

one fifth of the total calories) but with whole wheat instead of white read or patent flour, young were successfully suckled (though at the cost of considerable loss of weight on the part of the mother) and are growing at somewhat less than the average rate.

When about two fifths of the total calories were supplied by milk and the rest by whole wheat, the mother has suckled the young without undue loss of weight and the young have made a fully normal rate of growth.

When the market milk used has been replaced by dried milk, or when it has been incorporated into the bread in bread-making and, therefore, subjected to the heating involved in the baking of the bread, there has been no evidence of any serious destruction of either "fat-soluble A" or "water-soluble B." Since the experiments were made upon rats, they would, of course, throw little if any light upon the destruction of the antiscorbutic vitamine. We plan to continue the study of the effects of heating upon the vitamines in some of the staple articles of food.

5 (1465)

The rate of change of hereditary factors in *Drosophila*.

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A knowledge of the rate at which hereditary changes of various sorts occur is the necessary groundwork for an adequate understanding of evolution. The wide recognition given to this fact is attested to by the vast amount of literature on the subject of "variation," but, with our new exact knowledge of the Mendelian and chromosomal method of inheritance of the so-called "variations," it is evident that this literature has very little bearing on the real question of how often changes in the hereditary factors, *i.e.*, mutations, actually occur: for the breeding procedures used in the experiments there considered were not of the type necessary for ferretting out the new mutant factors as they arise, and for distinguishing between them and the apparent variations

caused by the sorting out of old mutant factors into new combinations. There is, to be sure, enough work to show that the real mutations are "rare"—whatever that term may mean; but, so far as an approximate quantitative determination of the rate of factor change is concerned, it is not possible, from the published work, to determine even its general order of magnitude. Some special scheme of crossing is required for this purpose.

In the present series of experiments with *Drosophila*, the X chromosome was chosen as the most convenient one for the detection of mutation, since every hereditary factor in either of the X chromosomes of the female fly stand revealed in the characters of one half of her male offspring, no matter what their father was. Thus, if the female has a new mutated factor in one of her X chromosomes, even though she does not usually show that factor herself, and even though her mate does not contain it, nevertheless one half of her sons are bound to show it and the mutation will thus be recognized. There is reason to believe that by far the commonest type of mutation is that which gives rise to a lethal factor—which kills the organisms containing it—and such lethal factors, also, in the X chromosome of a female, would be revealed; in this case, by the fact that half the male offspring, receiving it, would die before hatching. There would thus be half as many sons hatched as daughters, giving a sex ratio of 2 ♀ : 1 ♂, instead of 1 ♀ : 1 ♂, the usual ratio. In the first set of experiments these lethal factors were looked for primarily, by making a count of the sex ratios.

As a preliminary measure, about 90 females were bred, and the sex ratios of their progeny counted. Those families which gave a lethal, *i.e.*, 2:1, sex ratio (there were three of these) were then discarded, since there was no way of knowing, in this preliminary cross, whether these lethals had just arisen by mutation or were of ancient origin. Females from the normal families (with 1:1 sex ratio) were bred, however, since any lethal later discovered in the descendants of these flies must be due to a really new mutation, inasmuch as the ancestors had been certified as normal. It was necessary, moreover, in selecting females for breeding the next generation, not to breed many females from the same family, but to choose them from as many separate families

as possible, in order to be sure that any mutations that might be discovered later had arisen separately, and were not merely sister representatives of one original mutation. By continuing this method of breeding from separate families over five or more generations after the preliminary tests, the sex ratios in 385 families were counted. Thirteen of these were found to be 2:1 ratios; this is a proportion of one new lethal mutant among each thirty females that are bred. This figure is of a far higher magnitude than any which had been anticipated. It should be noted that at the same time as all these lethals arose, no mutations causing ordinary visible character variations were observed.

