*Genet. Res., Camb.* (1968), **12**, *pp.* 125–137
*With* 1 *plate and* 4 *text-figures*
*Printed in Great Britain*



# The XO and OY chromosome constitutions in the mouse

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(*Received* 29 *February* 1968)

## 1. INTRODUCTION

Evidence from cases of sex chromosome abnormality in man seems to indicate that it is the presence or absence of the *Y* chromosome which determines sex in mammals. Thus a single *Y* chromosome has a masculinizing effect in the presence of as many as four *X* chromosomes, although the greater the number of *X* chromosomes the greater the phenotypic abnormality, particularly in the direction of testicular under-development (Jacobs, 1966). In addition recent evidence (Jacobs *et al.* 1965) suggests that two *Y* chromosomes in an individual give rise to a characteristic syndrome, suggestive of an 'over-masculinizing' effect. However, from the point of view of general viability the *X* chromosome still seems to be of greater importance than the *Y*. Thus, although the *OY* chromosome constitution has been presumed to be lethal in the mouse (Welshons & Russell, 1959) the *XO* one in this species is viable, fertile and phenotypically normal.

This difference in genetic effect might be partly explained by the relative sizes of the *X* and *Y* chromosomes in the mouse, but the normality or near normality of *XO* individuals has also been judged to support the inactive-*X* hypothesis (Lyon, 1961), which offers a working explanation of both this and other aspects of mouse genetics. The hypothesis, briefly, postulates that in each somatic cell of a normal female mammal only one of the *X* chromosomes is active, and that in such an *XX* individual the inactivation occurs at an early stage of embryogenesis and is at random in each cell at that stage. From this it follows that an *XO* individual would have the same *X* chromosome active in each somatic cell, and thus that all the cells of such an individual would be effectively hemizygous for exactly the same set of *X* chromosome alleles, as is the case in a normal *XY* male. This is in contrast to the case in an *XX* individual, the cells of which would be hemizygous for different *X*-chromosome alleles. Consequently a normal female on this view is, in effect, a mosaic for all *X*-chromosome loci exhibiting heterozygosity. In view of this genetic difference between *XO* and *XX* females, the normality of *XO* mice is of some interest. In the present investigation it was hoped to assess the degree of this normality from the point of view of breeding performance, and also to find evidence of the stage of embryogenesis at which the *OY* zygotes are lost.

## 2. MATERIALS AND METHODS

The data presented in this paper were obtained from four main sources. The first part is breeding data accumulated in the process of setting up and maintaining a

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stock of *XO* females. The stock was basically similar to the one described by Cattanach (1962), having the sex-linked gene *tabby* as a marker; the *XO* females in succeeding generations, *Ta/O* and *+/O* females, are mated to *+/Y* and *Ta/Y* males respectively. The stock is outcrossed once in every two generations, the *+/Y* males coming from a C3H × 101 hybrid stock. Useful though the breeding data are, the lack of data from control females makes them unsuitable for detailed analysis, especially with regard to litter sizes. Matings were therefore set up, using sib pairs of *+/O* and *Ta/+* females; each pair was mated to a *tabby* male in order to make the data as comparable as possible with that from the stock matings. The females were then allowed to produce, pregnant females being checked twice per day for litters and the offspring classified at weaning age. Placing females in mesh-bottomed cages would have given more exact estimates of litter sizes at birth, but this was considered to be wasteful of both data and breeding material. The third body of data was obtained by setting up matings similar to the above, but by dissecting the pregnant females after approximately 15 days' gestation. From these it was possible to assess the number of eggs shed and the amount of pre-implantation and post-implantation loss in both types of female. On the basis of data thus obtained, some female mice were dissected at approximately 3½ days after the finding of a copulatory plug. Each uterine horn was flushed with saline, and the embryos found (usually late morulae or early blastocysts) were examined under a binocular microscope for signs of abnormality.

Table 1. *Litters of XO mice*

| Mating type | Age at which scored | *XO* | *XX* | *XY* | $\frac{XO+XX}{XY}$ | $\frac{XO}{XX}$ |
|---|---|---|---|---|---|---|
| *Ta O*♀ × *+Y*♂ | Birth | 1148 | | 821 | 1·40* | |
| | Weaning | 252 | 674 | 608 | 1·52 | 0·374 |
| *+O*♀ × *Ta Y*♂ | Birth | 1117 | | 746 | 1·50* | |
| | Weaning | 287 | 679 | 650 | 1·49 | 0·423 |
| Mean | — | — | — | — | 1·45 | 0·399 |

* Denotes the values for which the mean is given.

## 3. RESULTS

The data accumulated in setting up the stock are shown in Table 1. Much of it is of interest mainly in so far as it corroborates that of Cattanach (1962). He found that in a stock comparable to the one described here the frequency of *XO* females was much lower than that expected on the basis of a normal segregation of nullo-*X* gametes. In addition he found the overall litter size at birth in both types of mating to be considerably reduced. From the similarity in sex ratio at birth and at weaning age in the offspring of *XO* females, he concluded that *XO* females were as viable as their *XX* sibs throughout the first 3 weeks of life.

