

SEX IN BACTERIA AND VIRUSES

THE manifestations of sex are known to all, but its biological meaning is clear to few since it can only be understood in terms of evolution. Evolution by natural selection takes place because there are present in natural populations large numbers of different combinations of hereditary characters, some of which have greater chance than others of survival and propagation.

New characters arise by mutations, that is, by rare and unpredictable changes of determinants of heredity, or "genes." One mutation seldom gives rise to an individual better fit for life than the original. Favorable mutations do, however, arise, if only with low frequency. How will they be made use of for the survival and improvement of the species? As pointed out by Muller in 1932, in asexual organisms, that is, in organisms reproducing from one parent only, a mutant gene will be tested for its survival value only in combination with the other genes already

present in the line of descent in which it has arisen. If several such favorable mutations arise in different lines, they will compete with one another and tend to crowd each other out. Combinations of several favorable mutant genes can only be formed if the mutations happen to occur successively within the same line of descent, necessarily a very rare event. Much good material for evolution will thus be wasted.

Sexuality prevents or at least greatly reduces this waste. In the process of sexual, biparental reproduction the genes of one individual have at each generation a chance to be reshuffled with those of another individual, producing a variety of offspring types. In natural populations, these are generally all more or less different from one another and from their parents. Reshuffling occurs because the genes are carried in chromosomes, nucleoprotein threads present in various number of pairs in the nucleus of each cell, each

member of a pair being contributed by one parent. The variety of combinations, arising from the random assortment of the members of each chromosome pair, is further increased by exchanges of parts between chromosomes of each pair within the parents (crossing-over) in the course of the formation of the sexual cells, the sperm and the egg. As a consequence, no set of genes of a grandchild is identical with any one of those found in his four grandparents.

Moreover, the very increase in the total number of gene combinations resulting from sexual reproduction is an advantage for the species: if environmental conditions vary, gene combinations that might previously have been unfavorable may prove useful in the new exceptional situation and increase the chances of survival of the species.

Finally, mutant genes that would be a handicap in one combination might prove actually advantageous in other combinations. Sexuality, so to speak, gives them a chance. In Muller's words, "sexuality, through recombination, is a means for making the fullest use of the possibilities of gene mutations."

Since sex is such a powerful factor of survival, evolutionists have often wondered how organisms like bacteria manage to survive at all if they are, as is generally believed, completely sexless and only reproduce by repeated fissions. As pointed out before, the number of available genetic combinations will be quite limited, and the chance for the appearance of more favorable ones rather small. In part, this limitation might be compensated for by the large size of bacterial populations, which allows the occurrence of even rare mutations, so that a number of different combinations might actually be formed within one hereditary line. In the long run, however, bacteria would probably be better off if they had some kind of sex.

In 1946 Lederberg and Tatum announced the results of experiments strongly suggesting sexlike phenomena in bacteria. From one original parent strain of *Escherichia coli*, a common intestinal bacterium, capable of manufacturing all its protoplasmic materials and of growing in a mixture of very simple chemicals (sugar, ammonia, and inorganic salts), these authors first isolated several

"nutritionally deficient" mutants, that is, mutants unable to manufacture some essential chemical needed for their growth. These mutants are easily obtained by irradiation of the parent strain with ultraviolet light. A mutant can only grow if the chemical or chemicals which it is unable to produce is supplied in the culture medium. Indirect evidence, mainly the analogy with the situation in the mold *Neurospora*, had already suggested that each nutritional deficiency is tied up with a modification of one gene.

Let us suppose that the original strain is capable of synthesizing the four substances A, B, C, and D. A mutant $A-B-C+D+$ (deficient for compounds A and B as a result of two mutations, but capable of manufacturing C and D) is grown together with another double mutant with reverse synthetic abilities, $A+B+C-D-$ in a medium containing plenty of all four substances A, B, C, and D. If the cells of the two mutants, while growing together, undergo some type of sexual fusion, exchanges of genetic determinants might occur. Among such exchanges there may be some leading to the formation of cells $A+B+C+D+$. These would be nutritionally identical with the original strain (prototrophic, from *protos*, "original," and *trophe*, "nutrition") and, like the latter, easily distinguishable because able to grow in the absence of all four substances A, B, C, and D.

Strains with at least two deficiencies had to be used to eliminate the possibility of prototrophic organisms being produced by one mutation. The chance of two mutations occurring in the same line is low enough to be completely negligible.

