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EVOLUTION IN SEXUAL AND ASEXUAL POPULATIONS*

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It has often been said that sexual reproduction is advantageous because of the enormous number of genotypes that can be produced by a recombination of a relatively small number of genes (for example, *Issues in Evolution*, p. 114–115). The number of potential combinations is indeed great, but the number produced in any single generation is limited by the population size, and gene combinations are broken up by recombination just as effectively as they are produced by it. Furthermore, for a given amount of variability, the efficiency of selection is greater in an asexual population than in one with free recombination since the rate is measured by the total genotypic variance rather than by just the additive component thereof.

On the other hand, unless new mutations occur, an asexual population has a selection limit determined by the best existing genotype, whereas directional selection in a sexual population can progress far beyond the initial extreme, as has been demonstrated by selection experiments. The purpose of this article is to compare sexual and asexual systems as to the rate at which favorable gene combinations can be incorporated into the population, considering the effect of gene interaction, mutation rate, population size, and magnitude of gene effect. Most of the material is not new, but the various ideas have not been brought together in this context and we have introduced some refinements.

HISTORICAL

The question was first discussed from the viewpoint in which we are here interested by Fisher (1930) and Muller (1932). We shall follow mainly the argument given by Muller.

In an asexual population, two beneficial mutants can be incorporated into the population only if the second occurs in a descendant of the individual in which the first occurred. On the other hand, in a sexual population the various mutants can get into the same individual by recombination. Only if the mutation rate were so low or the population so small that each mutant became established before another favorable mutant occurred would the two systems be equivalent.

The situation is illustrated in figure 1, adapted from Muller's original drawings. The three mutants, A, B, and C are all beneficial. In the asexual

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population when all three arise at approximately the same time only one can persist. In figure 1, A is better adapted than B or C (or perhaps luckier in happening to occur in an individual that for other reasons was more fit than those in which B and C arose) so that A is eventually incorporated. B is incorporated only after it occurs in an individual that already carries A, and C only in an individual that already carries both A and B. In the sexual system, on the other hand, all three mutants are incorporated approximately as fast as any one of them is in the asexual system.

The lower part of the figure shows a small population. Here the favorable mutants are so infrequent that one has time to be incorporated before another occurs. Thus there is no advantage to the sexual system.

In general, several favorable mutants arising at the same time can all be incorporated in a sexual system whereas only one can be without recombination. There is, of course, a high probability of random loss of even a favorable mutation in the first few generations after its occurrence. This problem has been solved by Fisher (1930), but since the result is essentially the same in an asexual and sexual system it is irrelevant to the present discussion.

Muller's verbal argument was made quantitative in later papers (1958, 1964). We have improved Muller's calculations slightly by taking into consideration the decelerating rate of increase in the frequency of a favorable mutant as it becomes common.

MATHEMATICAL FORMULATION

Consider first a population without recombination. We ignore the large majority of mutants that are unfavorable, for these are eliminated and thus are not incorporated into the population. Our interest is only in mutants that are favorable.

Let N = the population number

U = the total rate of occurrence per individual per generation of favorable mutations at all loci

g = the average number of generations between the occurrence of a favorable mutation and the occurrence of another favorable mutation in a descendant of the first

$x = 1/U$ = the number of individuals such that on the average one favorable mutation will occur

s = the average selective advantage of a favorable mutant

Thus, g is the number of generations required for the cumulative number of descendants of a mutant to equal x, this being a number of such size that on the average one mutant will have occurred. Letting p_i be the proportion of individuals carrying the mutant gene in the i^{th} generation, g is given by

$$x = Np_1 + Np_2 + \ldots + Np_g \qquad (1)$$

the summation being continued until there have been enough generations, g, to make the total number of mutant individuals equal to x. We assume that