In the present set of data the sex ratio at birth is approximately the same as at weaning age in the *+/O* × *Ta/Y* matings, whilst in the reciprocal cross the higher ♀/♂ sex ratio at weaning compared with that at birth would appear to be due to the

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lowered viability of $Ta/Y$ males during the first 3 weeks of life: this can be seen from the increased $XX/XY$ ratio at weaning in this cross. There is, therefore, no evidence of a differential loss of $XO$ females between birth and weaning age.

Assuming normal segregation and normal viability of the zygotes, there should, of course, be equal numbers of the three types of offspring, $XX$ females, $XO$ females, and $XY$ males. Cattanach found the overall $XO/XX$ ratio at weaning age to be 0·30 in $Ta/O \times +/Y$ matings, and 0·37 in $+/O \times Ta/Y$ ones, whilst from the data in Table 1 the corresponding figures are 0·37 and 0·42 respectively. Although the difference between the reciprocal crosses is fairly small in each case, it is in the same direction, that is, of a higher proportion of $Ta/O$ compared with $+/O$ females at weaning. This is surprising, since animals hemizygous for *tabby* are usually less viable than heterozygotes. As it stands, when the data in Table 1 are combined with those of Cattanach the difference between the two crosses is not quite significant at the 5% level ($\chi^2_1 = 3{\cdot}72$). Nevertheless, there is a suggestion from the data of a difference in the frequency of $XO$ females from the two types of mating; since postnatal inviability appears to be ruled out, the alternative explanations would be either a difference in embryonic viability or a difference between the two types of $XO$ in the segregation ratio of nullo-$X$-bearing gametes.

Table 2. *Litters of XO and XX sibs*

| | Number of litters | Total animals born | Average litter-size at birth | Sexes at birth ♀ | Sexes at birth ♂ | ♀/♂ |
|---|---|---|---|---|---|---|
| $+/O$ | 41 | 183 | 4·46 | 113 | 66 | 1·71 |
| $Ta/+$ | 53 | 433 | 8·17 | 220 | 207 | 1·06 |

The data on litter sizes of the $+/O$ and $Ta/+$ sibs are shown in Table 2 and in Text-fig. 1. The average litter size of the $XO$ females, 4·46, is greatly below that of the $XX$ ones, 8·17 ($P = < 0{\cdot}001$). The former figure is similar to that of Cattanach, who found a litter size of 5·3 among stock $XO$ mice. This he considered abnormally high for a stock in which half the males and two-thirds of the females were presumed to die pre-natally, and he suggested that preferential segregation of $X$-chromosome carrying gametes might be taking place, giving less than 50% segregation of nullo-$X$ gametes and therefore correspondingly lower proportions of $XO$ and $OY$ zygotes. However, from the present data it can be seen that the average litter size in the $XX$ females is 8·17; if one assumes that all $OY$ and two-thirds of $XO$ zygotes die pre-natally, one would expect a litter size in $XO$ females of around 4·7. This is very close to the litter size in the present set of data (4·46) and not significantly different from that of Cattanach. Thus it would appear that the data given here would be quite consistent with the prenatal loss of all $OY$ and two-thirds of $XO$ zygotes with normal segregation ratios. However they would also be consistent with alternative distributions of the lethality. The sex ratio at birth of 1·7 is a little higher than that in the stock matings but is clearly based on much smaller numbers and the difference is not significant.

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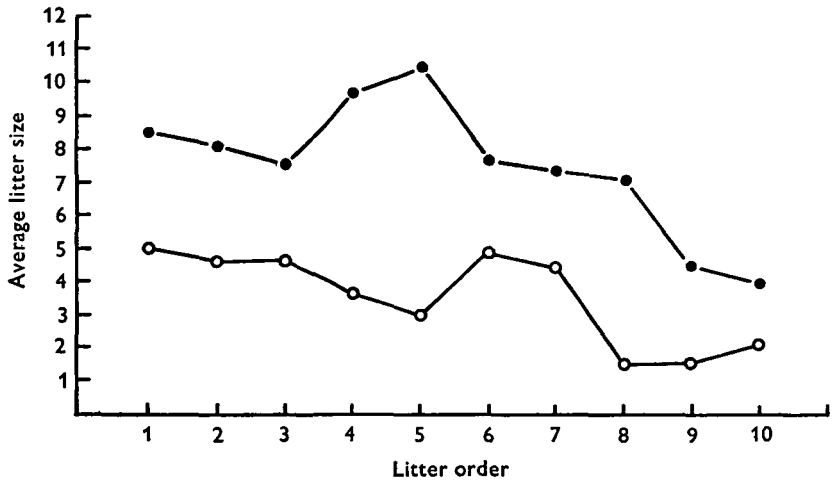
Text-fig. 1 shows the variation in litter size with litter order. The difference in size between $XX$ and $XO$ litters is consistent from the 1st to the 10th litter. The graphs are based on data from eight sib pairs of females, comprising a total of fifty-three $XX$ litters and forty-four $XO$ ones.




