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RISK OF ANENCEPHALY IN MIGRANT AND NON-MIGRANT WOMEN IN THE OXFORD AREA

BY

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Geographical variation in the incidence of neural tube abnormalities, particularly anencephalus, is well documented. Penrose (1957) reviewed the available European data and found that the highest rates for anencephalus were found in Ireland, Wales, and western regions of England and Scotland, and that they decreased progressively towards Eastern Europe. Stevenson, Johnston, Stewart, and Golding (1966), in their comparative study of congenital malformations, confirmed a wide variation in the incidence of neural tube defects in the 24 centres studied.

From national statistics (Fig. 1) it is apparent that the highest stillbirth rates in the British Isles due to neural tube abnormalities in the years 1961-1965 occurred in Northern Ireland, Scotland, and Wales and decreased progressively towards the south and east of England.

An important question arising from these observations is whether the geographical variations in neural abnormalities noted above are related to environmental factors operating during pregnancy, or whether they may be due to other long-term influences, including the genetic structure of the population. A possible method of resolving this problem in polytypic populations, as shown by Carter and Woolf (1961) in a study of phenyl ketonuria, is to examine the parental birthplaces of cases to determine whether migrant groups share the experience of the host population or the population from which they originated. Thus Carter and Woolf, by examining the birthplaces of parents and grandparents of children with phenyl ketonuria born in south-east England, were able to demonstrate that the gene frequency for this disorder is approximately four times greater in the population of Ireland and west Scotland than in south-east England.

In this paper a study is made of the risk of neural tube defects occurring in babies born in the Oxford Record Linkage Study Area in the five years 1962-1966 according to the mother's own birthplace, in order to determine whether mothers born elsewhere in the British Isles share the local experience or that of the areas where they were born.

Material and Methods

The area, population, and methods of the Oxford Record Linkage Study have been described elsewhere in detail by Acheson (1964).

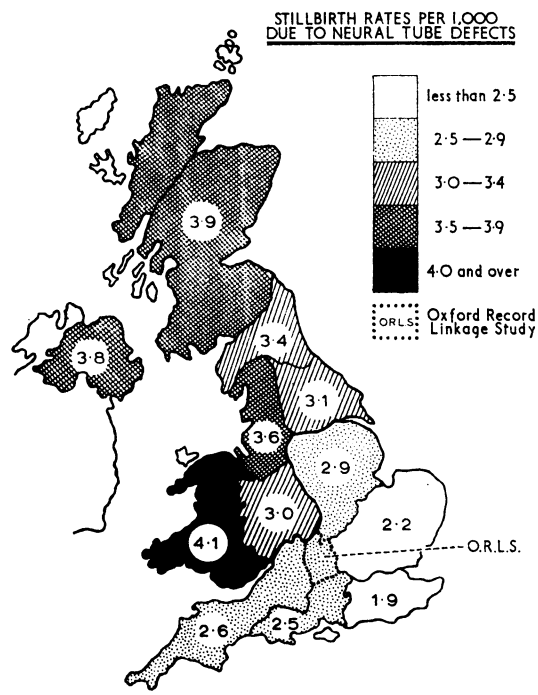

FIG. 1. Geographical variation in stillbirth rates due to neural tube abnormalities in the British Isles.

Sources: Registrar-General's Statistical Reviews for England and Wales 1961-1964;
Registrar-General's Annual Reports for Scotland 1961-1965;
Registrar-General's Annual Reports for Northern Ireland 1963-1965.

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During the five years 1962-1966, 46,651 single births occurred within the study area, for which an abstract from the mother's obstetric record was received in 99·5%. This contained a record of whether any congenital abnormality was noted at birth. In addition, birth, stillbirth, and death certificates relating to all children born in the area were received from the General Register Office, and an abstract was also received for any child admitted to one of the paediatric departments in the area. From these different sources it is believed that ascertainment of all neural tube abnormalities sufficiently obvious to be noted at birth or in infancy was virtually complete. Included in the information on the obstetric abstract was the mother's own place of birth which was available from 88% of obstetric records. In the case of babies with neural tube abnormalities, the mother's birthplace was determined for all but two cases through the generous assistance of the National Health Service central register at Southport. The social class of all mothers was derived from the 'Father's Occupation' recorded on the appropriate birth certificates of the babies included in the study.

Classification of Neural Tube Abnormalities

The babies with neural tube abnormalities have been divided into three groups as follows:

(1) Anencephalus alone or with other abnormality, including meningomyelocoele or spina bifida;

(2) Spina bifida alone or with hydrocephalus;

(3) Hydrocephalus alone.

Two cases of microcephaly and the two further cases of neural tube abnormality where the mother's birthplace was not determined were excluded from further analysis.

