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A Biographical Memoir by

EDWARD B. LEWIS

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A.H. Sturtevant

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BY EDWARD B. LEWIS

STURTEVANT WAS THE youngest of six children of Alfred Henry Sturtevant and Harriet Evelyn Morse. His grandfather Julian M. Sturtevant graduated from Yale Divinity School and was a founder and later president of Illinois College. Sturtevant's father taught mathematics for a time at Illinois College but subsequently turned to farming, first in Illinois and later in southern Alabama, where the family moved when Sturtevant was seven. His early education was in Alabama in a one-room country school, but for the last three years of high school he went to a public school in Mobile.

In the fall of 1908 Sturtevant entered Columbia University. The choice, a crucial one, was made because Sturtevant's oldest brother, Edgar, was then teaching Latin and Greek at Barnard College; Edgar and his wife made it possible for Sturtevant to attend the university by taking him into their home. Sturtevant was greatly influenced by Edgar, from whom he learned the aims and standards of scholarship and research.

As a boy Sturtevant had drawn up the pedigrees of his father's horses and of his own family. He pursued this inter-

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est as a hobby while he was at Columbia. Edgar encouraged him to read works on heredity and to learn more about the meaning of pedigrees. As a result Sturtevant read a book on Mendelism by Punnett that greatly stimulated his interest, since he saw how Mendel's principles could be used to explain the pattern of inheritance of certain coat colors in horses. Edgar suggested that Sturtevant work out the genetic relationships, write an account of his findings, and submit it to Thomas Hunt Morgan, who held the chair of experimental zoology at Columbia and from whom Sturtevant had already taken a course. Morgan clearly was impressed, since he not only encouraged Sturtevant to publish the account, which appeared in *Biological Bulletin* in 1910, but also, in the fall of that year, gave Sturtevant a desk in his laboratory, which came to be known as the "fly room." Only a few months before, Morgan had found the first white-eyed mutant in *Drosophila* and had worked out the principles of sex linkage.

After completing his doctoral work with Morgan in 1914, Sturtevant remained at Columbia as a research investigator for the Carnegie Institution of Washington. He was a member of a research team that Morgan had assembled a few years earlier and that consisted principally of two other students of Morgan's, C. B. Bridges and H. J. Muller. The "fly room" in which they conducted all of their experiments was only sixteen by twenty-three feet, and at times as many as eight people had desks in it. According to Sturtevant, the atmosphere was one of high excitement, each new idea being freely put forth and debated. Morgan, Bridges, and Sturtevant remained at Columbia until 1928; Muller left the group in 1921 to take a position at the University of Texas.

In 1922 Sturtevant married Phoebe Curtis Reed; and in the same year they made their first trip to Europe, visiting museums and laboratories in England, Norway, Sweden, and Holland. They had three children.

In 1928 Sturtevant moved to Pasadena to become professor of genetics in the new division of biology that Morgan had established in that year at the California Institute of Technology. Much of the same stimulating atmosphere and unpretentious way of conducting science that Morgan and his students had practiced at Columbia was transferred to the new Kerckhoff Laboratory at Caltech. Sturtevant became the acknowledged and natural leader of the new genetics group established there. He maintained an active research program in which he often collaborated with other members of the genetics staff, including George W. Beadle, Theodosius Dobzhansky, Sterling Emerson, and Jack Schultz. He gave lectures in the general biology course and taught elementary and advanced courses in genetics and, on occasion, a course in entomology. He remained at Caltech until his death except for a year in England and Germany in 1932, as visiting professor of the Carnegie Endowment for International Peace, and shorter periods when he held visiting professorships at a number of American universities. He received many honors, including the National Medal of Science in 1968.

In addition to his principal publications dealing with the genetics and taxonomy of *Drosophila*, Sturtevant contributed papers on the genetics of horses, fowl, mice, moths, snails, iris, and especially the evening primroses *(Oenothera)*. Although his chief contributions are in genetics, he was also a leading authority on the taxonomy of several groups of Diptera, especially the genus *Drosophila*, of which he described many new species. He was much interested in the social insects and published several papers on the behavior of ants.

Sturtevant had a prodigious memory and truly encyclopedic interests. He had a natural bent for mathematics but little formal training in it. He especially enjoyed, and was expert at solving, all kinds of puzzles, especially those involving geometrical situations. For him scientific research was an exciting and rewarding activity not unlike puzzle-solving. a common theme of his investigations was an effort to analyze and explain exceptions to established principles.

Sturtevant knew how to design and execute simple, elegant experiments, describing the results in concise, lucid prose. He set high standards for his own research and expected others to do the same.