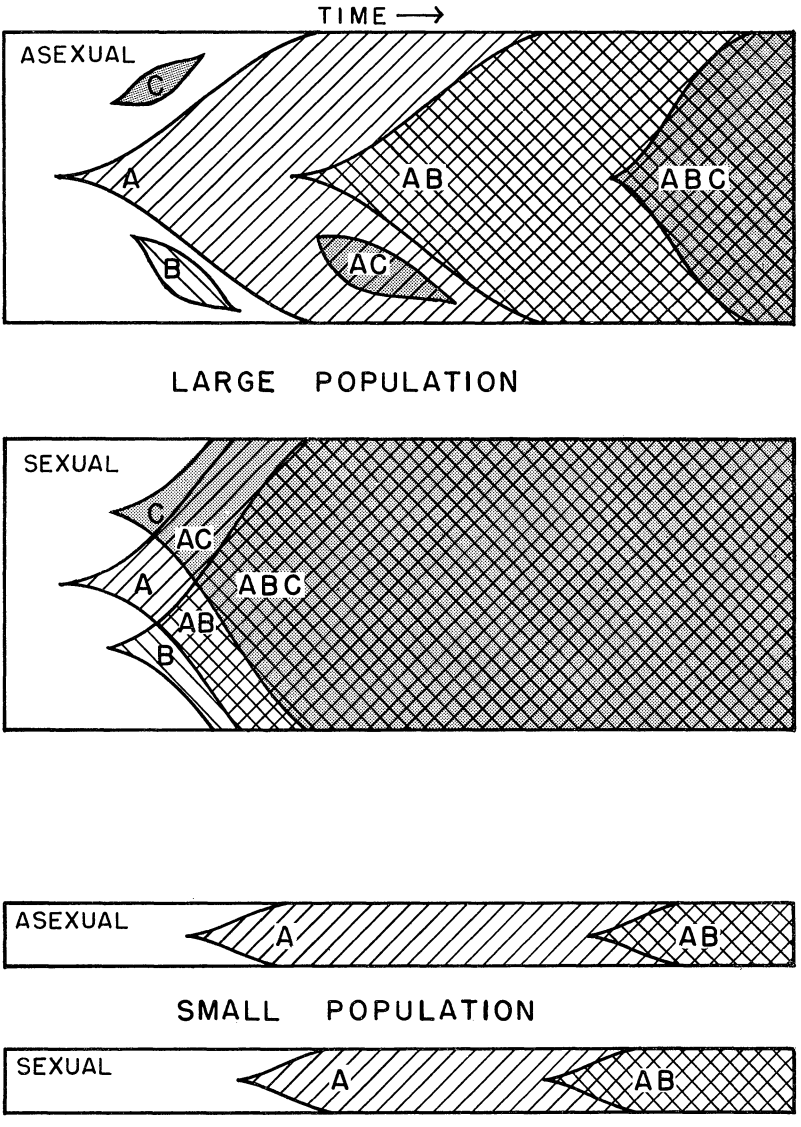

FIGURE 1. Evolution in sexual and asexual populations. The hatched and shaded areas show the increased number of mutant individuals following the occurrence of a favorable mutation. The abscissa is time. Modified from Muller (1932).

s is small, and therefore that p changes very slowly so that it is appropriate to replace addition by integration. This leads to

$$x = \int_0^g Np\, dt \qquad (2)$$

In the absence of recombination, p follows the logistic curve

$$p = \frac{p_0}{p_0 + (1 - p_0)e^{-st}} \tag{3}$$

where p_0 is the initial proportion of mutants, as first shown by Haldane (1924). If we start with a single mutant, $p_0 = 1/N$, and (3) becomes

$$p = \frac{1}{1 + (N - 1)e^{-st}} \tag{4}$$

Substituting this for p in (2) and integrating, we obtain

$$x = \frac{N}{s} \ln \frac{N - 1 + e^{sg}}{N}$$

or, rewriting and recalling that $x = 1/U$,

$$g = \frac{1}{s} \ln [N(e^{s/UN} - 1) + 1] \tag{5}$$

In an asexual population one new mutant that will eventually be incorporated into the population arises every g generations. On the other hand, if reproduction is sexual, all the mutants that occur during this interval can eventually be incorporated. The number of mutants that arise per generation is NU, or in g generations, NUg. Thus the ratio of incorporated mutations in a sexual population to that in an asexual population is $NUg : 1$, or

$$\frac{NU}{s} \ln [N(e^{s/UN} - 1) + 1] \tag{6}$$

The favorable genes need not be mutants that are occurring for the first time. They may, for example, be genes brought in by immigrants or previously harmful mutants that have become beneficial because of a changed environment and already exist in the population at low frequencies.