Classification of Mothers according to Birthplace

Because of the relatively small number of babies with neural tube abnormalities available for study, mothers born in the British Isles were arbitrarily divided according to whether they were born in areas of high or low risk of neural tube abnormalities. The high risk area consists of those areas shown in Fig. 1 where the stillbirth rate from neural tube abnormalities was 3 per 1,000 births or more, while the low risk areas are those in which the rate was less than 3 per 1,000. Mothers born outside the British Isles (6·9%) and those whose birthplace was unknown (12·0%) have been excluded from the analysis which follows.

Results

Maternal Birthplace

The Table shows the number of babies with each type of neural tube abnormality and those without such abnormalities occurring among mothers born in the high and low risk areas of the British Isles as defined above. The numbers in brackets indicate the expected number for each cell of the table, assuming that no relationship exists between the occurrence of neural tube abnormalities and the mother's place of birth. When the table is tested for heterogeneity, it is found that variation in neural tube abnormalities with mother's birthplace is greater than could be expected by chance ($\chi^2 = 9{\cdot}75$, df = 3, $P < 0{\cdot}05$). From inspection of the table it is clear that this result is mainly due to an excess of anencephaly in babies of mothers born in the high risk areas. When the test of heterogeneity is applied to anencephalus and the normal cases alone, this excess is found to be highly significant ($\chi^2 = 7{\cdot}42$, df = 1, $P < 0{\cdot}01$). In contrast there is no excess of spina bifida in the babies of mothers born in high risk areas. In the case of hydrocephalus there is a slight excess of cases among babies of mothers born in the high risk areas, but the total number of cases is too small for any firm conclusion to be drawn.

Table

DISTRIBUTION OF CENTRAL NERVOUS SYSTEM MALFORMATIONS IN THE OXFORD RECORD LINKAGE STUDY AREA ACCORDING TO MOTHERS' OWN BIRTHPLACE

C.N.S. Malformation	Mothers' Birthplace: High Risk Areas		Low Risk Areas		All Born in British Isles
Anencephalus alone or with spina bifida	19	(10·6)*	30	(38·4)	49
Spina bifida alone or with hydrocephalus	13	(14·3)	53	(51·7)	66
Hydrocephalus alone	5	(3·3)	10	(11·7)	15
No malformation	7,775	(7,783·8)	28,065	(28,056·2)	35,830
All births	7,812		28,158		35,960

*Expected numbers shown in brackets

Social Class

A possible explanation for the higher risk of anencephaly in women from high risk areas might be that they compare unfavourably in their social class distribution with those born in low risk areas (Edwards, 1958; Anderson, Baird and Thomson, 1958). A comparison of the social class distributions of the two groups is made in Figure 2. Interpretation of the figure is made difficult by the high proportion of mothers from the high risk group married to men in the Armed Forces. However, even if the

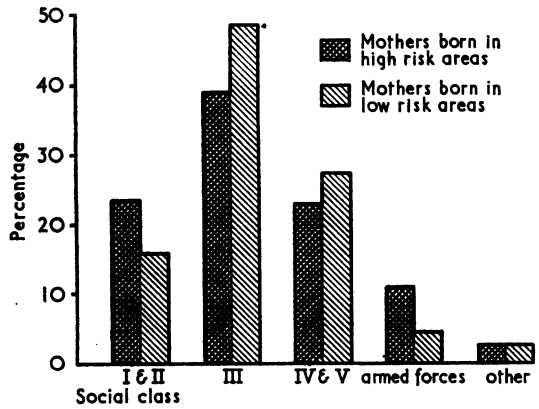

FIG. 2. Comparison of the social class distribution of mothers born in high and low risk areas.

Armed Forces group is considered in the most unfavourable light, *i.e.*, as equivalent to social classes IV and V, it will be seen that the mothers born in high risk areas have, if anything, a more favourable class distribution than those born in low risk areas. It will be seen that the proportion of mothers in social classes IV and V and the Armed Forces group combined is only slightly greater among mothers born in high risk areas (34·2%) than in the remainder (32·7%). On the other hand, the proportion of mothers in social classes I and II in those born in high risk areas (23·6%) is considerably greater than in those born in low risk areas (16·2%) while the proportion of mothers from social class III is greater in those born in low risk areas (48·5%) than in those born in high risk areas (39·4%). It is concluded that differences in the incidence of anencephaly in the two groups of mothers cannot be accounted for by social class differences.

Discussion

Previous studies of anencephaly in mixed populations indicate, as in the present study, that migrant groups tend to share the experience of the population from which they originate rather than the host communities. MacMahon, Pugh and Ingalls (1953), in a study of anencephaly in the population of Rhode Island, observed lower rates in anencephaly in Negroes and in Jews than in other parts of the community of European origin. The low rates observed in Negroes in this study, although based on limited data, are in agreement with low rates observed in African populations by other workers (Penrose, 1957; Stevenson *et al.*, 1966).

