ANENCEPHALUS: A CHANGING SEX RATIO

S. C. ROGERS AND MICHAEL MORRIS

General Practice, 4 Clifton Road, Rugby and School of Social Studies, University of East Anglia

The sex ratio of infants born with certain congenital abnormalities diverges widely from unity. There is evidence that these sex ratios vary from place to place and in different races (Gittlesohn and Milham, 1962; Emanuel, 1972). Stocks (1970) has shown that within 25 countries of largely European stock there is a close positive correlation between the divergence of the sex ratio of congenital abnormalities of the central nervous system from unity and the infant mortality of these conditions, and also between the sex ratio of combined infant deaths and stillbirths from these conditions and their perinatal loss rates in the Hospital Regions of England and Wales. Czeizel, Vizkelety, and Szentpéteri (1972) have pointed out a similar relationship between the prevalence of congenital dislocation of the hip and the sex ratio of affected infants.

Few studies have been made of secular changes in the sex ratio of congenital abnormalities. The significant variations in the sex ratio of infant deaths from various congenital abnormalities in

England and Wales reported by Rogers and Morris (1971) present problems in interpretation because of difficulties in classification and lack of data concerning stillbirths and surviving infants. The secular variations in the sex ratio of anencephalus in Belfast reported by Elwood (1970) are based on 221 cases occurring over six years, and with a study on this scale significant results are not to be expected, nor are they claimed. The present study of the sex ratio of anencephalus in the United Kingdom has been undertaken in the hope that it might give some insight into the nature of these relationships.

METHOD

From data from the Registrar General's Annual Statistical Reviews of Scotland, England and Wales, and Northern Ireland biennial infant loss rates for each sex have been calculated and plotted graphically by combining data for stillbirths and infant deaths from anencephalus. The significance of

FIG. 1. Incidence of anencephalus in Scotland in female and male births per 1000 total births: — stillborn anencephalus (including monster not otherwise specified before 1951); x—x stillborn anencephalus excluding monster not otherwise specified; ---- live and stillborn anencephalus (from Reports of Registrar General for Scotland).

FIG. 2. Anencephalus in Northern Ireland. See legend to Fig. 1. for key.

FIG. 3. Anencephalus in England and Wales. See legend to Fig. 1. for key.

TABLE I
SIGNIFICANCE OF SECULAR CHANGES IN INFANT LOSS RATES FROM ANENCEPHALUS: BY SEX

	Total No. of Births	No. of Cases of Anencephalus	Rate per 1000 births	χ^2	DF	P
England and Wales 1961-70						
Males	4,350,900	4,831	1.11	16.78	4	<0.003
Females	4,108,400	11,214	2.73	108.9	4	<0.00001
Scotland 1951-70						
Males	1,013,100	1,588	1.57	19.21	9	<0.025
Females	959,000	4,237	4.42	58.17	9	<0.00001
Northern Ireland 1963-70						
Males	139,700	272	1.95	1.15	3	>0.75 NS
Females	130,900	651	4.97	2.74	3	>0.4 NS

Table I summarizes data from the Registrar General's reports for England and Wales, Scotland, and Northern Ireland and gives the results of testing the null hypothesis that the secular variations might have arisen by chance.

variations in incidence has been tested by homogeneity χ^2 tests, and the significance of variations in the sex ratios has been tested by the method of Woolf (1965) and Plackett (1962). These methods have also been applied to stillbirth data from congenital hydrocephalus in England and Wales.

RESULTS

Figure 1 shows separate male and female stillbirth rates and the combined stillbirth and infant death rates from anencephalus in Scotland from 1951 to 1970. Stillbirth rates for anencephalus including and excluding cases reported under the rubric 'monster type not otherwise specified' from 1939 to 1950 are included for comparison, but these data have not been included in the statistical analysis that follows.

Figures 2 and 3 show comparable rates for Northern Ireland and England and Wales.

Table I gives the results of testing the null hypothesis that the variations in male and female incidence might have arisen by chance by the homogeneity χ^2 test.

The results given in Table I show that there have been highly significant variations in the female incidence in England and Wales and in Scotland, and less significant variations in the male rates. The changes in Northern Ireland are not statistically significant. Referring back to the figures it can be

seen that since 1965 there has been a marked fall in female incidence in all three countries and that the male rate has risen slightly but not significantly in England and Wales and Northern Ireland. Over this period the male rate in Scotland shows on average a slight fall.