Some numerical results are shown in table 1. For example, if the selective advantage of a favorable mutation is 0.01 and the total rate of occur-

TABLE 1

The relative rate of incorporation of new mutations into the population with and without recombination

$\frac{U}{s}$	N						
	10^3	10^4	10^5	10^6	10^7	10^8	10^9
10^{-7}	1.0007	1.01	1.12	2.38	16.7	162	1.6×10^3
10^{-6}	1.007	1.09	2.15	14.4	139	1.4×10^3	1.4×10^4
10^{-5}	1.07	1.92	12.1	116	1.2×10^3	1.2×10^4	1.2×10^5
10^{-4}	1.69	9.75	92.6	922	9.2×10^3	9.2×10^4	9.2×10^5
10^{-3}	7.50	69.6	691	6.9×10^3	6.9×10^4	6.9×10^5	6.9×10^6
10^{-2}	46.7	462	4.6×10^3	4.6×10^4	4.6×10^5	4.6×10^6	4.6×10^7
10^{-1}	240	2.4×10^3	2.4×10^4	2.4×10^5	2.4×10^6	2.4×10^7	2.4×10^8

The ratio of the two rates is given in the body of the table. N is the population number, U is the total rate of occurrence of all favorable mutants, and s is the average selective advantage of such mutants.

rence of such mutations is 10^{-8}, the ratio U/s is 10^{-6}. As can be seen from the table, the advantage of recombination is negligible in a population of 10^3, but the rate ratio is 2.15 in a population of 10^5 and 1380 in a population of 10^8. If the selective advantage is smaller, the advantage of a sexual system is greater. Likewise, with a higher mutation rate the advantage is greater.

We have discussed mutants that were beneficial at the time of their first occurrence. Similar considerations are involved when a previously deleterious mutant type is rendered beneficial, such as by a change in the environment.

We do not intend to imply that the very high values in the lower right part of the table are realistic. Doubtless other factors become limiting. But the table does show the general trend and emphasizes the enormous advantage of an evolutionary system with recombination.

It is likely that the probability of a mutant being favorable is greater when the effect of the mutant is small. Thus, with small s, U tends to become larger. Since increasing U and decreasing s both have the effect of enhancing the advantage of recombination, the more that evolution proceeds by small micromutational steps, the greater the advantage of sexuality.

It is interesting that U and s enter the formula always in the form U/s, and never separately. This exact reciprocal dependence is understandable; for with slow selection the number of generations required for a given gene frequency change is inversely proportional to s (Haldane, 1924). Thus a reduction in s means that proportionately more mutations will occur during the time that one is being incorporated.

Table 1 also shows that the advantage of recombination increases with an increase in the population size. In fact, with large populations the advantage is nearly proportional to the population number.

To summarize: The advantage of a reproductive system that permits free recombination is greatest for the incorporation of mutant genes with individually small effects, occurring at relatively high rates, and in a large population.

THE EFFECT OF GENE INTERACTION

So far we have been concerned only with mutant genes that are beneficial. We have also assumed that the combination of two mutant genes is more beneficial than either by itself; otherwise there would be no advantage of incorporating the second one.

The situation is quite different with some kinds of gene interaction. Where two or more mutants are individually harmful, but beneficial in combination, sexual reproduction may actually be disadvantageous.

The essential situation is clear with a haploid model, so we shall consider this simpler case. Suppose that the existing wild type in the population is genotype ab. The mutant types Ab and aB have fitnesses that, relative to ab, are reduced by the proportions s_1 and s_2. On the other hand, we assume that the double mutant has an enhanced fitness, greater

than ab by a proportion t. The quantities s_1, s_2, and t are all taken to be positive.

Both single mutant types, Ab and aB, will be found in low frequency in the population, their exact numbers being determined by the ratio of their rate of occurrence by mutation to their rate of elimination by selection. The double mutant, AB, will occasionally arise, but infrequently.

However, once such a double mutant does arise, its fate will be quite different in a population with and without recombination. Ignoring the question of chance elimination during the early generations (which, as we said earlier, is not significantly different in the two kinds of populations), an AB double mutant in an asexual population will increase and eventually be incorporated at a rate determined by the value of t.