Sturtevant's discoveries of the principle of gene mapping, of the first reparable gene defect, of the principle underlying fate mapping, of the phenomena of unequal crossing-over, and of position effect were perhaps his greatest scientific achievements. The account of these and some of his other major contributions to science is arranged in approximate chronological order.

Mendel had found that all of the hereditary factors with which he worked assorted independently of one another at the time of gamete formation. Exceptions to this second Mendelian law began to accumulate in 1900-1909. Morgan was the first to provide a satisfactory explanation for such exceptions in terms of a hypothesis, which assumes that genes tending to remain together in passing from one generation to the next must be located in the same chromosome. He further postulated that the extent to which such linked genes recombine at meiosis is a relative measure of their physical distance.

Sturtevant introduced the concept that the frequency of crossing-over between two genes furnishes an index of their distance on a linear genetic map. He proposed that 1 percent of crossing-over be taken as equal to one map unit. He then reasoned that if the distance between two genes, A and B, is equal to x map units and the distance between B and a third gene, C, is equal to y map units, then the distance between A and C will be $x + y$ if B is the middle gene; $x - y$ if C is the middle gene, and $y - x$ if A is the middle gene. The germ of this idea occurred to Sturtevant in conversation with Morgan. In his *History of Genetics*, Sturtevant recorded that he "went home, and spent most of the night (to the neglect of my undergraduate homework) in producing the first chromosome map, including the linked genes, y, w, v, m, and r, in that order, and approximately the relative spacing, as they still appear on the standard maps" (p. 47).

Sturtevant devised a crucial test of the principles of mapping genes by constructing crosses in which all three genes were segregating simultaneously. In the progeny of such "three-factor" crosses, Sturtevant discovered that double crossing-over can occur and that its frequency is equal to, or less than, the product of the two single crossing-over frequencies. Conversely, the frequency of double crossing-over can be used to deduce the order of the three genes. Sturtevant showed that the order obtained from two-factor crosses was fully confirmed and that the three-factor crosses provided a more powerful method of ordering and mapping genes than did two-factor crosses. He published these findings in 1913. His principles and methods of chromosome mapping have enabled geneticists to map the chromosomes of a wide variety of higher organisms, including man.

Sturtevant was as much concerned with the role of genes in development as with the laws governing their transmission from one generation to the next. In 1915 he published an account of the sexual behavior of *Drosophila* that included a study of sexual selection based on the use of specific mutant genes that altered the eye color or body color of the fly. This work was the forerunner of an extensive line of research by others and constituted one of the first examples of the use of specific mutant genes to dissect the behavior of an organism.

One of the more conspicuous roles that genes play in development is their control of the processes of sexual differentiation. In 1919 Sturtevant reported the first case in which intersexuality could be shown to result from the presence of specific recessive genes. Years later he found a similar type of gene that resulted in the virtually complete transformation of females into males. Mutants of still other "sex genes" have been found in *Drosophila* and in many other organisms, including man. As a result, sex has come to be viewed as a complex trait controlled by a number of different genes, mutants of which can be expected to produce various grades of intersexuality.

Sturtevant pioneered in providing experimental approaches to a central problem in biology—how genes produce their effects. An important break-through came in 1920, with his discovery of the first reparable gene defect. In studying gynandromorphs of *Drosophila* in which there was somatic mosaicism for the vermilion eye-color mutant, he noticed that the eyes developed the dark red color of the wild type instead of the bright red color of the vermilion mutant, even when the eye could be shown to be genetically vermilion. Evidently, vermilion eye tissue lacked some substance that could be supplied by genetically nonvermilion tissue from another portion of the body. As G. W. Beadle pointed out, much of modern biochemical genetics stems directly from this early work.

Sturtevant had shown in 1913 that for each of the major chromosomes of *Drosophila* there is a corresponding linkage map. He and others had noticed, however, that excessive variation in the amount of crossing-over sometimes occurs. The factors responsible were isolated by Sturtevant and by Muller around 1915 and were shown to act as dominant cross-over suppressors. The first clue to the nature of these factors came in 1921, when Sturtevant compared the chromosome maps of *Drosophila melanogaster* with those of *D. simulans*, a closely related species that he had first described in 1919. These maps closely paralleled one another except for a region of the third chromosome, in which it appeared likely that the two species differed by an inversion in their gene sequences. It was only later that sufficient numbers of mutants were obtained in the various inversion-containing chromosomes of *D. melanogaster* for Sturtevant to establish that the dominant cross-over suppressors were indeed inversions. What had first been a disturbing exception to the generality of Sturtevant's principles of chromosome mapping became, in his hands, another demonstration of their validity. In 1935, after the discovery of the giant salivary gland chromosomes of the Diptera by Emile Heitz and H. Bauer (1933), T. S. Painter, C. B. Bridges, and others demonstrated the existence of inversions and their points of rearrangement by direct microscopic analysis. These cytological studies fully confirmed the standard and inverted sequences that Sturtevant had deduced by purely abstract genetic analysis.

