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Differences between the events preceding spina bifida and anencephaly

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SUMMARY It is usually held that there is a time continuum in the formation of monozygotic (MZ) twins which is indexed by their placentation, running from dichorionic to monochorionic diamniotic to monochorionic monoamniotic and conjoined pairs. There is good evidence that this continuum is characterised by a continuum of predisposition to anencephaly, slightly raised in dichorionic pairs but very high in some sorts of conjoined pairs.

Although MZ twins, especially monoamniotic and conjoined pairs, are peculiarly liable to anencephaly, they are not particularly susceptible to spina bifida. Among twin pairs concordant for anencephaly or spina bifida, there are strikingly few concordant in the sense of one twin having anencephaly and the other spina bifida, in contrast with the numbers of pairs concordant for the same malformation. The prevalence of anencephaly in double monsters varies with the type of monster, being high in diprosopus. These findings may be explained by the timing of embryonic events.

There can be no reasonable doubt that the causes of anencephaly and spina bifida have considerable overlap, but there is evidence that either the causes of the two conditions are not identical, or that, if they are, they are applied at different times in gestation. For instance it is well known that the two malformations tend to recur within the same sibships, but there is, nevertheless, a tendency for sibships to be 'true' to one condition or the other. An index case with one of the conditions is more likely to be followed by a sib affected by the same, rather than the other, condition.[1 2] Moreover, the epidemiologies of the two conditions differ in that

(1) although the sex ratio of anencephaly varies with its prevalence, the same does not seem to apply to spina bifida,[3] and

(2) although the prevalence rates of the two conditions are rather similar in many populations, there is a curious disparity in regard to race. Anencephaly is commoner than spina bifida in Japanese[4] and Chinese,[5] whereas spina bifida is commoner than anencephaly in Negroes.[6 7]

Thus it seemed worth trying to unearth further evidence of such differences. The present paper will offer two lines of evidence.

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The continuum of anencephaly ratios across the various sorts of twin zygote

Table 1 gives estimates of anencephaly ratios in members of twin pairs by their placentation. Notes will be given here on each of the values in that table.

(a) These values are taken simply as representative. The evidence that the incidence of anencephaly is higher in MZ twins than DZ twins is of three sorts:

(1) the high proportion of same-sexed as compared with opposite-sexed twin pairs affected with anencephaly. This is demonstrated in table 2 and has been previously discussed[10];

(2) the high anencephaly rates in same-sexed twin pairs as compared with rates in opposite-sexed twin pairs and singletons in the same populations[8 10];

(3) the evidence that monoamniotic twin pairs are peculiarly liable to anencephaly.[10 11]

TABLE 1 *Estimates of anencephaly ratio in various forms of zygote*

DZ twins and singletons	*All MZ twins*	*All monoamniotic twins*	*Conjoined twins*
0·0015 (a)	0·0025 (a)	Say 0·015 (b)	High (c)

TABLE 2 *Twin pairs in which at least one of the pair has anencephaly*

Source	*Same sexed*	*Opposite sexed*
Lorber and Rogers[8]	348	123
Janerich and Piper[9]	22	9
Totals observed	370	132
Totals expected	334·7	167·3

Oriental data are omitted from this table because of the low DZ twinning rates in Orientals. For that reason opposite-sexed twins are comparatively uncommon in Oriental populations, so that even granted the truth of the null hypothesis (that MZ and DZ pairs are equally liable to anencephaly), one would expect the ratio of affected same-sexed pairs to opposite-sexed pairs in Orientals to be in excess of 2:1 (the ratio invoked in regard to Caucasian populations[10]). The 'expected' totals in the table are based on an expected ratio of 2:1, which closely approximates the ratio of same-sexed to opposite-sexed twin births in Caucasian populations during the relevant years.