Text-fig. 1. Change of litter size with litter order in $+/O$ and $Ta/+$ sibs. ●, $XX$ litters; ○, $XO$ litters.

Table 3. *Offspring weaned from XO and XX sibs*

| | Offspring | | | | |
|---|---|---|---|---|---|
| | $Ta/O$ | $Ta/+$ | $Ta/Ta$ | $+/Y$ | $Ta/Y$ |
| Mothers $+/O$ | 15 | 63 | — | 59 | — |
| $Ta/+$ | — | 70 | 89 | 85 | 39 |

Table 3 shows the weaning totals of the various genotypes from the $Ta/+$ and $+/O$ sibs. An interesting feature is the $XO/XX$ ratio at weaning of 0·24 in the $+/O$ females, compared with that of 0·42 in the corresponding stock matings. This suggests, that compared to the stock matings, more $XO$ females were born but fewer survived to weaning age. Since the $XO$ females born were $Ta/O$, this does fit in with the post-natal loss of $Ta/Y$ males, which can be seen from the same table. However, the data also show evidence of a somewhat anomalous effect of the tabby gene, since female homozygotes seem to show no decreased viability, despite the fact that animals hemizygous and those homozygous for *tabby* are phenotypically identical.

Since the $OY$ constitution was presumed to be lethal, and since there was a deficiency in the number of $XO$ females, matings of $+/O$ and $Ta/+$ sibs were set up as before and the pregnant females dissected at approximately 15 days' gestation. In such openings the embryonic death can be apportioned between pre-implantation (0–4 days), early post-implantation (4–9 days, seen as small moles),

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later post implantation (9–12 days, seen as large moles) and observable dead embryos (12–15 days' gestation). Apart from the $+/O$ and $Ta/+$ sibs, other $XO$ and $XX$ females were also opened, almost all the random $XO$ females being $Ta/O$. The results are shown in Table 4. No significant differences were found in the amount of embryonic death at any stage between the $+/O$ and random $XO$ females, or between the two series of $Ta/+$ females. This suggests that there was no difference in embryonic mortality due to the different genotypes of the $XO$ females. The two sets of results were therefore added and are compared in Table 5.

Table 4. *Dissections at* 15 *days' gestation of XO and XX females*

| | Sib $+/O$ | Random $XO$ | Total $XO$ | Mean | Sib $Ta/+$ | Random $XX$ | Total $XX$ | Mean |
|---|---|---|---|---|---|---|---|---|
| Females opened | 76 | 54 | 130 | — | 76 | 78 | 154 | — |
| Corpora lutea | 804 | 570 | 1374 | 10·57 | 837 | 846 | 1683 | 10·92 |
| Implants | 503 | 324 | 827 | 6·36 | 577 | 686 | 1363 | 8·85 |
| Small moles | 62 | 47 | 109 | 0·84 | 47 | 38 | 85 | 0·55 |
| Large moles | 20 | 15 | 35 | 0·27 | 6 | 11 | 17 | 0·11 |
| Dead embryos | 7 | 7 | 14 | 0·11 | 5 | 14 | 19 | 0·12 |
| Alive | 414 | 255 | 669 | 5·14 | 619 | 623 | 1242 | 8·07 |

Table 5. *Totals from XO and XX dissections at* 15 *days' gestation*

| | $XO$ | $XX$ | $\chi^2$ |
|---|---|---|---|
| Number of females | 130 | 154 | — |
| Corpora lutea | 1374 | 1683 | 0·84 |
| Implants | 827 | 1363 | 56·64* |
| Small moles | 109 | 85 | 8·47* |
| Large moles | 35 | 17 | 9·71* |
| Dead embryos | 14 | 19 | 0·15 |
| Alive at 15 days | 669 | 1242 | 89·25* |

* Denotes a significant difference.

As may be seen, there were significant differences between the $XO$ and $XX$ females in the loss of embryos before implantation, at the small mole stage and at the large mole stage. Since all the differences were in the same direction, that is, increased loss at all these stages in the $XO$ series, there was a resultant large deficiency in embryos alive at 15 days' gestation in the $XO$ females. This can be clearly seen in Text-fig. 2. The mean number of live embryos in the $XO$ females (5·14) is considerably higher than the mean litter size at birth seen in Table 2 (4·46), compared with the corresponding figures from the $XX$ females of 8·07 and 8·17 respectively. However, this difference is no more significant than that between the number of dead embryos in the $XO$ and $XX$ series of dissections. If these data are combined, therefore, there is no significant evidence of excess embryonic mortality in $XO$ females between approximately 12 days' gestation and birth.