The correctness of classification of most of the thirteen lethals was verified by further breeding tests, but there were a few doubtful cases, and it was realized that ratios intermediate between 1:1 and 2:1 are sometimes brought about in other ways. Although the possible error due to these cases was not enough to change the order of magnitude of the frequency found, a new set of experiments was undertaken in which a still more definite test of lethal factors than the sex ratio was used—namely, the test of linkage to known factors in the X chromosome. The breeding procedure—having preliminary tests, breeding from many separate families, etc.—was the same as before, but instead of using pure wild type flies for the work, the following cross was made in each generation:

tion: $\frac{w^e v f}{W V F} \text{♀} \times w^e v f \text{♂}$. In this case a lethal arising in either

X chromosome makes itself known not only by the 2:1 sex ratio, but by the practically total absence of all males containing factors on both sides of the lethal. By noting whether any expected class of males was absent, it could thus be determined whether a lethal was present, and, if so, approximately where it was located in the chromosome. 1,062 families were examined in this way, after the preliminary tests, and twenty lethals were found—a ratio of one in fifty-three. Enough work has been done on them thus far to know that they occurred in at least ten different loci scattered along the X chromosome—but this is a bare minimum. Four of the lethals (perhaps five) are more strictly speaking “semi-lethals,” as they occasionally allow the male possessing them to live (and then produce some curious morphological effects in him)

but lethal mutations are so much more frequent than the type of visible character variation ordinarily dealt with, that none of the latter were observed in the whole experiment.

The above figure of 20 in 1,062 has a probable error due to chance of about ± 3 in 1,062. There can, therefore, be no doubt about the correctness of the order of magnitude of the ratio 1:53, so far as any error caused by random sampling is concerned. The ratio 1:53 is, however, a composite result, for the families were kept in two main lots, one at about 66° F., the other at about 80°. The 445 grown at the lower temperature produced five lethals, or one in ninety; the 517 at the higher temperature produced 13 lethals, or one in forty. The other two were new lethals which occurred in the 100 bottles kept at room temperature, in which the lethals found in the two main series were being tested out. In this connection, it should be pointed out that the high ratio of one in thirty observed in the earlier experiment was obtained in bottles kept at room temperature in the warm climate of southern Texas. Although the absolute numbers of lethals are small, the difference between the two series in the later experiment is probably statistically significant,—at least, it may be calculated that if the lots had really been similar, the chances would have been about twenty to one against a difference of this magnitude occurring between figures of the given size. Taking the figures at their face value, we should obtain Q_{10} for mutation between 2 and 3, as is usual for chemical reactions.

If we accept the one in fifty-three ratio as representing the average frequency for the X chromosome, and if, as there is reason to believe, mutation occurs at the same rate in the other chromosomes as in the X chromosome, then, since the X's form about one fourth of the entire chromosome mass, we may figure that about one fly in every thirteen has a new lethal mutation in some chromosome or other. It is evident that, at this rate, without natural selection to weed out the "unfit," the race would soon become filled with lethal factors. For the X chromosome alone, since each female has two X's, and one female in fifty has a new lethal, we may figure that one X chromosome in every 100 contains a lethal factor just arisen in the present generation. Or, to put the matter differently, each X chromosome would, on the

average, tend to contain one lethal factor after 100 generations—which means about four years in *Drosophila*. The rate of change for the X in *Drosophila* is thus about one detectable mutation in four years. This immediately shows us that *Drosophila* must have a different rate from some other organisms—man for example—for if the X chromosome of man mutated at anything like a similar rate, all the X chromosomes in a female would contain several lethal factors by the time she was ready to reproduce, and none of her sons would be viable.

The rate of one mutation in four years is the rate for the whole chromosome. It is of greater interest to know the rate for the individual factors. There is good reason to believe that there are at least 500 factors in the X chromosome of *Drosophila*—probably many times that number. But, taking this undoubtedly much too low minimum figure, it is easy to see that, if 500 factors show only one mutation in four years, each individual factor must on the average show a change in its composition only once in 2,000 years. (Yet this is in the mutable *Drosophila*.) It will be interesting to observe the difference in mutation rate in different organisms and under different conditions.

6 (1466)

The influence of lactic acid upon the metabolism of the dog.¹

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Lactic acid, when given to a dog, causes the same increase in metabolism that is noticed when a similar amount of alanin is administered. It was also noted that the metabolism was increased after giving 500 c.c. of water in which there was 2.5 c.c. of Liebig's extract of beef, whereas the administration of 150 c.c. of water had no influence whatever. When a large quantity of water was given about 100 c.c. per hour were eliminated in the urine. This indicates that for the transport of a large volume of fluid through the circulation increased energy is needed.

¹ A brief report of this work was also published in the *Compt. rendus de l'academie des sciences*, 1919, 168, No. 20, 1012.