In 1923 Sturtevant provided the first satisfactory explanation of the puzzling pattern of inheritance that others had found for direction of shell-coiling in snails. He showed that it was sufficient to assume a simple Mendelian gene, with dextrality being determined by the dominant allele and with the direction of coiling in the individual being determined not by its own genetic constitution but by that of its mother. He pointed out that such characters are "fundamental," in the sense that they are impressed on the egg by the action of genes in the mother. In 1946 he showed that intersexuality in a species hybrid—that of the *repleta* and *neorepleta* species of *Drosophila*—is an unusually subtle case of maternal inheritance conditioned by an autosomal dominant gene.

In the early 1920's Sturtevant and Morgan had begun a study of the unstable *Bar* mutant of *Drosophila* in order to learn more about the nature of mutations and the mechanisms by which new ones arise. It was known by then that mutations, in the sense of simply inherited changes, could take the form of changes in numbers of chromosomes (such as trisomy or polyploidy), changes involving several genes at a time (deficiencies or duplications), or changes that appeared to be within the gene (point mutations). Efficient methods for the experimental induction and detection of mutations had yet to be worked out, however. Moreover, spontaneous mutants were too rare, for the most part, to permit practical study of specific genes, except in the case of *Bar*. This small-eye mutant had already been found by C. Zeleny to mutate occasionally to either revered *Bar*, with eyes of normal size, or *Ultra-Bar*, with eyes distinctly smaller than those of *Bar*. In 1925 Sturtevant demonstrated that these derivatives of *Bar* arise at meiosis and are associated, at the time of their origin, with an unusual type of recombination process that he termed "unequal crossing-over." He postulated that the reverted type had lost the *Bar* gene and the *Ultra-Bar* was a tandem duplication for the *Bar* gene.

After the discovery of the giant salivary gland chromosomes, it was shown by H. J. Muller and A. A. Prokofieva, and by C. B. Bridges, that *Bar* itself is a small tandem duplication of a short section of the sex chromosome of *Drosophila*. The exact nature of the unequal crossing-over process then became evident. If the chromosome containing the *Bar* mutant is symbolized as ABCBCDE . . ., where BC is a small segment that has become tandemly repeated, then, in the germ cells of an individual homozygous for such a chromosome, the leftmost BC region of one chromosome may occasionally come to pair with the rightmost BC region of the other chromosome. If a crossing-over then occurs within such unequally paired BC regions, it is evident that two new types of chromosome sequences will be produced: ABCDE . . . and ABCBCBCDE. . . . The former sequence corresponds to reverted *Bar* and the latter to *Ultra-Bar*. Thus, orthodox crossing-over within unequally paired, tandemly duplicated chromosomal segments accounts for the instability of the *Bar* mutant and provides a mechanism for progressively increasing the number of genes in a chromosome.

The process of unequal crossing-over has come to assume increasing prominence in biology as possibly one of the main forces of evolution. To illustrate, this process may have been involved in the evolution of the cluster of closely linked genes controlling the production of the β, γ, and δ polypeptide chains of the human hemoglobin molecule. The extremely close similarity of these chains at the molecular level strongly implies that the genes determining them all arose from a single ancestral gene, presumably by repeated unequal crossing-over. In turn, the resultant duplicated genes evidently diverged gradually from one another by mutation until the gene cluster acquired its present form.

Sturtevant realized that *Bar* and its derivatives provided a unique opportunity to determine whether the position of a gene in the chromosome can affect its function. He devised a critical test that consisted of comparing the sizes of the eyes of two types of flies: homozygotes for *Bar*, the genetic composition of which can be symbolized as BCBC/BCBC; and heterozygotes for reverted *Bar* and *Ultra-Bar*, of composition BC/BCBCBC. He compared the eye sizes by counting the number of facets and showed that the second type of fly had significantly fewer facets than did the first. Since the total content of genic material in the two chromosomes is the same in both cases, the observed differences in eye size constitute a demonstration that the effect of the *Bar* gene (or *Bar* region) does indeed depend upon the position of that gene in the chromosome. Sturtevant's discovery of this phenomenon of "position effect" was the first demonstration that primary genic interactions occur at the site of the genes in the chromosome, as opposed to elsewhere in the nucleus or cytoplasm.

The position effect was shown by H. J. Muller, J. Schultz, and others to take many forms. Moreover, the more primitive the organism, the more prominent (apparently) is the role played by position effect. Thus, in bacteria the chromosome consists of a series of gene clusters, or operons, that are examples par excellence of the position-effect phenomenon, in the sense that the order of the genes in an operon, as François Jacob and Jacques Monod first showed, directly determines the order in which those genes are expressed.