By far the greatest difference between the $XO$ and $XX$ dissections is in the ratio of implantations to corpora lutea, that is, in the amount of pre-implantation loss. If the amount of this excess loss were to constitute a constant fraction of the total number of eggs (as would be expected if a whole class of zygotes was being lost),

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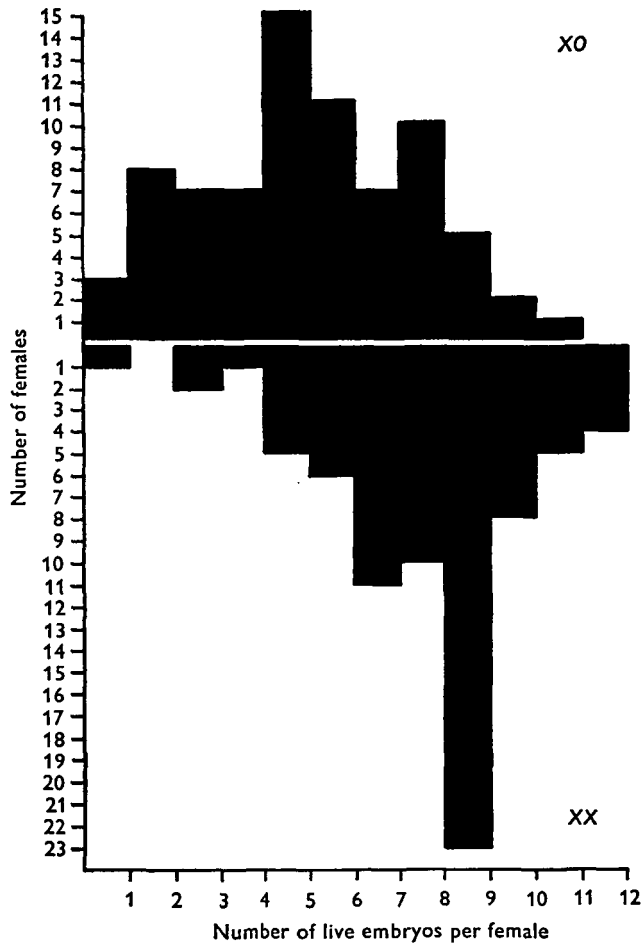
the difference between the $XO$ and $XX$ data would be more or less independent of the number of ova shed from each ovary. In Text-fig. 3 the implantation/corpora lutea ratio in each uterine horn is plotted against the number of ova shed from each ovary (as measured by the number of fresh corpora lutea). Linear regressions (straight lines) were fitted for both the $XO$ and $XX$ data, and each showed a significant negative slope when tested at the 5% level. The data support three conclusions.




Text-fig. 2. Number of live embryos in dissections of $+/O$ and $Ta/+$ sibs after 15 days' gestation.

1. In each series of dissections, as the number of eggs shed from the ovary increases, the probability of each individual egg implanting decreases; this result corroborates the finding of Bowman & Roberts (1958).

2. The difference in implantation rate between the $XO$ and $XX$ series remains more or less constant, irrespective of the number of corpora lutea and therefore of the number of ova shed from each ovary.

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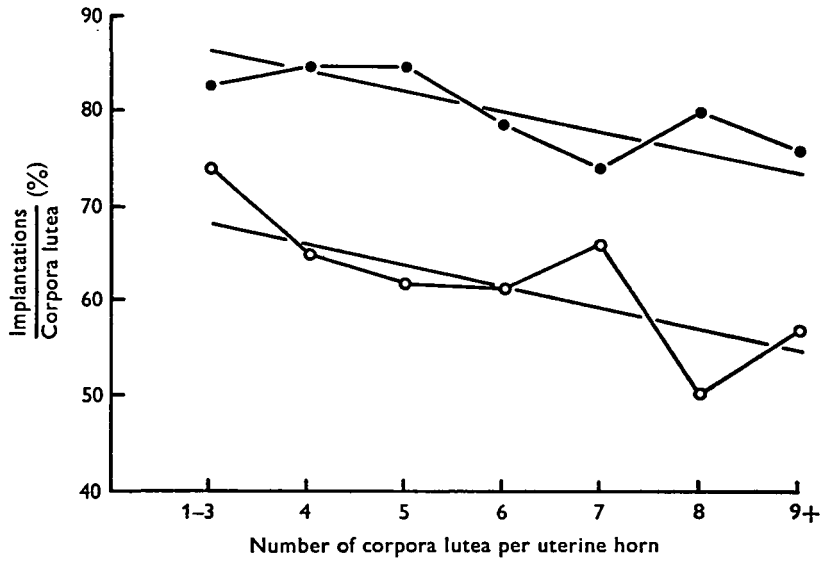
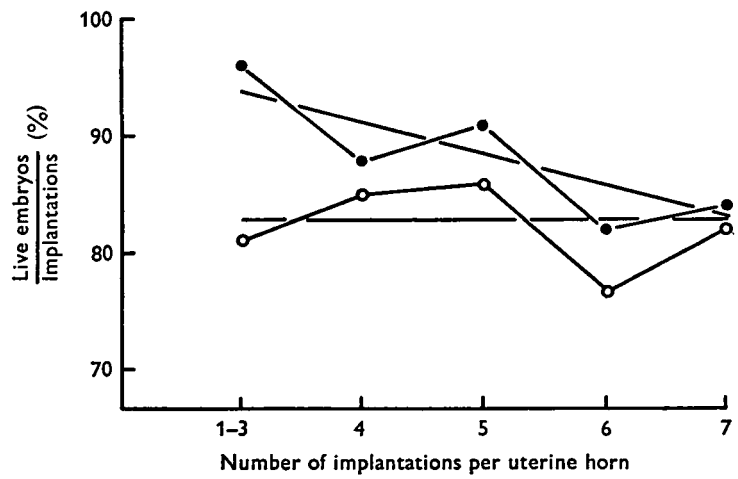
3. The decline in implantation rate with increasing rate of ovulation is of the same order in both series; that is, the regression lines for the *XO* and *XX* data are of more or less the same slope.




