Hypothesis

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Origin of Sex Chromosome Monosomy in Man

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There are striking contrasts when the apparent origin of the 45,X anomaly is compared with most trisomic conditions, and recent work gives interesting clues to the causes of sex-chromosome monosomy.

Except for a small proportion of cases arising from secondary non-disjunction of primary trisomic subjects—or cells—and a further group of segregational examples arising from centric fusion heterozygous subjects—or cells—Down's syndrome is the result of primary non-disjunction of chromosome number '21' during female meiosis. The indirect evidence of this is that the majority of cases arises in a maternal-age-dependent manner, so that the incidence of the condition rises with advancing age of the mother. Although primary non-disjunction of chromosome number '21', as of any chromosome, could in theory occur also at spermatogenesis, there is neither direct nor indirect support for this as a cause of Down's syndrome, but disomic '21' sperm appear to be capable of fertilization. By contrast, disregarding first the abortuses, the production of 45,X or presumptive 45,X survivors (Boyer, Ferguson-Smith, and Grumbach, 1961; Polani, 1965; Lenz, 1968; Court Brown, Law, and Smith, 1969) does not seem to correlate with advancing maternal age. Therefore it would seem that the mechanism of origin of these subjects must differ from that of maternal-age-dependent Down's syndrome, and indeed from that of the presumably maternal-age-dependent fraction of the other viable trisomic conditions in man, all of which show a correlation with parental age (and parity) with the exception of the 47,XYY.

Data on 45,X survivors, using genetic markers, had indicated that frequently the single X chromosome was maternal and that it was the paternal sex chromosome that was absent (Polani and Briggs, 1959; Polani, 1961). The use of the Xg sex-linked blood group has now enabled this to be more usefully explored and it is estimated that 75% of 45,X patients carry a single maternal X chromosome and 25% one of paternal origin (Race, 1970). Thus the majority of these patients results from an error that has caused loss or elimination of the paternal sex chromosome and, as these errors are or seem unlikely to result from ageing of the female, and obvious maternal-age effect is not to be expected among 45,X subjects taken as a whole. The causative non-disjunctional or other loss of the paternal sex chromosome could occur at either the first or second meiotic division of spermatogenesis. Another possibility is its elimination at fertilization or earliest cleavage if we extend to man (Polani, 1965) the observations on the origin of 39,X mice (Russell, 1961). In the mouse, the 39,X sex-chromosome complement is relatively common, though there is evidence that the propensity to this anomaly is not equal for all strains of animals. Almost universally, when the anomaly originates spontaneously, the missing sex chromosome is the paternal one; thus the abnormal animals are $39,X^M$. The frequency of 39,X mice is increased by irradiation after sperm penetration of the vitellus (Russell and Saylors, 1960; Russell, 1962) and this gives support to the idea that one of the mechanisms of origin of the anomaly is possibly selective sex-chromosome elimination at syngamy. It seems that the paternal sex chromosome may be particularly liable to be excluded, since ovum irradiation at fertilization increases the formation of $39,X^M$ animals, though admittedly also some $39,X^P$ may be detected. In addition, partial or complete paternal sex-chromosome loss can result from the irradiation of spermatozoa of experimental animals, but the effect seems to be less marked and results less often in the production of 39,X mice, than when ova are irradiated between sperm entry and first cleavage (Russell and Saylors, 1962).

A third possible origin of an XO sex-chromosome complement is from secondary non-disjunction, but this mechanism could probably only exceptionally—and if so, perhaps, in 45,X mosaic subjects—account for 45,X humans, though it operates in the mouse.

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Concerning specifically the origin of sex-chromosome monosomy in man, we must turn for evidence to the origin of other sex-chromosome anomalies. Meiotic non-disjunction at, or not later than, first meiotic division is known to lead to the formation of 24,XY sperm, capable of fertilizing the ovum and accounting for the production of $47,X^{M}X^{P}Y$ males with Klinefelter's syndrome: indeed it is calculated that some 40% of males with this syndrome, about 0·025% of conceptions, may owe their origin to an error of paternal gametogenesis (Race, 1970). 47,XYY males, about 0·07% of all conceptions, can best be accounted for by a non-disjunctional error of the Y chromosome at the second meiotic division of spermatogenesis and only exceptional 47,XYY males should result from secondary non-disjunction because there seems to be a relative bar to the formation of XYY primary spermatocytes by 47,XYY males (see, for instance, Thompson, Melynk, and Hecht, 1967; Tettenborn *et al*, 1970), though the failure of secondary non-disjunction need not be absolute (Diasio and Glass, 1970; Hultén, 1970; Hultén and Pearson, 1971). Both types of meiotic events at spermatogenesis, those resulting in the production of 47,XXY and those responsible for 47,XYY males, should produce complementary sex-chromosome nullisomic sperm (n = 22) which, granted their fertilizing ability, might account for the production of $45,X^{M}$ zygotes. However, the frequencies of the complementary zygotes (47,XXY and 45,X or 47,XYY and 45,X) may well be different. Certainly in the mouse, when the output of both 41,XXY and 39,X naturally occurring animals can be observed, the former are only about 0·02% as against 0·72% of the latter. Unfortunately the frequency of 41,XYY mice is unknown and, of course, some of the 39,X mice may owe their origin to errors of syngamy or post-fertilization rather than to errors of meiosis. In man, the frequencies of the two types of zygote with 47,XXY and 45,X sex chromosomes (0·06 *vs* 0·8%, see below) could be rather similar to the relative frequencies in the mouse; and human zygotes with 47,XYY sex chromosomes are about 0·07%.

