A SEX DIFFERENCE IN LINKAGE IN RATS AND MICE

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In a series of experimental studies of heredity in mice and rats, extending over a number of years, DUNN, WACHTER and I thought we had obtained conclusive evidence that crossing over between linked genes occurs more frequently in females than in males; in other words, that the crossover percentage is higher in oögenesis than in spermatogenesis. DETLEFSEN (1925), who has also studied linkage in mice, challenges this conclusion, maintaining that "a significant sex difference occurs in only one set of experiments in mice" and one in rats, the latter being "the best and practically the only unobjectionable evidence of a case of sex difference in crossing over in mammals."

Now, it happens that in every single experiment in which the question of a possible sex difference has been studied, in DETLEFSEN'S own experiments quite as emphatically as in our own, the crossover percentage has always been found to be higher in females than in males, in both mice and rats. DETLEFSEN'S strange skepticism about the matter seems to rest on a peculiar conception of what is and what is not a statistically significant result.

PEARL and MINER (1914) have written on this subject with great clarity and have given us a useful table which shows that at no particular point, such as three times or five times the probable error, does a result suddenly become "significant." Its significance increases steadily as the limits of the probable error are transgressed. A result, which in particular cases scarcely exceeded the probable error, would be full of significance if it occurred *regularly*.

DETLEFSEN'S table 6 summarizes nine different experiments on linkage in mice and rats, some of them made in his laboratory, some in mine. All of these are backcross experiments, the most advantageous form of experiment for the measurement of linkage strength. No experiment includes less than a thousand young; one includes over 30,000. Every experiment shows a *higher percentage* of crossovers among the gametes produced by females than among those produced by males. The difference, as estimated by DETLEFSEN, ranges from 1.2 times the probable error to 7.3 times the probable error. A tenth experiment might be added

to the nine summarized in DETLEFSEN'S table 6, namely, an experiment on the linkage between albinism and red-eyed yellow in rats, wherein over 12,000 young were produced and the crossover percentage was found to be three times as great in females as in males.

It is surely not an accident that all these ten independent experiments have the same qualitative result. All show greater crossing over in females. If we disregard this uniformity and assume that it is due to chance alone, we ascribe to chance something against which the odds are enormous. An event for which the chances are even (greater crossing over in males or in females) would not come out *the same way in ten successive trials*, twice in a thousand times. The odds against it are 520 to 1, according to PEARL and MINER.

But it should be remembered, that even on DETLEFSEN'S conservatively low estimate, the excess of crossovers in oögenesis exceeds the probable error in every case,—in fact, is between once and twice the probable error in five experiments, between twice and three times the probable error in two experiments, exceeds five times the probable error in one experiment, and seven times in another. These are minimum figures, for I am not at all convinced that DETLEFSEN'S peculiar formula for calculating the probable error of a crossover percentage is superior to that commonly in use, which would give lower values for the probable error. DETLEFSEN rightly observes that where one of the two complementary crossover classes is incapable of identification, and is therefore assumed to be equal to the identified one, a possible error is introduced. He meets this by adopting a peculiar method of calculating the probable error. I have met it in a different way by basing the probable error on the half population. If one is not satisfied with this approximation, he can deal simply with the identified crossover class, which should be one-fourth of the whole population, if no linkage exists. If linkage is found, its strength will be measured by its departure from one-fourth of the population, and the probable error will be based on a 3 : 1 Mendelian ratio. Such procedure would be beyond criticism, since only actual observations would enter as data into the calculation and only approved formulae for calculation would be employed. Personally I am satisfied with the simple device of basing the probable error as ordinarily calculated on the half population. I am not willing to accept DETLEFSEN'S round-about method as an improvement on accepted usage.

DETLEFSEN admits that one case for greater crossing over in females is unobjectionable, the one involving pink-eyed yellow and albinism in rats, where the difference exceeds seven times the probable error. But there

are two other cases in rats involving the identically same genes in relation to a third gene, red-eyed yellow. The linkage map for females may be expressed thus:

$$\underline{C \quad 0.5 \quad R \qquad 20.5 \qquad P}$$
$$c \qquad\qquad 21.9 \qquad\qquad p$$

DETLEFSEN admits that the evidence is conclusive for greater crossing over in females in the map region between the genes *C* and *P*. But the gene *R* has been shown to lie between *C* and *P*. Therefore, the regions *CR* and *RP* together cover the entire chromosome region between *C* and *P*. If there is, in the region *CP*, greater crossing over in females than in males (as is admitted by DETLEFSEN), then, there must be more frequent crossing over in one or both of the constituent parts of *CP*, namely, *CR* and *RP*. It will accordingly have to be accepted as certain that either *CR* or *RP* is also "unobjectionably" established as "a case of sex difference in crossing over in mammals." The experimental evidence indicates that in *both* regions crossing over is more frequent in females than in males.

The experiments in mice, as to the relative frequency of crossing over in the two sexes, all have to do with one and the same pair of genes, *C* and *P*, which are possibly homologous with the genes similarly designated in rats, and certainly have a similar somatic expression as well as similar linkage relations. DETLEFSEN presents data based on his own observations, showing that, in a total of 2544 backcross young, female parents gave crossovers more often than males, the difference being 5.8 times the probable error. This, in his summary, he designates a "significant sex difference." If the case is proved by his own experiments, it is certainly not disproved by the previously published observations of others, who obtained the same qualitative results from data several times as great in amount as his own. DETLEFSEN fails to recognize the force of cumulative evidence. I think, accordingly, that the case is fully established for more frequent crossing over in females than in males, at least for that portion of a chromosome which lies between the genes *C* and *P*, both in rats and in mice. Why egg cells and sperm cells show these consistent differences in behavior at maturation remains to be demonstrated.

LITERATURE CITED

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