Text-fig. 3. Implantation rates in *XO* (○) and *XX* (●) females.




Text-fig. 4. Proportion of embryos alive at 15 days' gestation in *XO* (○) and *XX* (●) females.

Text-fig. 4 shows the equivalent graph for the proportion of live embryos/total implantation sites plotted against the number of implantations per uterine horn. The difference between the two plots reflects the significant excess of embryonic death between days 4 and 12 of gestation in *XO* females; as can be seen, the difference in post-implantational mortality between *XO* and *XX* females is indepen-

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dent of the overall number of implantations in each uterine horn. Linear regressions (straight lines) were fitted for both sets of data but only that for the $XX$ data showed a significant negative slope. However, notwithstanding the non-significant slope for the $XO$ data, there is no significant difference between the slopes of the two regressions and, in fact, the combined slope is negative and significantly different from zero. There is therefore no evidence for a difference between $XO$ and $XX$ females in the rate at which the embryonic survival frequency declines with the increase in implantational events.

Table 6. *Embryos from dissections of XO and XX females at 3½ days' gestation*

| | Type A abnormality | Type B abnormality | Normal embryos | Total embryos | Females |
|---|---|---|---|---|---|
| *Ta*/*O*♀♀ | 26 | 4 | 107 | 137 | 18 |
| +/*O* ♀♀ | 34 | 1 | 108 | 143 | 16 |
| Total *XO* | 60 | 5 | 215 | 280 | 34 |
| Total *XX* | 4 | 4 | 181 | 189 | 22 |

Since the greater part of the embryonic mortality was clearly occurring before implantation, some females were dissected at approximately 3½ days *post coitus*. The embryos found were examined for signs of abnormality and abnormal embryos were classified into two types, A and B, type A being fairly homogeneous class, group B a heterogeneous one. Plate 1*a* shows an example of type A abnormality together with normal embryos from the same female. In the abnormal embryo two large cells can be clearly seen, together with several smaller cells which often appear to lack cytoplasm. There is some variation in the number and size of the smaller cells, some embryos having very few. Plate 1*b* shows an extreme example in which there are no small cells at all and this embryo is morphologically a normal two-cell embryo. However, in view of the fact that such examples are retarded by approximately 3 days in development and that the dividing line between 'normal' two-cell embryos and presumptive abnormal ones is not very clear, both types have been classified as type A abnormality. Type B abnormality is based upon a much more subjective classification and includes a variety of later embryos (sixteen cells or more) in which the individual cells appear to be less differentiated than normal.

The first two rows in Table 6 show the results of openings of $XO$ females of both genotypes (+/$O$ and *Ta*/$O$). Since there was found to be no significant difference between the two sets of data, these were added and are compared below with the data from $XX$ openings (all of which were *Ta*/+ females). There is, as may be seen, a marked excess of embryos showing the type A abnormality in the openings of $XO$ females. If the four abnormalities of this type in the $XX$ females are assumed to be representative of the spontaneous incidence of such lethals, there is an excess in $XO$ females of fifty-six zygotes of this type out of a total of 280, equivalent to a frequency of 20·0 %. There is no significant difference in the frequency of type B abnormalities between the embryos of the two types of female.

