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On *X* inactivation in *XO* embryos of mammals

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SUMMARY

By analogy with the situation in coccids it is suggested that in mammalian *XO* embryos the single *X* turns heterochromatic in some cells, but that such a change does not result in cell death because the *X* then reverts back to an euchromatic and active state. This testable alternative to the Gartler–Sparkes hypothesis would imply that the anomalies of the *XO* Turner syndrome are largely due to imbalance of sex-linked genes rather than developmental damage resulting from cell death and that mammalian *X* inactivation might become reversed in response to special developmental needs.

In the vast majority of mammalian females with altered *X* chromosomes, it is the abnormal *X* that is late-replicating and forms sex chromatin. This non-randomness in inactivation has been interpreted by Gartler & Sparkes (1963) as being due to cell selection, the cells in which the *normal X* was inactive being lethal or less able to survive. Similarly, in *XO* embryos, according to their reasoning, in some cells the single *X* turns heterochromatic and these cells would not be expected to survive because they would in effect be nullisomic for the *X* chromosome. The resulting cell death could account for the abnormal features of *XO* women, including their short stature. This is an appealing idea and has been frequently discussed (e.g. Lyon *et al.* 1964; Beutler, 1964; Polani & Polani, 1969), most recently by Hecht & Macfarlane (1969). Implicit in the Gartler–Sparkes hypothesis is the idea of the irreversibility of *X* inactivation. Indeed Lyon (1961) made such irreversibility an important feature of the first statement of her hypothesis. However, since cytological data about these early events in *XO* (and other chromosomally abnormal) embryos are lacking, it is not known whether this interpretation is the correct one.

On the basis of experience with an analogous situation in coccids (a group of homopteran insects), we wish to suggest the possibility that in *XO* embryos the single *X* turns heterochromatic, as expected, in some cells, but that such cells do not die because the *X* then reverts back to an euchromatic and active state. A precedent for such a sequence exists among mealy bug embryos from triploid female × diploid male matings. During a cytological study of over 300 embryos resulting from such crosses, Chandra (1963) observed that in twelve of them there were haploid sectors of varying sizes, apparently originating from supernumerary sperm. Five of these embryos were male and showed heterochromatization of the paternal complement in the diploid, zygotic sector of the embryo. In two of these embryos, which were very young, the haploid complement first turned heterochromatic (as paternal chromosomes normally do in male embryos) and then in a series of gradations reverted back to an euchromatic state. It thus appears that in coccids a heterochromatic set cannot remain as such without at least one or more euchromatic chromosomes in the same nucleus (Chandra, 1963). This change in condensation was referred to as deheterochromatization, but, more recently, it has been called reversal of heterochromatization (Brown, 1966) or, simply, reversal (Nur, 1967).

Since in terms of facultative heterochromatization of whole chromosomes, the *XO* state in man and mouse is formally equivalent to the haploid state in coccids, it is not inconceivable that a similar reversal of heterochromatization occurs in *XO* embryos. If this is indeed the case, then the sexual and other anomalies of *XO* women would more likely be attributable to imbalance of sex-determining and other genes rather than embryological damage resulting from cell death. Such reversal of heterochromatization, if demonstrated, would not in any way lessen the attractiveness of the inactive *X* hypothesis. In fact, some genetic data from a *X*-autosome translocation in the mouse have been interpreted as being consistent with reversion of two *X*-linked genes to an active state from an earlier, inactive state (Cattanach, Pollard & Perez, 1969). As Gartler and Sparkes have indicated, it may be possible to obtain data bearing on these ideas by studying young embryos from *XO* mice.

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