On the other hand, in a sexual population, an AB individual will ordinarily mate with an ab genotype, in which case the progeny will consist of all four genotypes in proportions depending on the amount of recombination. Only if the fitness of the AB type is great enough to compensate for the loss of AB types through recombination will this genotype increase. The relationships can be set forth as follows:

Genotype	ab	Ab	aB	AB
Relative fitness, w	1	$1 - s_1$	$1 - s_2$	$1 + t$
Frequency	$(1 - x)(1 - y)$	$x(1 - y)$	$(1 - x)y$	xy

$$\bar{w} = 1 - s_1x(1 - y) - s_2(1 - x)y + txy$$

$$\frac{\partial w}{\partial x} = y(s_1 + s_2 + t) - s_1$$

$$\frac{\partial w}{\partial y} = x(s_1 + s_2 + t) - s_2$$

These relationships assume that the two loci change independently under the action of natural selection, which is not strictly true unless $(1 + t) = (1 - s_1)(1 - s_2)$; but the formulae are approximately correct for unlinked loci when s_1, s_2, and t are small.

Gene A will increase when $\partial \bar{w}/\partial x$ is positive and decrease when this is negative. Therefore there is an unstable equilibrium at $y = s_1/(s_1 + s_2 + t)$. Below this value of y, x will decrease; above this value, x will increase. The situation is symmetrical for x and y by interchanging s_1 and s_2. Thus there is no way for the frequency of the AB type to increase unless it somehow gets past the equilibrium point. This problem was discussed extensively by Haldane (1931).

The formulae are identical in a diploid population with complete dominance, on replacement of x by p^2 and y by q^2, where p and q are the frequencies of the recessive alleles at the two loci (see Wright, 1959, p. 442).

The situation is the familiar bottleneck frequently discussed by Wright (1931 and later). In his metaphor, the population is at one adaptive peak composed mainly of ab genotypes and there is no way for it to go to the

higher peak composed mainly of *AB* genotypes without passing through a valley where *Ab* and *aB* types predominate.

There are several ways in which a sexual population might conceivably solve this problem. Some populations have several generations of asexual reproduction intervening between sexual generations. Another possibility would be strong assortative mating among the *AB* types; but the *a priori* probability of the genes that gave the increased fitness also producing the right type of mating behavior seems small indeed. Another possibility is random drift across the adaptive valley because of variable conditions or small effective population number, but this, as Wright (1931 and later) has emphasized, would lead to a considerable lowering of fitness (see also Kimura, Maruyama, and Crow, 1963). Furthermore, Kimura (unpublished) has shown that the probability of joint fixation of two genes such as are being discussed here is very small, even in small populations. For example, in a population of effective size $N = 1000$, the single mutants with 1 per cent selective disadvantage and the double mutant with 5 per cent advantage, the probability of joint fixation is about $2.5\, p_0 q_0 \times 10^{-6}$, where p_0 and q_0 are the initial frequencies of the single mutants. The corresponding probability for completely neutral genes is $p_0 q_0$. Note that $p_0\, q_0$ is a very small quantity. For individually deleterious but collectively advantageous mutant genes to have a reasonably high probability of joint fixation, the population must be so small that the inbreeding effect causes a serious effect on the viability.

In general, sexual reproduction can be a distinct disadvantage if evolution progresses mainly by putting together groups of individually deleterious, but collectively beneficial mutations. It seems to us that if this type of gene action were the limiting factor in evolution at the time sexual reproduction first evolved, sexual recombination might never have been "invented."

THE EFFECT OF LINKAGE

Two closely linked genes in a sexual organism can be quite similar to genes in an asexual organism as far as their relations to each other are concerned, for they may stay together for a great length of time. If r is the recombination frequency between two linked genes, they will stay together $1/r$ generations on the average before being separated by crossing over. This can easily be seen by noting that the probability that they will remain together g generations and separate in the next is $(1 - r)^g r$. Then the average number of generations during which they remain together is

$$\bar{g} = r + 2(1 - r)r + 3(1 - r)^2 r + 4(1 - r)^3 r + \ldots$$

$$= r(1 + 2x + 3x^2 + 4x^3 + \ldots$$

where $x = 1 - r$. But $1 + 2x + 3x^2 + \ldots$ is the derivative of $1 + x + x^2 + x^3 + \ldots = 1/(1 - x)$. Therefore

$$\bar{g} = r \frac{d}{dx}\left(\frac{1}{1 - x}\right) = \frac{1}{r}$$

Thus, two genes linked together with a recombination value of 0.1 per cent would remain linked on the average for 1000 generations before separating.