(b) de Bellefeuille,[11] reviewing anencephaly in multiple maternities, noted that (ignoring double monsters and triplet sets) among 20 affected pairs of which the zygosity had been diagnosed as probably or certainly MZ, 9 (45%) were monoamniotic, and other cases have been described.[12–14] In general the percentage of MZ twins which are monoamniotic is of the order of 4.[15] Therefore, the ratio of observed to expected affected monoamniotic pairs here is roughly 11 to 1. Possibly the cachet of reporting such a rarity as an anencephalic twin pair which is also monoamniotic has introduced bias here, but it is difficult to believe that the eleven-fold differential is entirely the result of bias. Indeed it is perfectly possible that bias lies in the opposite direction, that is, of underestimating the differential. This is so because of the high proportion of pairs in which placentation is unreported, and which must contain missed monoamniotic pairs. The reason for wondering whether these cases contain an unrepresentatively high proportion of monoamniotic pairs is that when incidental mention is made in the pathology report of the 'bag of water', one may not code the placentation as monoamniotic, because one has no assurance that this is the only bag of waters, whereas if incidental mention is made of the bags of waters, one can record the placentation as diamniotic. Rather arbitrarily, members of monoamniotic pairs have been taken here to have a susceptibility to anencephaly that is six times that of members of other MZ pairs, though perhaps values of two to 20 might be plausible.

(c) It has been estimated that conjoined twin pairs occur about once in 100 000 births,[15] although higher estimates have been offered.[16] If anencephaly were independent of this condition, then (taking Bulmer's[15] estimate) it should occur in such twins once or twice in 50 million births, that is to say, depending on the number of heads such monsters usually have, once or twice in this century in England and Wales. Yet the combination has been reported quite often in man.[17–41] It would be hazardous to estimate the incidence of anencephaly in conjoined twins. But some idea may be gained from a consideration of diprosopus. This is a form of monster in which a partially or completely duplicated head surmounts a single torso. Such monsters are quite exceptionally rare. If we accept the above estimate that double monsters occur once in 100 000 births, and Hirst's[42] report of only one diprosopus among 145 double monsters, then the incidence of diprosopus is of the order of one in every 15 million births (so rare, one might suppose, that the probability of a case being reported would not greatly be affected by whether it was anencephalic). Changaris and McGavran[36] note that though there are published records of only about a dozen cases of diprosopus, at least two of these monsters had anencephaly, and though there have been other unaffected diprosopus cases of which Changaris and McGavran were not aware,[42 43] there have been still others which were affected by neural tube defects.[17 20 26 32 38 40] Thus, there can be no reasonable doubt that the probability of anencephaly is very high indeed in cases of diprosopus. It is not clear, though, whether the risk of anencephaly is raised in other forms of double monster. The association of anencephaly with diprosopus is referred to in the appendix.

One may wonder whether this apparent continuum of liability to anencephaly across the various forms of twin placentation applies also to spina bifida. It seems not. The numbers of same-sexed and of opposite-sexed pairs of twins with anencephaly and with spina bifida in the data cited by Lorber and Rogers[8] are given in table 3. The χ^2 value for this partition is 3·15, $p<0·075$. This value may be thought suggestive. The ratio of same-sexed to opposite-sexed pairs with spina bifida in these data

TABLE 3 *Data cited by Lorber and Rogers.[8] Twin pairs in which one or both members suffer from anencephaly or spina bifida (omitting cases with spina bifida in one, and anencephaly in the other twin)*

	Spina bifida	*Anencephaly*
Same-sexed pairs	207	343
Opposite-sexed pairs	100	123

is almost exactly 2 : 1, in contrast with the corresponding ratio of 2¾ : 1 for anencephaly. Moreover, 2 : 1 is the ratio one would expect from these data if MZ and DZ twins had equal liability,[10] so it seems that MZ twins are peculiarly liable to anencephaly but not, or not so markedly, to spina bifida.

This conclusion seems to be reinforced by a consideration of the relative frequency of reports of monoamniotic twins containing anencephalics and spina bifidas. I made a systematic survey of published reports on monoamniotic twins[44] in which reference was made to a far larger number of such pairs than had hitherto ever been assembled. Reports of anencephaly in monoamniotic twins seem relatively common. I cited data on ten such cases and three further cases have since some to notice.[12–14] In contrast there have been rather few cases of spina bifida reported in monoamniotic twins. One concordant case has been the subject of two reports.[45 46] A further concordant pair has been reported[47] and a discordant pair.[48] I know of no other reports of spina bifida in monoamniotic twins.

In this context, it is interesting to note too that though anencephaly seems relatively common in conjoined twins and double monsters, spina bifida does not. After a search for anencephaly and spina bifida in such pairs, 25 cases were located,[17–41] but in none of these 25 cases does spina bifida seem unequivocally to have occurred in the absence of anencephaly.

It seems fair then to conclude that the continuum in liability to anencephaly across the varying placentations of twins does not apply to spina bifida.

