The sex ratio in anencephaly

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SUMMARY   A review of the data supports the suggestion of Knox (1974) that the sex ratio and incidence of anencephalics vary together within populations, as they are known to do between populations.

There seems some doubt, though, whether Knox was correct in hypothesising that the sex ratio of anencephalics varies with their incidence in relation to the dizygotic twinning rate.

The pattern of variation seems to suggest that there are two sorts of cause of anencephaly, one of which is environmental and affects predominantly female embryos. The other may be environmental or genetic, and seems to attack the sexes in roughly equal numbers.

If this hypothesis were correct, it would carry implications for the testing of specific teratogens.

It is well known that anencephalic infants include a high proportion of females. Under the circumstances it is convenient, following Knox (1974), to refer to the F/M ratio of the affected. Knox established that in general this ratio is higher in populations in which the incidence of anencephaly is high than in populations in which the incidence is low. The question arises whether this feature also occurs within populations: are the anencephalics born to particularly susceptible subgroups within populations also disproportionately often female? Knox, in elaborating his fetus-fetus interaction hypothesis, suggested that the sex ratio of anencephalics varies with the incidence of anencephaly in relation to the dizygotic (DZ) twinning rate. More recently, I have suggested that the sex ratio of anencephalics simply varies with their incidence (James, 1979). Dizygotic twinning only varies appreciably with some variables (maternal age, race, parity), so both Knox's hypothesis and mine would predict similar associations of anencephaly incidence and sex ratio over those other variables (social class, season, etc.), which do not greatly affect dizygotic twinning.

In this paper, two questions will be considered. Firstly, is there some general association between the incidence and sex ratio of anencephalics within populations? Secondly, if so, is it better described by Knox's hypothesis or mine? I shall first consider the variation of anencephaly rates and sex ratios across those variables which do not greatly affect DZ twinning (that is, those variables in regard to which Knox's hypothesis and mine would predict similar outcomes). Later I shall consider the variation in

relation to the other variables to see whether the data favour either hypothesis.

Social class

Of all the environmental factors, social class is the one which seems to have the most powerful association with anencephaly within populations, so, *prima facie*, it is the one best suited to test the present hypothesis. Table 1 gives the anencephaly rates and the sex ratios of anencephalic stillborn infants by social class for Scotland 1961 to 1976. The trend in sex ratio with social class may be assessed by a rank correlation. For these data, Kendall's τ (corrected for ties) takes a value of 0·0354 and the one-tailed probability associated with this value is 0·0170. So, though the association is weak, it is decidedly significant.

Season

Knox (1974) discussed the data on the anencephalic births for Scotland 1961 to 1969. He was uncertain as to whether the data supported his hypothesis.

Table 1   *Anencephalic stillbirths by social class and sex, Scotland, 1961 to 1976*

| | Social class | | | | |
	1	2	3	4	5
	M F	M F	M F	M F	M F
	29 64	60 148	513 1243	157 506	131 355
F/M	2·2	2·47	2·42	3·22	2·71
All births	82 395	154 841	710 937	234 959	138 981
Anen-cephaly rate per 1000 births	1·13	1·34	2·47	2·82	3·50

However, these data are not suitable to test the point because, as he remarks, seasonality itself is practically absent from them. Elwood (1975) showed that there was a slight, but significant, excess of anencephalics in the winter in Canada. The F/M ratio of these winter cases was 2·22 and the summer F/M ratio was 2·03. Elwood dismissed the difference as 'not significant'. However, the 2×2 χ^2 value for this difference is 2·04, and the one-tailed P value corresponding to this is 0·076. Lastly, Czeizel and Revesz (1970) presented data on the seasonal incidence and sex ratios of anencephalics in Hungary. They were inclined to dismiss the seasonality in incidence, yet, using the test of Hewitt *et al.* (1971), their data show a seasonality which is significant at the 5% level. The anencephalics born in the six months with the highest incidence have a higher F/M ratio than those born in the other six months. Taken together, these sets of data seem suggestive. It would be interesting to see the more numerous data for England and Wales tested on this point.

