News of Science

Pseudoalleles

Fifty years from now it seems very likely that the most significant development of genetics in the current decade (1945–55) will stand out as being the discovery of pseudoallelism. First found by E. B. Lewis in *Drosophila melanogaster* in 1945, no other genetic phenomenon recently discovered seems to have the generality of this one, or to promise so much insight into the nature of the "gene"—its action, its mutation, its evolution. The phenomenon is difficult to define precisely; in fact, different observers have set forward different criteria for its definition. In general, however, it means that mutant genes that were once thought to be alleles of one another, because they were located in the same chromosome and always seemed to segregate from one another, and because the heterozygote between them displayed a mutant phenotype that was commonly intermediate between the phenotypes of the two respective homozygotes, were now found by more refined and laborious tests to lie at different, although adjacent, loci capable of undergoing occasional recombination by means of genetic crossing over. Thus even the classical *Drosophila* series of multiple alleles at the white eye-color locus has been shown to involve two separate loci, representing the mutants "white" and "apricot," respectively.

The importance of this phenomenon in current genetics is well indicated in a symposium on *Pseudoallelism and the Theory of the Gene,* held by the Genetics Society of America last September, and now published [*Am. Naturalist* **89**, 65 (Mar.–Apr., 1955)]. M. M. Green and E. B. Lewis here discussed the known cases in *Drosophila,* Green emphasizing the relation of pseudoallelism to the gene concept and to the problem of the origin of new genes in evolution, while Lewis devoted himself to interesting aspects of the alteration in gene function occurring when the pseudoalleles are in *cis* or in *trans* arrangements in the two homologous chromosomes. J. R. Laughnan presented the first analysis of the existence of pseudoalleles in maize. Since this case involved the well-known series of alleles at the *A* (anthocyanin color) locus, it seems highly probable that other multiple allelic series in maize may also turn out to involve pseudoalleles. S. G. Stephens, who concluded the symposium, pointed out the existence of similar cases in cotton and dealt with the origin of new genetic loci from old ones by the occurrence of small duplications, or "repeats," in the chromosomes, followed by a gradual differentiation of function and increasing independence of action, until the new loci have passed beyond the stage of pseudoalleles into that of clearly distinct genes. It is his belief that in *Gossypium* probably all stages in this evolution of the gene can be found. Only C. Stormont, among the participants, sounded a note of reservation. In cattle, and similarly in man, there are extensive series of multiple alleles that determine various blood groups. In cattle, no case of recombination between the antigenic components of a single locus has been detected; and, although such recombination has been postulated to occur in human beings, and indeed has aroused acrimonious discussion, no crucial case has been reported as positive evidence of pseudoallelism.

Meanwhile evidence of the generality of the phenomonon has been growing rapidly. It has previously been reported in at least one microorganism, the mold *Aspergillus nidulans.* The June 1955 issue of the *Proceedings of the National Academy of Sciences (U.S.)* contains no less than three new reports of pseudoallelism. One, that of Green, demonstrates pseudoallelism at the classic locus of *forked* in *Drosophila melanogaster,* a locus that has been used in literally thousands of genetical experiments in the course of the past 43 years. The two others are even more startling. S. Benzer presents evidence of pseudoallelism in the *Escherichia coli* bacteriophage between two subgroups of *rII* mutants; and M. Demerec, I. Blomstrand, and Z. E. Demerec demonstrate the same for biochemical mutants in *Salmonella typhimurium.*

Benzer's evidence comes from crosses between two *rII* mutants made to infect the same bacterium in equal proportions. Eight different mutants were found to fall into two groups, of six and two, respectively. If both mutants belong to the same group, then a mixed infection of the susceptible bacteria gives the mutant phenotype, namely, a lysis of very few bacteria; whereas if the mutants belong to different groups, extensive lysis occurs, both types of phage are liberated, and recombinations occur with a higher frequency. However, in contradistinction to the behavior in higher organisms, in the phage some recombination, up to about 3 percent, occurs even between mutants belonging to the same functional group. Thus a map of the eight *rII* mutants shows that all the mutants of each group are located in a sequence adjacent to the mutants of the other group; but the recombination between the closest mutants of the two different groups is actually less than that between the most separated mutants belonging to the same group. Certainly mutants of the two distinct groups qualify as pseudoalleles, for they are functionally, as well as spatially, distinct. One is left in some doubt whether or not to call the mutants that belong to the same group and are functionally alike yet able to recombine, "pseudoalleles."

The study by Demerec and his coworkers offers one further conclusion of the most extraordinary interest. In *Salmonella* the combinations were made by transduction to determine the allelic relationships of 25 mutants, all of which require that cystine be added to the medium. When wild-type colonies are recovered by transduction between two different cystineless mutants, they may be regarded as functionally distinct. Three groups of mutants were found, corresponding to three different biochemical blocks in the series of steps from sulfate to cystine; and the arrangement of these three groups in the chromosome corresponds, it is said, to the sequence of biochemical steps. Such an arrangement implies a sort of assembly-line of genes in the chromosome working on successive steps in a single biochemical sequence. It is assumed that this arrangement has come about through duplication of a single original locus, followed by functional differentiation through mutation and natural selection, just as Stephens and others have suggested.

As to the gene—clearly when we have before us a process of continuous differentiation in the genetic material by means of pseudoallelism, the nature of the "gene" depends upon the stage in the process. A single biochemical unit, a segment, a repetitive sequence of identical units that can undergo recombination, or a sequence of functionally different pseudoalleles—the gene might be any of these up until the time when it has become clearly a multiplicity of genes.

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