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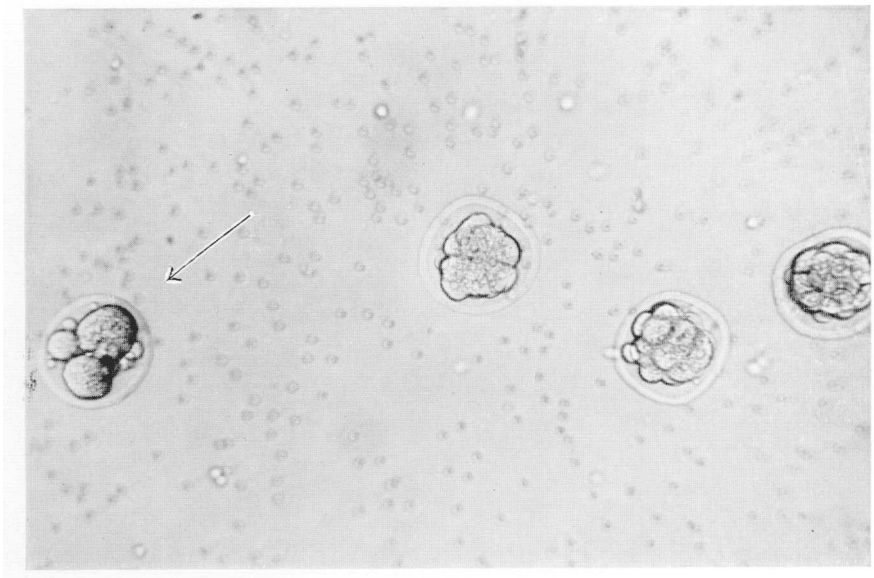

Plate 1*a*. Four zygotes from *XO* female after 3–3½ days' gestation. Three zygotes appear to be normal morulae, whereas one (arrowed) is an example of a type A abnormality.

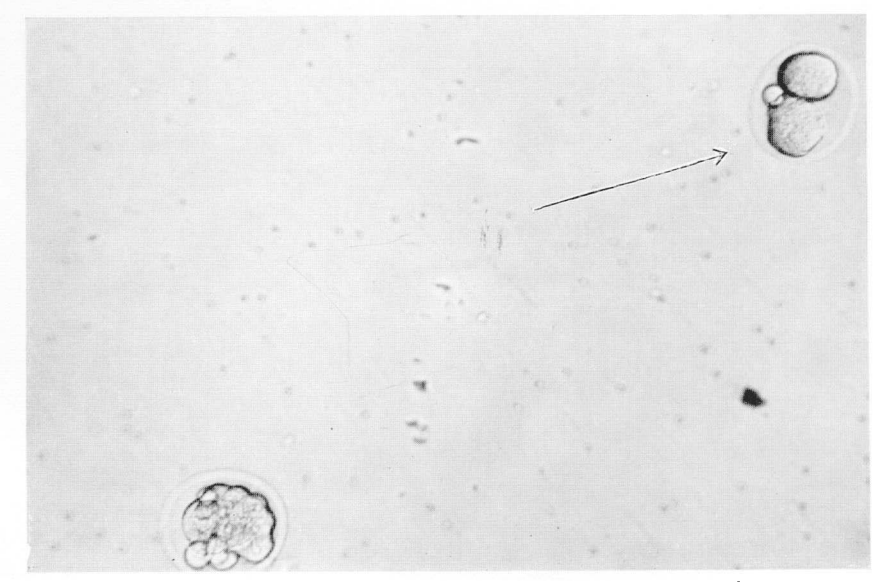

Plate 1*b*. Two zygotes from an *XO* female after 3–3½ days' gestation. In one of them (arrowed) development has ceased after the first cleavage division.



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## 4. DISCUSSION

The results previously described support several conclusions regarding the biology of embryos with *XO* and *OY* karyotypes in the mouse. First, a marked deficiency of *XO* females among the offspring of such females may be observed at weaning age, and a comparable one at birth may be inferred from the data. The scale of this deficiency is of the order of two-thirds of all *XO* animals expected. Since some nullo-*X* gametes are obviously formed, the cause of the deficiency of *XO* animals could be either abnormal segregation, lowered viability, or a combination of the two. The results from dissections after 15 days' gestation, shown in Table 4, afford considerable information as to the amount of extra embryonic loss in the *XO* series compared with that in the *XX* one. If one assumes that the ratio 1363/1683 is equivalent to the spontaneous implantation rate in normal females, the expected number of implantations in the *XO* series would be 1113. There is thus evidence of a pre-implantational loss in the *XO* females of 1113–827 = 286 zygotes above the spontaneous level. If one treats in the same way the data from the other stages showing a significant difference, namely, those showing death at the small and large mole stage, one finds that the number of extra zygotes lost at these stages in the *XO* series is 37 and 20 respectively. The excess pre-implantation loss of 286 zygotes is equivalent to a fraction of 25·7 % of the total, and is obviously a good enough estimate to account for the whole class of presumptive lethal *OY* zygotes. However, if the expected number of *OY* zygotes are formed but then die, this would suggest that the segregation of nullo-*X* gametes is normal. Consequently, the expected number of *XO* zygotes would be formed at fertilization and the deficiency observed at birth would be caused purely by reduced viability at post-implantational stages. There is evidence of some excess death at these stages, but it is certainly not on a large enough scale to account for the death of two-thirds of all *XO* females. It follows that the likeliest explanation is that there is *both* abnormally low segregation of nullo-*X* gametes in *XO* females (or reduced viability of such gametes before fertilization), *and* a reduction in viability of *XO* females during embryogenesis; the latter would now include some death at pre-implantational stages. Some support for this can be found in the data from dissections at 3½ days. In these the frequency of embryos showing type A abnormalities was seen to be 20·0 % of the whole, and this frequency is significantly different from the 25·7 % excess pre-implantational death found in the 15-day series ($\chi_1^2 = 3{\cdot}918$, $P = < 0{\cdot}05$). If the 20 % of embryos showing type A abnormalities are presumed to comprise the whole class of *OY* zygotes, then the remaining 5 % of pre-implantational death (not seen as gross abnormalities at 3½ days' gestation) may be assigned to additional loss of *XO* embryos. A hypothetical 'balance-sheet' of such a distribution of lethality is shown in Table 7. The bottom line shows the data derived from the series of 15 day dissections, treated as though there was no normal or 'background' loss of embryos. It must be presumed that normal loss does not alter the relative proportions of the various karyotypes. The first column shows the total expected zygotes distributed as though only 20 % of the zygotes formed