Region

Stocks (1970) gave the male and female anencephaly rates for each of the 15 hospital regions of England and Wales for the years 1963 to 1966. The correlation of the overall rate (M+F) with the ratio F/M is given by a Spearman's ρ of 0·4. This value falls just short of the one-tailed 5% significance level, so it could be suggestive.

In Eire, the anencephaly rate varies considerably from one region to another. Coffey and Jessop (1957) gave a rate of 5·93 per 1000 for Dublin in 1953 to 1955, whereas Spellman (1969) estimated a rate of 2·05 per 1000 for Cork in 1962 to 1966. The F/M ratios of the affected were 4·2 and 2·3, respectively. The differences between these two ratios is assessed by a χ^2 of 2·71, which is significant at the one-tailed 5% level. Elwood (1976) failed to find a clear association between the incidence and sex ratio of anencephaly across the provinces of Canada; nevertheless, the suspicion remains that there may generally be such a relationship.

Secular variation

If the suggestion being examined here were true, then secular variation in the anencephaly rate should be disproportionately due to variation in the female rate contrasted with the male rate. A number of studies have established that this is so. For instance, Leck (1972) noted that the 1955 to 1959 peak in anencephaly rates in Birmingham was only evident for the female rate; the male rate showed little fluctuation across the years 1950 to 1969. Rogers and

Morris (1973) showed that secular variation in the female anencephaly rate was greater than in the male rate in Scotland in the years 1939 to 1970, in Northern Ireland in the years 1963 to 1970, and significantly so in England and Wales in the years 1961 to 1970. This latter point has been reaffirmed on the data for England and Wales 1964 to 1972 by Rogers and Weatherall (1976), who found no significant secular variation in the male anencephaly rate, but highly significant variation in the female rate during those years.

Elsewhere, Overbeke (1971) reported annual rates and sex ratios for anencephaly in Holland 1951 to 1968. The rank correlation between the F/M ratio and incidence across the years was given by a Spearman's ρ of 0·701, n = 18, P<0·01. Turnbull *et al.* (1977) found that the rise in anencephaly rates in North Carolina, 1947 to 1970, was caused by a 3-fold increase in the female rate while the male rate remained practically unchanged. Janerich (1975) reported data for New York State (excluding New York City) over the years 1945 to 1971: the correlation between the 3-yearly anencephaly rates and F/M ratios is given by a Spearman's ρ of 0·822, n = 9, P < 0·01. It is true that Elwood (1976) failed to detect greater secular variation in the female rate than in the male rate in Canada during the years 1943 to 1969, but this failure seems to stand alone in an area where the evidence is otherwise strong.

Religion

Naggan (1971) reanalysed the data of Naggan and MacMahon (1967): these data suggested that, in Boston, Catholics had the highest anencephaly rate and Jews the lowest, the Protestant rates taking a midway value. Naggan found that the F/M ratio of the affected followed the same pattern, being highest in Catholic, and lowest in Jewish, births.

Maternal age

The regression of anencephaly rates on maternal age has often, but not invariably, been found to be U-shaped, higher rates being characteristic of both young and old gravidae contrasted with those in the middle childbearing years. Tables 2 and 3 reproduce the anencephaly rates and the F/M ratios of the affected for England and Wales 1961 to 1970 and Scotland 1960 to 1969 as given by Knox (1974). Addition of a further five years' data to those for England and Wales, and a further seven years' data to those for Scotland, makes no appreciable difference to the curves of regression of F/M ratio on maternal age. Knox (1974) hypothesised that the F/M ratio should vary with the anencephaly rate compared with the dizygotic twinning rate. In Great

Table 2 *Anencephalic stillbirths by maternal age and sex, Scotland 1960 to 1969 (reproduced from Knox, 1974)*

| | Maternal age | | | | | |
	−19	−24	−29	−34	−39	40+
Males	58	216	202	137	79	19
Females	188	634	532	348	202	71
F/M	3·24	2·94	2·63	2·54	2·56	3·74
Incidence per 1000 births	3·02	2·63	2·38	2·69	3·09	3·38