Consider again the earlier model where the four haploid genotypes, *ab*, *Ab*, *aB*, and *AB* have fitnesses in the ratio $1 : 1 - s_1 : 1 - s_2 : 1 + t$, and assume that the amount of recombination between the loci is r. If the rare *AB* individual mates with an *ab* type, which will usually be the case, the proportion of *AB* progeny will be reduced by a fraction r because of recombination. However, the *AB* type will increase from these matings if the extra fitness of the *AB* type is enough to more than compensate for this; that is, if $(1 + t)(1 - r) > 1$, or $t > r/(1 - r)$.

The conditions for increase of *AB* genotypes in general are a little less stringent because some *AB* matings are with *AB*, *aB*, or *Ab* types and in these there is no effect of crossing over. Furthermore, *AB* types are being added by recombination from $Ab \times aB$ matings. Finally, $\bar{w}$, the average fitness is not 1, but slightly less. However, these do not change the direction of the inequality, so we can still say that a sufficient condition for the double mutant type to increase is $t > r/(1 - r)$. This is also the condition for increase in diploids, where t is now the advantage of the double heterozygote over the prevailing type (Bodmer and Parsons, 1962, p. 73).

In Wright's metaphor, the effect of linkage is to raise the valley between the two adaptive peaks and with extremely close linkage to provide a direct bridge.

For closely linked genes where r is small, the *AB* type will increase and ultimately become fixed if $t > r$. Thus, the closer the linkage, the greater the tendency to build up coadapted complexes—provided, of course, that such closely linked, mutually beneficial mutants occur. The extreme example is the high degree of functional interdependence within a cistron.

COADAPTATION

We have seen that asexual organisms are in a better position than sexual species to build up coadapted complexes, except under conditions of close linkage. In an asexual population the mutants accumulate in a certain sequence; first we have mutant *A*, then *AB*, then *ABC*, and so on. In this case the effect of *B* in the absence of *A* is irrelevant; it may be beneficial or harmful, or simply be a modifier that is neutral in the absence of *A*. Of all the mutants that arise in the species after *A* has been incorporated, the one that is most likely to persist is the one that in the presence of *A* gives the greatest fitness. Therefore, there will be a tendency for combinations to be mutually coadapted, and these genes may be less beneficial or even harmful in other combinations (Cavalli and Maccacaro, 1952). That is to say, they may well be what Mayr has called "narrow specialists."

In a sexual population, on the other hand, genes *A* and *B* are likely to be incorporated only if they are beneficial both individually and in combination. The type of gene that is most efficiently selected in a sexual population is one that is beneficial in combination with a large number of genes. We can only guess about the *a priori* distribution of gene interactions; but it

is clear that in a population with free recombination the "good mixers" (that is, those having a large additive component) will be most efficiently selected.

The best opportunity to test these possibilities would be populations exposed to an entirely new environment. Drug resistance in bacteria and insecticide resistance in insects offer such a possibility. Chloramphenicol resistance in *Escherichia coli* is polygenic and has been analyzed by Cavalli and Maccacaro (1952). During the selection for resistance the reproduction was asexual, though recombination was used later for analyzing the genetic basis of the resistance. Recombinants between resistant and susceptible strains were skewed in the direction of greater susceptibility, as were crosses between different resistant strains. The results, therefore, suggest considerable coadaptation with complementary action of the genes accumulated during the selection process.

DDT resistance in Drosophila is also polygenic and has been analyzed genetically (Crow, 1957; King and Somme, 1958). Analysis of variance of the contribution of various chromosomes to the resistance showed an almost complete additivity, as would be expected in a sexual species according to the view we have been discussing. Thus, at least in these two cases, there is good agreement with what our theoretical speculations would predict.

We should emphasize that the genetic variability in sexual populations that have had a long history of selection for the traits under consideration may not have a large additive component. The genes that act additively may already have been incorporated into the population so that those that remain in unfixed condition are the ones that are not responsive to selection; that is, they are genes with complex interactions. Thus it is not surprising if, in a stable natural environment or in an artificial population where selection has been practiced for a long time, the nonadditive components of variance predominate.

