Correspondence

not be the result of a more fundamental process in the egg or blastocyst. This unusual non-random inactivation and the MZ twinning process do not need to have a cause and effect relationship, but both can be consequences of a factor in the ovum itself. The same applies for the fortuitous association with gonadal dysgenesis. In animal experiments on ageing of the egg before ovulation or fertilisation indeed, an increase of abnormal cleavage divisions leading to one egg twins and chromosomal non-disjunctions, as well as of gonadal dysgenesis, has been observed at the preimplantation stages and in mid-gestation, respectively.6-8

Backed by these animal experiments and by the phenomenon of MZ 46,XX twins discordant for colour vision defect2 (and particularly the pair associated with primary amenorrhoea5), I have postulated that ovopathy can lead to MZ twinning associated or not with "a pathological course of the inactivation of a gonosome, causing its structural deficiency and eventually its loss".5 This concept also explains the frequent association of MZ twinning with defects, 'syndromes of obscure aetiology', and discordant karyotypes.9

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References

These letters were shown to Dr Burn who replies as follows.

Sir,

I read with interest the two preceding letters. In our original paper the temptation to expand the hypothesis into the biology of twinning in general was resisted in view of the limited experimental data. Nevertheless, the widespread use of MZ twins as an experimental tool in genetics justifies rigorous examination of the underlying assumptions. James presents an elegant review of the excess of female pairs among MZ twins with the lowered sex ratio showing a progressive decline through the range of MZ twins from dichorionic to conjoined. The ability of the ‘unequal X inactivation’ theory to account for this female excess has prompted us to extend our experiments on X inactivation patterns into other MZ twins including a conjoined pair. The results of this study will not be available for some months.

Jongbloet concentrates on the interesting phenomenon of the ovum release. He presents evidence in favour of ‘ovopathy’ being a potential teratogenic influence, but regards the female excess in MZ twins as being more likely to be the consequence of preferential early loss of males. His letter does not offer a specific reason why there should be contrasting X inactivation in the reported twin girls unless this clonal grouping caused the twinning.

A recent report of an excess of MZ twins among the products of in vitro fertilisation, together with the demonstration that an experimentally induced delay in ovulation in the rabbit considerably increased the incidence of MZ twinning and chromosome defects, prompt me to wonder whether there may be an element of truth in all these arguments.

If delayed fertilisation has an adverse effect on development this may be because one part of the ‘developmental clock’ starts at ovum release rather than fertilisation. If the gap between these is greater than normal the cytoplasmic stimulus to differentiate might find the cell mass too small or ‘immature’ or both. In consequence the capacity to initiate more than one centre of development may be increased. If X inactivation is influenced by the ‘ovum clock’, it too might occur at a relatively earlier stage of cell division when the smaller cell number might be expected to ‘cluster’ more readily.
Studies in mouse embryos and in teratocarcinoma cell cultures support the belief that X inactivation occurs at different times in different tissues and, more important in the present discussion, is triggered by the start of differentiation.3

Seller,4 in her study of neural tube defects, has drawn attention to a specific defect in neurulation as opposed to canalisation in females and has related this to slower cell division in females compared to males in early mouse embryos. She suggests that a relatively smaller cell mass may predispose to the neurulation defect. The excess of anencephaly among MZ twins5 and female excess in anencephaly fit better with a direct effect of X inactivation, as suggested by Hall6 and supported by James above.

I am grateful to Dr Gerald Corney for his comments and his observation that my hypothesis has similarities to Newman’s suggestion7 that early developmental arrest may trigger the consistent MZ twinning unique to the armadillo. Comments on this attempt at synthesis will be welcomed; with preimplantation genetic diagnosis now under serious consideration such issues may assume considerable significance.

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References