The effects of these changes on the sex ratios are illustrated in Fig. 4 and the results of testing the null hypothesis that these variations in sex ratio might have arisen by chance by the method of Woolf and Plackett are given in Table II.

It can be seen from Fig. 4 and Table II that while only in England and Wales does the change in the sex ratio reach statistical significance there has been a trend of the sex ratio in the direction of unity over the last few years in all three countries.

A similar analysis of data concerning stillbirths from congenital hydrocephalus in England and Wales shows a fall in male stillbirth rates from 0.71 per 1,000 male births in 1961-62 to 0.32 in 1969-70 ($\chi^2=156.3$; DF 4; $P<0.00001$). The female stillbirth rates have fallen from 0.60 in 1961-62 to 0.34 in 1969-70 ($\chi^2=80.4$; DF 4; $P<0.00001$). Over this period the male:female sex ratio has fallen from 1.18 in 1961-62 to 0.94 in 1969-70. This change in the direction of unity of the sex ratio, when tested by the method of Woolf and Plackett, approaches the conventional levels of significance ($\chi^2=8.79$; DF 4; $P<0.07$).

TABLE II
SIGNIFICANCE OF CHANGE IN SEX RATIO (MALE/FEMALE) OF INFANTS LOST FROM ANENCEPHALUS

	Average Sex Ratio	Range	χ^2	DF	P
England and Wales, 1961-70	0.41	0.38-0.45	12.98	4	<0.02
Scotland, 1951-70	0.36	0.31-0.44	7.82	9	>0.5 NS
Northern Ireland, 1963-70	0.39	0.35-0.45	1.45	3	>0.06 NS

Table II gives average sex ratio (male/female) of infants lost from anencephalus, range of biennially calculated sex ratios, and results of testing the null hypothesis that these changes in sex ratio might have arisen by chance (Woolf and Plackett's method).

FIG. 4. Change in sex ratio of combined stillbirths and infant deaths from anencephalus: — Scotland; - - - - England and Wales; x—x Northern Ireland.

DISCUSSION

In all three series of anencephalus the sex ratio has increased over the period under study, but only in the case of England and Wales is it possible to establish that statistically significant changes have occurred. This is probably a reflection of the fact that there are many more births per annum in England and Wales than in Scotland and Northern Ireland and the number of cases of anencephalus is correspondingly greater. Hence for similar changes in the sex ratio it will be easier to establish significance in England and Wales.

The failure of the male infant loss rate from anencephalus to fall in the last few years despite the continuing significant falls in the female rates in England and Wales and Scotland requires explanation. Renwick (1972) has suggested that the disparate incidence of anencephalus and spina bifida in the sexes may be due to different rates of development of the male and female embryos, leading to windows of susceptibility to the actions of teratogens which extend over different periods of time. It seems unlikely that in a given population such windows would vary secularly in their duration.

These results are more easily understood on the basis of different teratogenic thresholds for an environmental factor in the two sexes (Falconer, 1965; Edwards, 1966).

We suggest that the environmental factor which has been postulated as the cause of the recurrent epidemics of anencephalus that have occurred in the British Isles (Leck and Rogers, 1967) has in recent years fallen to such a level that it is no longer influencing the incidence of anencephalus in males, having fallen below the male threshold, but it is still influencing the incidence of anencephalus in female infants who have a lower threshold.

It must not be concluded that the remaining male incidence is entirely genetically predetermined. There may well be a second teratogen or a second source of the same teratogen that has not varied with time and is responsible for the present male incidence and a proportion of the female incidence.

This study does, however, illustrate the urgency of the present efforts to identify and reach an understanding of the postulated teratogen (Renwick, 1972; Poswillo, Sopher, and Mitchell, 1972; Knox, 1972).

In view of the close similarity of the epidemiology of spina bifida to that of anencephalus (Rogers, 1969) this study may have some relevance to the problem of spina bifida.

If secular or regional variations in the sex ratio of other congenital abnormalities can be firmly established, such results could be an indication of the part played by environmental factors in their aetiology.

SUMMARY

A study is reported of the stillbirths and infant deaths from anencephalus in the United Kingdom, using data from the Registrar General's Statistical Reviews for Scotland, Northern Ireland, and England and Wales.

A statistically significant change in the sex ratio of anencephalus in England and Wales is shown to have occurred recently and similar (but not statistically significant) trends are reported in Scotland and Northern Ireland.

The implications of this change are discussed in the light of threshold theories, and it is suggested that the environmental factor which is thought to have been responsible for recent epidemics of anencephalus may have fallen below the threshold for the male embryo.

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