HAPLOIDY VERSUS DIPLOIDY

The evolutionary advantages of recombination can be obtained in haploid as well as diploid species. Yet diploidy is the rule in a great many complex organisms and there must have been a regular trend of evolution from haploidy to diploidy.

At first glance it would appear that there is an obvious advantage of diploidy in that dominant alleles from one haploid set can prevent the deleterious effects of harmful recessive alleles in the other. However, when equilibrium is reached the situation is roughly the same in a diploid as in a haploid. In a haploid species the mutation load will equal the total mutation rate when equilibrium is reached. With diploidy the load will be somewhere between this value and twice this value, depending on the level of dominance. With any substantial heterozygous effect of deleterious recessive genes, the mutation load is nearly twice the mutation rate (Haldane, 1937; Kimura, 1961). So the effect of diploidy is generally to double the

mutation load by doubling the number of genes. From this standpoint diploidy certainly offers no advantages, only disadvantages.

However, when the population has reached equilibrium as a haploid, a change to diploidy offers an immediate advantage (Muller, 1932). To be sure, when the population reaches a new diploid equilibrium the advantage is lost; but by then there is no turning back, for a return to haploidy would greatly increase the load by uncovering deleterious recessives. Thus, it is easy to see how diploidy might evolve from haploidy, even if the population did not gain any permanent benefit therefrom.

On the other hand, there are some other possible advantages of diploidy, of which we shall mention two. One that has frequently been suggested is the possibility of overdominance. To the extent that the heterozygote is fitter than either homozygote at some loci there is an advantage of diploidy, provided the average fitness of the diploid population is enough greater than the haploid to compensate for the greater mutation load.

A second possible advantage of diploidy is the protection it affords against the effects of somatic mutation, a possibility that also occurred independently to Muller. The zygote in a diploid species or the post-meiotic cell from which the organism develops in a haploid species might have approximately the same fitness at equilibrium, but the effects of somatic mutation would be quite different. If the soma were large and complicated, as in higher plants and especially animals, a diploid soma might provide a significant protection against the effects of recessive mutations in critical organs.

THE EVOLUTION OF SEXUALITY

The development of sexual reproduction confers no immediate advantage on the individual in which this occurs. In fact, the result is far more likely to be deleterious. The benefit is only to the descendants, perhaps quite remote, and to the population as a whole. Thus, it seems likely that the selective mechanism by which recombination was established was intergroup selection. Fisher (1930) goes so far as to suggest that sexuality may be the only character that evolved for species rather than for individual advantage.

On the other hand, despite the great evolutionary advantages of sexual reproduction, there are immediate advantages in a return to asexual reproduction. An advantageous type whose recombinant progeny were disadvantageous would have an advantage for its immediate descendants by developing an asexual mode of reproduction, other things being equal. In diploids there is the additional advantage of fixing heterotic combinations.

This all accords with the conventional belief that sexuality developed very early in the evolution of living forms and is therefore found in all major groups; but that numerous independent retrogressions to vegetative reproduction continue to occur, conferring an immediate advantage but a long time evolutionary disadvantage.

SUMMARY

In an asexual population two favorable mutants can be incorporated into the population only if one occurs in a descendant of the individual in which the other occurred. In a sexual population both mutants can be incorporated through recombination. A mathematical formulation is given of the relative rates of incorporation of the new mutations with and without recombination. Recombination is of the greatest advantage when the double mutant is more advantageous than either single mutant, when the mutant effects are small, when mutations occur with high frequency, and when the population is large.

On the other hand, for the incorporation of individually deleterious but collectively beneficial mutations, recombination can be disadvantageous. Close linkage has effects similar to those of asexual reproduction. Experimental data on DDT resistance in Drosophila and chloramphenicol resistance in bacteria are cited showing greater development of coadaptation in an asexual system.

The evolution of diploidy from haploidy confers an immediate reduction in the mutation load by concealment of deleterious recessives, but this advantage is lost once a new equilibrium is reached. Thus the development of diploidy may be because of an immediate advantage rather than because of any permanent benefit. On the other hand, there are other possible advantages of diploidy, such as heterosis and protection from somatic mutations.

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