followed for the present purpose.

Some had never been located. Some had left Canada during their years of family formation and could not provide data suitable for comparison with infant and childhood mortality in the Canadian population. Some who had refused to reply to the first survey had no other co-operating family members who could provide information. The bias introduced by the loss of 279 (29 per cent) of the original cohort of married sibs is difficult to determine in view of the variety of reasons for exclusion and in the absence of information about variables that might be related both to exclusion and to the survival of offspring. Of the 690 for whom information could be sought, data were obtained for 511 (74 per cent) either directly from the sibs concerned or from another sib. Canadian mortality rates for the first year of life and for

TABLE I

Deaths among nieces and nephews

	Under age 1	Age 1–19	Birth to age 19
Observed ..	34	17	51
Expected ..	50	20	70
Obs./Exp. ..	0·68	0·85	0·73

5-year age groups from ages 1–19 years, specific for province, calendar year and sex were used to compute the expected number of deaths among their children. These calculations employed standard life-table techniques.

RESULTS

The observed and expected mortality among all nephews and nieces is shown in Table I.

The deficit of deaths, particularly in infancy, is striking and far greater than the theoretical calculation of heterozygote advantage calls for. One explanation of this surprising result would be that some infant deaths have been forgotten, particularly by older sibs or by one sib when reporting about the children of another.

The analysis was therefore repeated, subdividing the data according to the age of the person reporting and the directness of reporting. The result, shown in Table II, strongly suggests that there has been under-reporting of infant deaths by older parents and by sibs reporting for other sibs.

TABLE II

Deaths among nieces and nephews by source of report

	Under age 1		Age 1–19		Birth to age 19	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
Report by parent < age 50 ..	20	18	5	6	25*	24*
Report by parent aged 50+ ..	8	16	5	7	13	23
Report by other than parent	6	16	7	7	13	23

* Obs./Exp. = 1·03 with 95 per cent confidence limits 0·67–1·54.

The degree of under-reporting that can be estimated from Table II is not out of line with that found in a study in India of the accuracy of reporting an infant death many years after the event (Gupta, 1957).

If we deal only with mortality among the nieces and nephews born to parents who reported for themselves and who were under age 50 at the time of reporting, the observed deaths are almost identical to the number expected. Therefore, no evidence of improved survival has been obtained. Unfortunately, our sample size is small in relation to the frequency of death. The confidence limits of the ratio of observed to expected deaths show that improved survival among the nieces and nephews cannot be ruled out with an acceptable degree of assurance.

DISCUSSION

The inconclusive negative results of this investigation on the one hand, and the doubtful positive results of the Swedish study on the other, suggest the need for further work. Given that increased fertility among the sibs of schizophrenics has been fairly conclusively ruled out, it would be most important to eliminate the possibility of a biological advantage arising from enhanced survival in the pre-reproductive years of life. Clear negative findings in both areas would strongly favour the polygenic theory of schizophrenia, since it requires little in the way of heterozygote advantage to explain the apparently stable incidence of schizophrenia (Gottesman and Shields, 1973).

A large number of observations will be required to offer conclusive evidence against a small survival advantage. We therefore make a plea for a collaborative effort among other interested investigators. Cousins of schizophrenic patients as well as nieces and nephews would be suitable for study.

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