Table 3 *Anencephaly by maternal age and sex, England and Wales 1961 to 1970 (reproduced from Knox, 1974)*

| | Maternal age | | | | | |
	−19	−24	−29	−34	−39	40+
Males	436	1366	1094	643	375	119
Females	1187	3487	2710	1546	899	270
F/M	2·72	2·55	2·48	2·40	2·40	2·27
Incidence per 1000 births	2·07	1·72	1·49	1·55	1·87	1·86

Britain, the dizygotic twinning rate increases sharply with maternal age until the age of 35 to 39, and thereafter declines sharply. So, if I understand it, Knox's hypothesis would predict an F/M ratio that declines with maternal age until the age of 35 to 39, and thereafter rises (a reverse J-shaped curve). Neither of the regressions here exactly fits that description, though admittedly one would accept that the Scottish data make a very tolerable fit. It is not easy to test whether the data from England and Wales contradict either of the hypotheses that:

(1) the regression of the F/M ratio on age is U-shaped (like the regression of the incidence on age), or

(2) reverse J-shaped (to which Knox would presumably be committed).

This is so because the exact specifications of the curves are not deducible from the hypotheses.

Parity

Anencephaly rates usually show a U-shaped regression on parity. Record and McKeown (1949) note such a feature in the anencephalic births in Birmingham 1940 to 1947. MacMahon and McKeown (1952) give the sex ratios (F/M) of the anencephalics in Birmingham 1940 to 1951 as 2·80, 1·73, and 1·93 for birth orders 1, 2, and 3+. Table 4 gives the incidence rates and F/M ratios by parity for anencephalic births in Scotland 1961 to 1976. It will be seen that in both sets of data the anencephalic F/M ratio and incidence rates have similar curves.

These data seem to point to a lacuna in Knox's hypothesis. Dizygotic twinning rates increase monotonically and sharply with parity (Bulmer, 1970), so

Table 4 *Anencephalic stillbirths by parity and sex, Scotland 1961 to 1976*

| | Parity | | | | | |
	0	1	2	3	4	5+
Males	312	242	136	105	52	42
Females	894	583	350	202	130	157
F/M	2·87	2·41	2·57	1·92	2·50	3·74
Incidence	2·52	2·05	2·20	2·80	3·37	3·48

Knox's formulation seems to commit him to predict an anencephalic F/M ratio which declines monotonically with parity.

Race

The dizygotic twinning rates, anencephaly rates, and anencephaly F/M ratios in the three principal races may be summarised as in Table 5. It will be noted from the two bottom rows of the Table that the F/M ratio of anencephalics seems roughly to parallel the incidence rates across the races. However, the Table throws some doubt on Knox's suggestion that the dizygotic twinning rate is also involved. If the suggestion were correct, then the Mongoloid and Negroid anencephalic F/M ratios should differ, because their dizygotic twinning rates do differ.

Discussion

In the foregoing section, I have reviewed data on the simultaneous variation of the F/M ratio and incidence of anencephalics within populations. The question at issue is whether these two parameters vary together within populations, as they are known to do between populations. The evidence suggests that they do. It is strong in respect to secular variation and social class variation; good in respect to variation in maternal age, parity, and race; and suggestive in respect to seasonal and regional

Table 5 *Dizygotic twinning rates, anencephaly rates, and anencephaly sex ratios by race*

| | Race | | | Reference |
	Caucasian	Negroid	Mongoloid	
DZ twinning rate	Medium	High	Low	Bulmer (1970)
Anencephaly rate	High	Low	Low	Leck (1972)
Anencephaly sex ratio (F/M)	High	Low	Low	Gittelsohn and Milham (1965) Stevenson et al. (1966) Emanuel et al. (1972)

variation. It seems reasonable, then, to think that this is a general principle (to which there may be exceptions).