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were $XO$ or $OY$, instead of the normal 25%. The second column shows the loss of the whole $OY$ class (probably comprising the type A abnormalities) together with the extra 5% of presumed $XO$ deaths. The number of later $XO$ deaths of thirty-seven and twenty leave the figure of 103 $XO$ animals alive at 15 days, again ignoring the 'background' loss. This figure of 103 can be seen to be roughly equivalent to a proportion of 0·3 of the $XO$ females expected, and, since there was no evidence of differential viability during later foetal stages, the proportions of $XO$, $XX$ and $XY$ karyotypes shown in parentheses would persist until parturition and give rise to the genotypic frequencies observed in the stock matings.

Table 7. *The distribution (hypothetical) of lethality due to abnormal karyotypes in embryos of XO females. (For explanation see text)*

| Total zygotes | Excess pre-implantation death | Excess small-mole death | Excess large-mole death | Embryos alive at 15 days' gestation |
|---|---|---|---|---|
| $OY$ 223 (20%) | 223 | — | — | — |
| $XO$ 223 (20%) | 63 | 37 | 20 | 103 (0·3) |
| $XX$ 333·5 (30%) | — | — | — | 333·5 (1) |
| $XY$ 333·5 (30%) | — | — | — | 333·5 (1) |
| 1113 | 286 | 37 | 20 | 770 |

Thus, there is strong circumstantial evidence that the $OY$ zygotes probably die before implantation, the abnormality becoming apparent after the first cleavage division. It also seems probable that there is a comparative deficiency of nullo-$X$ gametes at fertilization, since the inferred frequencies of the $OY$ and $XO$ zygotes are rather lower than the 25% expected in each case. Of the $XO$ zygotes, in fact, not all survive, since there is some evidence of lower viability of embryos with this karyotype throughout the early stages of development. This is in contrast to their seemingly normal viability after birth.

If the preceding interpretation of the data is correct, the most interesting aspect is the stage at which the abnormality of the $OY$ zygotes becomes apparent. Mintz (1965) has recently reviewed the evidence for RNA formation in the pre-implantation mouse embryo. Much of this information comes from the work of Flax (1953), who studied mouse embryos *in vivo* and measured the relative amounts of cytoplasmic RNA at various stages. He found that cytoplasmic RNA increases with the diameter of the egg until just before ovulation. There follows a sharp drop until the stage of the fertilized ovum; the amount then remains level until the four to five cell stage, after which it starts to rise again.

Mintz herself showed that the initiation of RNA production by the nucleoli occurs after the second cleavage division (i.e. the four to five cell stage), but that protein synthesis occurs before this stage. She suggested that ribosomes of maternal origin (constituted during oocyte growth) remain effective to some extent after fertilization. If protein synthesis and cell division are interdependent in a direct sense, the fact that the development of $OY$ zygotes appears to cease at the two-cell stage suggests that Mintz's postulate may be partly true, but that the genomic

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initiation of protein synthesis is necessary for the second cleavage division. Thus, although no *X*-chromosome appears to be necessary for the first cleavage division, at least one *X* is for the subsequent ones.

These conclusions regarding the fate of *OY* zygotes have some relevance to human cytogenetics. In the chromosome studies on over 500 aborted human foetuses reviewed by Kerr (1966), despite the fact that most of the pregnancy wastage occurred during the first trimester, none was found with an *OY* karyotype, the majority being autosomal trisomics or *XO* embryos. The preponderance of the latter class of lethality at this stage is hardly surprising, considering both the data presented here on *XO* mouse embryos and the fact that the *XO* constitution in man is far more abnormal after birth than it is in the mouse. The data on human abortuses also lend some support to the probability that if any *OY* zygotes are formed spontaneously in man, they too will die before implantation and will never be found in the class of aborted foetuses; in fact, no pregnancy will normally be detected if such an embryo is conceived.