Searle (1959), in a study of anencephaly in different ethnic groups in Singapore, found the disorder to be several times more common in Sikhs than in Malays, Chinese or other Indians, when compared with a control group of normal births. The estimated rates for Chinese and the non-Sikh part of the Indian community were similar to figures available for Cantonese in Hong Kong and for Bombay respectively, while the high risk for Sikhs is consistent with the subsequent finding of Phillips, reported by Stevenson *et al.* (1966), that Sikhs in the Punjab have a significantly higher rate of anencephalus than Hindus. Lean, on the other hand, in a more recent study of anencephalus in Singapore, also reported by Stevenson and his colleagues, was unable to confirm a greater risk of anencephaly in Sikhs than in other groups in the community. Stevenson and his colleagues also report information from Fiji where immigrant Indians have rates similar to those found in Bombay, whereas in the indigenous Melanesian population the rates are much less. This study is, however, based on relatively few cases from which firm conclusions cannot be drawn.

Of particular interest is the more recent study of Naggan and MacMahon (1967) who examined rates of anencephaly and spina bifida in Boston by ethnic group. Jews were found to have much lower rates for these disorders than the general population, while in contrast the rates for parents of Irish ancestry were greatly increased. These findings are thus consistent with the low rates reported among Jews in Israel (Halevi, 1967) and the well-known high rates in Ireland (Penrose, 1957; Stevenson *et al.*, 1966; Registrar-General, Northern Ireland, 1963-1965).

In contrast to these studies in which different ethnic groups in polytypic population tend to have rates of anencephalus similar to the communities from which they originate, the rates for anencephaly in the Australian State of Victoria (Stoller and Collmann, 1965) are unexpectedly low when compared with even the most favoured areas of the British Isles from which the population of Victoria mainly originated.

However, most of the evidence available suggests that migrant groups bring with them the risk of their parent communities. This could be determined by genetic factors, acquired physical characteristics resulting from their previous environment or by the retention by migrant groups of social or cultural factors which determine their liability to the disorder. The last of these possibilities is difficult to exclude but in the present study it has at least been shown that the migrants from high risk areas did not compare unfavourably in social class structure with those from low risk areas. Moreover,

it is difficult to postulate the nature of such social factors considering the wide range of ethnic groups and geographic areas to which the above observation applies. It therefore appears most likely that the geographic variations of anencephaly in the British Isles and elsewhere depends not on environmental factors operating in pregnancy but on either genetic factors or alternatively environmental factors operating on the mother in early life. The further distinction between the importance of genetic factors and environmental factors operating in early life could only be made by a study of the risks of anencephaly in second generation migrants from areas of high risk. Unfortunately this has not been possible in our data.

This study has emphasized the relationship between the risk of anencephaly and the mother's birthplace. However, as a high degree of correlation might be expected between the birthplaces of husband and wife in migrant couples, the possibility of a paternal factor can by no means be excluded. The demonstration of such a factor would strengthen the evidence for a genetic cause of anencephaly. On the other hand, failure to demonstrate a paternal factor would not exclude the possibility of a genetic factor acting through the maternal genotype, *i.e.*, through the intra-uterine environment provided by the mother for the foetus. Further studies in which account is also taken of the birthplace of the father would therefore be of interest. As the separate effect of a paternal factor could only be demonstrated in large series, it would be of considerable value if information regarding the birthplace of both parents could be included on the form now routinely returned to the Registrar-General by Medical Officers of Health in cases of babies born with congenital malformations.

The frequent occurrence of anencephalus in association with spina bifida both in the same individual and within sibships suggests a common mechanism in these disorders (Record and McKeown, 1949; Carter, David, and Laurence, 1968). It is therefore of interest that in contrast to anencephalus, no association has been demonstrated here between spina bifida and mother's place of birth. Thus comparing maternal birthplace of anencephalus and spina bifida, $\chi^2 = 4{\cdot}19$, $df = 1$, $P < 0{\cdot}05$. This finding may be an artefact introduced by the method of classifying malformations used here or it may be due to the relatively small numbers of cases available for study. The difference between anencephalus and spina bifida is nevertheless consistent with observations elsewhere that spina bifida alone shows less marked geographical variation than anencephalus (Giroud, 1960; Stevenson *et al.*, 1966). This finding warrants further investigation when more material becomes available.

Summary and Conclusions

From a study of 46,651 single births occurring in the Oxford Record Linkage Study Area in the period 1962-1966, it was found that mothers born in areas of the British Isles where high stillbirth rates due to neural tube abnormalities prevail, had a significantly greater risk of anencephalic stillbirth than mothers born in low risk areas. No relationship between the risk of spina bifida and the mother's place of birth was demonstrated.

It is concluded that the geographical variation in the incidence of anencephalus in the British Isles is due to long-term influences, possibly genetic, rather than to environmental factors operating during pregnancy.

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