Lederberg and Tatum actually found prototrophic cells present in mixed cultures of a number of different mutants with several deficiencies and interpreted them as proof that genetic recombination had occurred. This conclusion was supported by the fact that, when strains differing by three or more mutations were grown together, there appeared in the mixed cultures some cells that showed all possible combinations of the characters of the two parents, indicating that the transfer could involve different numbers of genetic determinants.

The mechanism of fusion and gene ex-

change in bacteria is still unknown, and the results may need careful checking before their interpretation as genetic recombinations can be considered as proved beyond doubt. It seems likely that, if sexual phenomena like these are actually proved to occur at all in bacteria, they will be found to be frequent enough to play an important role in bacterial evolution. It would, in fact, seem strange that a mechanism so useful from the evolutionary standpoint, once arisen in a group of organisms, might remain confined to just a few strains of bacteria. The very fact of having been found in one of the few strains carefully tested would suggest its widespread occurrence.

If bacteria may have sex, what about the filterable viruses? This might seem to be asking too much indeed. After all, viruses are ultramicroscopic entities reproducing inside living cells and often thought to be hardly more than nucleoprotein molecules. And yet we know that some of them undergo changes very similar to sex in their genetic consequences. This was discovered in the course of work on bacteriophages, the viruses that reproduce inside bacteria somewhat as the virus of infantile paralysis reproduces in the cells of the spinal cord of man, or the virus of influenza in the lungs.

Bacteriophages can undergo a number of different and independent mutations, and this writer and Hershey have in recent years described a number of them. In 1946 Delbrück and Bailey infected the same bacterial cells simultaneously with two bacteriophages carrying different mutations. As a result of this mixed infection, new types of viruses, different in their combination of characters from those that had entered the cells, were produced. These workers, for example, used two bacteriophages, T2 and T4, somewhat related but serologically and otherwise distinct, which can give mutants called T2r and T4r. These are easily distinguishable from T2 and T4 by the peculiar appearance of the zones of destruction, or "plaques," that they cause in a layer of bacteria grown on solid media. When particles of both viruses T2 and T4r entered the same bacterial cells, the new phage produced inside these cells consisted of four types: T2, T2r, T4, and T4r.

It was necessary to conclude that the property designated as "r" had either been induced or else transferred from one phage to the other in the course of reproduction. Clearly, this amounted to the same result as that of a sexual cross, that is, the formation of new combinations of hereditary characters. These results were confirmed and extended by Hershey with the study of several other mutant properties. They can be taken to prove that, whatever the unknown mechanism of virus growth inside the cell may be, it must allow for some kind of reshuffling between the groups of hereditary determinants brought into the same cell by different virus particles.

In addition to this, this writer has recently found that genetic recombinations between viruses can do more than alter properties of the above kinds; they can restore their reproductive ability after this has been lost. Bacteriophage particles were inactivated by ultraviolet rays and, as a result, lost their ability to be transmitted from one bacterium to another without losing that of penetrating the host. Two or more such "inactive" particles were made to enter one bacterium, and active particles of bacteriophage reappeared. We have obtained evidence suggesting that this "resuscitation" depends on the fact that particles that have been damaged by radiation in different parts can transfer portions while inside the same host cell, with an opportunity for the formation of normally active particles. In other words, it seems that a lethal mutation can occur in any one of a number of parts of a virus particle, each of these parts being replaceable by transfer from another virus particle.

It is interesting to remember that more than ten years ago Berry and Dedrick discovered that the virus causing rabbit fibroma could be transformed into the virus of myxoma, a closely related virus of rabbits, by simultaneous injection of active fibroma and inactive myxoma virus. This phenomenon may find its explanation in some transfer of genetic properties similar to that occurring in bacteriophages.

It would be rash to draw from these results any general conclusion as to the origin of sexual processes and their evolution. It is

possible that different mechanisms permitting genetic recombination have appeared independently at various stages of the evolution of the biological world and that not all such mechanisms have developed along similar lines. The frequency of occurrence of genetic recombinations is likely to be very low in the case of bacteria and viruses, where reproduction by fission is probably the rule and conjugation between different individuals resulting in gene recombination, when present, is the exceptional occurrence. It is,

therefore, possible that mechanisms for genetic recombination that could prove too radical for higher organisms, where they would be repeated at each generation, might work successfully in viruses or bacteria. It would clearly be dangerous to try forcing analogies from the genetics of plants and animals to that of bacteria and viruses until the latter rests upon a more solid factual basis.

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