One way in which an *OY* embryo could arise is by loss of an *X* chromosome from an *XY* zygote immediately after fertilization. In this connexion, evidence suggests (Russell, 1961) that the majority of $X^MO$ mice are the result of events occurring after sperm penetration of the vitellus ($X^M$ refers to the maternal *X* chromosome, $X^P$ the paternal one). However, the explanation offered by Russell involves 'the existence of a vulnerable state of the paternal nuclear material some time between sperm penetration and completion of the first cleavage'. This would certainly explain the large number of $X^MO$ animals discovered but, if true, would suggest that few $X^PO$ or *OY* zygotes would be formed by this means (since these would require the loss of the maternal *X* chromosome.) If this is the case, and if it also applies to man, the number of *OY* embryos formed by this means will be extremely small.

Another way in which *OY* embryos could arise in mammals is by chromosomal non-disjunction in the female. This would give rise to $X^MX^M$ and nullo-*X* gametes and, after fertilization, to $X^MX^MX^P$, $X^PO$, $X^MX^MY$ and *OY* embryos. In the mouse the frequency of loss of maternal sex chromosomes is much lower than that of paternal ones. Moreover, since no cases of $X^MX^MY$ or $X^MX^MX^P$ have been demonstrated, there is no positive evidence for spontaneous non-disjunction (Russell & Saylors, 1963). In man, however, more evidence exists concerning the origin of the sex chromosomes. Nowakowski, Lenz & Parada (1959) reported three cases where colour-blind chromatin-positive men were shown to have had fathers with normal colour vision; the men were presumed to be $X^MX^MY$. More information has come from Xg blood grouping studies; from evidence of this kind, Lindsten *et al.* (1963) found that some *XO* females were $X^PO$ in chromosomal constitution. Race (1965) calculated that the data from the 102 cases of *XO* examined and reported until then in which the Xg genotype of both the propositus and the parents was known, were consistent with 24 % of non-mosaic Turners being due to loss of the maternal *X*, and 76 % to loss of paternal one. In contrast to the mouse, several cases have now been reported in man, again based on Xg analysis, in



https://doi.org/10.1017/S0016672300011745 Published online by Cambridge University Press

which both $X$ chromosomes in $XXY$ individuals were maternal. In such cases, there is a strong suggestion (Race, 1965) of an increased maternal age and therefore additional evidence that these $X^MX^MY$ types were due to maternal non-disjunction.

The frequency of formation of $OY$ zygotes by maternal non-disjunction might be expected to be equal to that of $X^PO$ ones. The $XO$ karyotype is reported to have a frequency of around 1 in 5000 at birth (MacLean *et al.* 1964), but is much more common in spontaneous abortions. Carr (1967) found that approximately 5% of 227 spontaneous abortions he had analysed were of the $XO$ type. On Race's calculations, one quarter of these would be $X^PO$, and one would thus expect an equal number (1·25% of all abortions) to be $OY$. Carr, in fact, recorded twelve $XO$ abortions but no $OY$ ones. On Race's calculations, only three of the latter would have been expected anyway, so there is no really significant evidence concerning the fate of $OY$ zygotes in man. However, if this deficiency of $OY$ types among spontaneous abortions is found in further analyses, they must, presumably, occur less frequently than expected, or, as in the mouse, die at a very early stage.

## SUMMARY

A study was made of reproductive performance and embryonic mortality in $XO$ and $XX$ females. In the stock used, the mean litter size of $XO$ females (4·46) was greatly below that of $XX$ ones (8·17). One series of pregnant females of both karyotypes was dissected after 15 days' gestation, and another series after $3\frac{1}{2}$ days' gestation. In the former, there was a significantly greater amount of embryonic mortality in $XO$ females both before implantation and at the small and large mole stages. By far the greater amount occurred before implantation. The data from dissections after $3\frac{1}{2}$ days' gestation concerned pre-implantation embryos, since normal embryos at this point are at the late morula or early blastocyst stage. The embryos from $XO$ females contained a large group of obviously and characteristically abnormal ones; they comprised 60/280 of the embryos from $XO$ females, compared with 4/189 of the $XX$ ones. They appeared to have developed abnormally from a very early stage, probably the two-cell stage, and were considered to represent the missing $OY$ class of zygotes. In addition, it was concluded that there was probably an abnormally low segregation of nullo-$X$ gametes from $XO$ females.

The author wishes to thank Dr M. F. Lyon for many helpful discussions, and Misses J. Butler, D. Humphreys, Y. Wakeling, M. Fuller and E. O'Grady, who have rendered technical assistance at various times.

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