The most obvious explanation of such a phenomenon is that some environmental factor causes predominantly female anencephalics, and that another factor affects the sexes almost equally. This latter factor might be genetic or environmental, but, to judge from Fig. 6 of Leck (1972), it seems to be rather evenly distributed across populations. The same Fig. suggests that the environmental factor only operates substantially within Caucasian populations. This presumably is the explanation of the general failure to find environmental variation of anencephaly rates (for example, by season and class) in those populations in which the incidence is low. It is not, I suggest, that low incidence populations can only provide small samples in which, for reasons of statistical power, such variation is not detectable, but that the variation does not exist to a comparable extent in those populations anyway.

Knox (1974) suggested that the sex ratio of anencephalics is dependent jointly on the incidence of anencephaly and the dizygotic twinning rate. In contrast, I have suggested (James, 1979) that the sex ratio of anencephalics is dependent on the incidence of anencephaly, regardless of the dizygotic twinning rate. The data reviewed above in relation to race and parity seem to favour my formulation rather than Knox's. However, the point could scarcely be regarded as a serious indictment of his hypothesis: doubtless that may be adjusted to accommodate such epidemiological detail. Indeed, I suppose that hypothesis will be tested, not by amassing epidemiological data (which sometimes seem interpretable by a skilled advocate to support any hypothesis), but by work in a pathology laboratory.

It has been argued here that there are two sorts of cause of anencephaly, but only one of them can be reasonably assumed to be environmental. This consideration has some implications for the testing for specific teratogens. It seems likely that the environmental cause(s) of anencephaly may be more readily discovered than the other(s). To make such a discovery, it would presumably be necessary to hold clinical trials aimed at lowering the incidence of anencephaly in women who are known to be at risk (those who have already produced a case). In order to improve the chance that such women are at high risk for the cause being tested, they should be selected in high risk areas only. This same aim might be better secured by choosing only women who had already borne female anencephalics.

So far this note has dealt exclusively with anencephaly. It is clear that anencephaly and spina bifida share causes. But do they share environmental causes? Spina bifida does not seem to show such pronounced variation with environmental variables as anencephaly. Nevertheless, it has been shown to vary with social class, with season (occasionally), and with time in ways which parallel the variation of anencephaly. Therefore, any environmental agent which can be shown to cause anencephaly may reasonably be expected to cause spina bifida too, though it may turn out not to be as important a cause of spina bifida as it is of anencephaly.

At present, a woman may avoid a second neural tube defect by the process of amniocentesis and selective abortion, but the fact that defective fetuses can be identified is no reason for relaxing efforts to diminish their incidence. An abortion can never be regarded more favourably than as the lesser of two evils. It seems unlikely that the unfortunate wisdom-after-the-event that followed the potato trials (Lemire et al., 1978) will indefinitely deter clinicians from further work in this field. So one may expect, and welcome the possibility, that clinical trials will sooner or later be initiated to test tea (Fedrick, 1974) and tinned meat (Knox, 1972). This being so, there seem two points worth making about the power of trials in this context.

(1) If it were true that only a proportion of anencephalics are caused by environmental agents, then we must recognise the limited power of trials to implicate them, even if they are correctly suspected. It would seem optimistic to expect any identifiable environmental teratogen to cause more than $\frac{2}{3}$ of cases. Let us assume that women are chosen in whom the probability of bearing a case of ASB is 0·05, and that half of them are assigned to an untreated control group, and that the other half are treated, so that their probability of yielding a case is 0·017. The size of each sample, experimental and control, required to stand an 80% chance of detecting this difference at a one-tailed significance level of 5% is 357 (Snedecor and Cochran, 1967).

(2) It might be more realistic to suppose that anencephaly is caused not by one environmental agent but several. Let us assume, for example, that tea caused 1 anencephalic in 5, and that tinned meat caused another 1 in 5. It would require experimental and control samples each numbering 5326 to stand an 80% chance of detecting, at the one-tailed 5% level of significance, the expected diminution in rate from 5% to 4% after proscribing one of those items. However, it would only require samples of 1187 to detect the expected diminution in rate from 5% to 3% after

proscribing both. So for practical purposes, it might be more politic to devise, if mothers were willing, a trial in which both items were proscribed.

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