The concordance in twin pairs for type of malformation (anencephaly or spina bifida)

Let us consider twin pairs, both members of which are affected by anencephaly or spina bifida. Let us take the null hypothesis that concordance for type of malformation is determined simply by the known slightly higher recurrence rates within sibships for the same (rather than the other) malformation.[1 2] This null hypothesis may be tested on data cited by Lorber and Rogers[8] and Cohen *et al.*[2] In the data cited by these latter authors, among pairs of ASB-affected sibs, the ratio of numbers of pairs concordant to discordant for type of malformation (that is, anencephaly or spina bifida) was 1·6 to 1. On this null hypothesis, therefore, the number of twin pairs concordant and discordant in this sense would be expected to be in the ratio of 1·6 to 1. In fact, of the 42 doubly affected ASB twin pairs cited by Lorber and Rogers,[8] only six were discordant for type of malformation and the other 36 were concordant for type of malformation ($\chi^2=10$, $p<0{\cdot}002$) and this null hypothesis is clearly false.

Discussion

There have been adduced here two lines of evidence suggesting that either the causes of anencephaly and spina bifida are not identical, or that, if they are identical, they are applied at different times in gestation. The appendix describes a hypothesis with which both sorts of evidence are compatible. The hypothesis suggests that the same teratogenic agent acting at slightly different times in gestation may produce either of the malformations: acting earlier it may produce anencephalics, and rather later, spina bifidas.

It remains to be seen whether any of the curious features of the sex ratio in anencephaly and spina bifida can be explained by invoking the present hypothesis in conjunction with the fact that the sex of a zygote seems also to be associated with time-related processes.[49–51] This speculation is given impetus by the fact that sex ratio declines across the continuum of placentation of MZ twins, being highest in dichorionic and lowest in conjoined pairs.[52] Indeed, it is tempting to wonder whether the curious sex ratios of many malformations[53] are associated with anomalous retardation (excess females?) or acceleration (excess males?) of embryonic development. The difficulty with this line of reasoning is that the regression of sex ratio on time of fertilisation seems not to be monotonic, but U-shaped.

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APPENDIX *Hypothesis on the timing of events preceding the initiation of malformations*

To fix ideas, one might suppose that during pregnancy the intrauterine environment has some absolute timing mechanism that operates independently of fertilisation and with which fertilisation and subsequent embryonic development require synchronisation. It is suggested that if an ovum is out of synchrony at one stage of the process, it is likely to be out of synchrony at a later stage. A train which is delayed at one stage of its journey is likely to be delayed at another stage too, and this is especially so if the two stages are separated by only a small distance (time). It seems reasonable to assume that a zygote that is delayed at one stage may sometimes 'catch up' and so escape the developmental

anomalies typical of delayed later stages of development (but it is tempting to suggest that the well-established tendency for malformations to cluster is the result of failure to 'catch up').

When MZ splitting occurs, we may suppose that this is a result of the overdue occurrence (or failure to occur) of some developmental event E which normally occurs earlier than the initiation of any sort of MZ twinning (and without giving rise to twinning). It is commonly accepted that among MZ twins, dichorionic pairs are formed early in development, then monochorionic diamniotic pairs at a slightly later stage, then monochorionic monoamniotic pairs, and lastly conjoined pairs.[15]

If this were true, then

(1) the higher anencephaly rate in MZ twins would be explained by the supposition that a zygote that is 'delayed' at an early stage of its development (at the time of the MZ split) is more likely to be 'delayed' later on (at the time of neural tube closure) and so is more likely to be affected with the malformation;

(2) the continuum of risk of anencephaly across the various sorts of MZ placentation is explained by the variation of the interval between the time of the MZ split (when the zygote is known to be delayed) and the optimum time of neural tube closure. In dichorionic pairs, this interval is greatest and so (ex hypothesi) the embryos have had more time to 'catch up' and so escape the malformation. In conjoined pairs, this interval is least and so the embryos have not had so much opportunity to 'catch up' and consequently they are more often affected;

(3) the lack of association between MZ twinning and spina bifida is, ex hypothesi, the result of the greater time lag between the formation of MZ twins and the initiation of the lesion;

(4) the especial association of anencephaly with diprosopus rather than with other sorts of double monster may be explained by the suggestion[54] that diprosopus is formed later than all the other sorts of double monster. It might be wondered, though, whether this association owes anything to the spatial proximity of the incomplete split and the malformation rather than to the close timing of the events preceding each.

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Notes