What are the frequencies in man of non-disjunctional errors in meiotic cells or gametes as opposed to conceptions or survivors relevant to the 45,X condition? As far as the sperm is concerned, recently it has been observed that over 1% of spermatoza that are morphologically normal contain two fluorescent bodies (P. Barlow, personal communication; Pearson and Bobrow, 1970), and presumably therefore two Y chromosomes. Furthermore, DNA measurements, which have indicated that spermatozoa with a single body are 23,Y (Sumner, Robinson, and Evans, 1971) and those without are mostly 23,X, suggest that the sperm with two fluorescent bodies are usually near haploid and therefore presumably have a 24,YY complement. This implies that a similar proportion, about one per cent, of sex-chromosome nullisomic sperm should arise as a complementary event during spermatogenesis. Additional nullisomic sperm should arise from the non-disjunction at first meiotic division that is complementary to the error that produces $47,X^{M}X^{P}Y$ males. Also it is entirely possible that the sex-chromosome nullisomic sperm could be formed as complementary gametes to non-disjunctional XX sperm. The latter sperm, if produced, and if they were competitive in fertilization, should produce 47,XXX zygotes. There is however, no evidence that 47,XXXs arise from errors of spermatogenesis. Rather, the evidence points to oogenesis: the maternal-age distribution at birth of 47,XXX women is very similar to that in Down's syndrome (for references see Polani, 1965) and the frequency of Xg(a+) among them is suggestive of an ultra-female distribution (R. Sanger, P. Tippett, and J. Gavin, personal communication) and hence of an error at oogenesis.

At any rate, whereas the frequency of the 45,X condition at birth is about 0·02% among early conceptuses the overall frequency may be estimated to approach one per cent. Thus, simply on a numerical basis, there could be sufficient sex-chromosome nullisomic sperm, if we assume that they have a high fertilizing ability, to account for the production of 45,X embryos even if we postulated that all 45,X abortuses carried only the maternal X chromosome. However, the source of the single X in 45,X abortuses is not known and, on frequency grounds, the fertilizing ability of the presumptive 24,YY sperm, at least, is judged to be impaired (Sumner *et al*, 1971). The sex-chromosome nullisomic sperm may also have an impaired fertilizing function. It has been suggested to me that the relative excess of $45,X^{M}$ survivors compared with $45,X^{P}$ may be attributable to maternal compatibility (S. Walker, personal communication). Selection against $45,X^{P}$ might account for their loss during early pregnancy as spontaneous abortion and, if so, at least a proportion of 45,X abortuses would not be the result of a non-disjunctional or similar error of spermatogenesis.

If we now consider the possible origin of $45,X^{P}$ zygotes in greater detail, we know that the average maternal age of 45,X survivors in general is normal (see above), as is that of 45,X/46,XX mosaics (Polani, 1965). Thus a possible zygotic origin of

some 45,X subjects is not excluded and clearly a proportion of these zygotes could be 45,X^P. On the other hand, among 45,X abortuses (Dhadial, Machin, and Tait, 1970), there is evidence for a slight maternal-age influence (paternal-age and parity effects, however, have not been excluded). Thus, maternal-age-dependent X-chromosome non-disjunction might account for a proportion of 45,X fetuses who would thus be 45,X^P, as it seems to account for a proportion, presumably greater, of the 47,XXY males whose two X chromosomes are maternally derived.

Lastly, in trying to apportion the origin of 45,X conceptions to the various chromosome errors that may cause the condition, we have to consider the fact that there is an increased frequency of 45,X abortuses (as well as triploids) from women who have been taking oral contraceptives compared with those who have never done so (Dhadial *et al*, 1970). The differences are not significant but if further work should show that contraceptives may significantly increase the frequency of 45,X abortuses (and triploids), this would mean that sex-chromosome behaviour of the egg is affected at polar-body formation, at syngamy or earliest cleavage. The missing sex chromosome may be maternal but paternal loss is not excluded from a normal male pronucleus at syngamy or earliest cleavage. It is also not altogether excluded that the contraceptive effect on the ovum may alter its permeability to abnormal sperm, for instance nullo-sex-chromosome. It must be stressed that there is no evidence to relate the taking of oral contraceptives, and therefore the proportionally increased frequency of 45,X *fetuses*, to an increased incidence of 45,X *survivors*.

In conclusion, it can now be suggested, with the support of some evidence, that meiotic non-disjunctional events could operate often during male meiosis perhaps mostly at the second meiotic division, and account for the production of 45,X zygotes; whether the events are random remains to be determined. There is genetic evidence for non-disjunction or other X-chromosome loss in female meiosis, though the important point as to which of the two meiotic divisions may be affected is unresolved. It is also possible that a proportion of 45,X embryos may derive from sex-chromosome loss at syngamy or at earliest cleavage. In the last two named cases, of course, loss of either the maternal or paternal sex chromosome seems possible.

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