As is often the case in basic science, Sturtevant's discovery of the position effect of *Bar* was a by-product of another study, in this case of the mutations of *Bar*. His accounts of the quite separate phenomena of unequal crossing-over and of position effect were published in 1925 in a paper that bore the modest title "The Effects of Unequal Crossing Over at the Bar Locus in *Drosophila*."

Sturtevant was able to exploit his early use of somatic mosaics to study the developmental effects of genes when he discovered a way of producing them in large numbers.

He found that females homozygous for the claret eye-color mutant of *D. simulans* produce a high proportion of gynandromorphs and other mosaics in their offspring. With the aid of this mutant he showed in 1929 that the degree of resemblance in genetic composition between two tissues in a somatic mosaic can serve to measure the degree to which those tissues have a common embryological origin. This principle, which underlies a kind of embryological-genetic mapping process now known as "fate mapping," has been widely exploited and has become a powerful tool of developmental and behavioral genetics.

In 1929 Sturtevant and S. Emerson showed that much of the extraordinarily complex genetics of the evening primrose (*Oenothera*) could be interpreted on a translocation hypothesis that had first been elaborated by John Belling for the jimsonweed, *Datura*. Many of the puzzling and bizarre "mutations" that Hugo de Vries and others had found in this organism remained disturbing thorns in the side of established genetic theory until Sturtevant and Emerson provided a detailed demonstration that they were not genuine mutations but, rather, the expected segregation products from the complex translocations of chromosome arms that are peculiar to, and widespread in, *Oenothera*.

Sturtevant and Dobzhansky collaborated in studying the plethora of inversions that occur in wild strains of many species of *Drosophila*, especially *pseudoobscura*. This work culminated in a paper (1936) that propounded an ingenious method by which inversions could be used as probes to trace phylogenetic relationships. They then successfully applied the method to constructing a detailed phylogeny of various strains and races of *pseudoobscura*.

In 1936 Sturtevant and Beadle published the results of an exhaustive study of the effects of inversions in *Drosophila* on crossing-over and disjunction. In this work they provided the first satisfactory explanation of the frequency and fate of certain aberrant chromosome types that arise as the result of crossing-over in inversion heterozygotes.

Sturtevant always maintained a keen interest in evolution and constantly examined the consequences for evolutionary theory of each new discovery in the rapidly developing science of genetics. He was an excellent naturalist and, as already noted, a taxonomist in his own right. In 1937 he published three "Essays on Evolution" in *Quarterly Review of Biology*. The first dealt with the effect of selection for mutator genes on the mutation rate of a species. The second pointed out some of the special problems of selection that are presented by the existence of sterile workers among the social insects. In the third essay he formulated a general scheme for interpreting one of the great puzzles of evolutionary theory—the origin of the sterility of hybrids.

In 1941 Sturtevant and Edward Novitski brought together the then-known mutational parallels in the genus *Drosophila*. Their results showed that the major chromosome arms of this organism tend to remain intact throughout the speciation process, although the specific order of genes within an arm gradually becomes scrambled, evidently by successive fixations of inversions.

The tiny fourth chromosome of *Drosophila* for many years resisted all efforts to map it genetically, until Sturtevant discovered special conditions that stimulated recombination to occur in that chromosome. His map of that chromosome appeared in 1951.

After 1951 Sturtevant's publications consisted mainly of original contributions to the genetics of iris; general articles on such topics as genetic effects of high-energy irradiation on human populations, the social implications of human genetics, and the theory of genetic recombination;

and several taxonomic studies, including a major monograph, written with Marshall R. Wheeler, on the taxonomy of the Ephydridae (Diptera).

In 1954, in his presidential address before the Pacific Division of the American Association for the Advancement of Science, Sturtevant warned of the genetic hazards of fallout from atmospheric testing of atomic bombs. He felt that although there might be a need for bomb testing, the public should be given the best scientific estimate of the biological hazards of fallout.

Sturtevant's last published work on *Drosophila* (1956) was an account of his discovery of a remarkable mutant gene that was without any obvious effect on the fly by itself but that, in combination with another specific mutant gene (determining a prune-colored eye), killed the organism at an early stage of development. In addition to posing a challenging problem in developmental genetics, such highly specific complementary lethal systems provide an opportunity for effecting the self-destruction of certain undesirable classes of flies.

Sturtevant's last major work, *A History of Genetics* (1965), was the outgrowth of a series of lectures given at several universities and of a lifelong interest in the history of science. True to his early love of pedigrees, he presents, in an appendix to that book, detailed intellectual pedigrees of geneticists of his day.

BIBLIOGRAPHY

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Sturtevant was the author of *An Analysis of the Effects of Selection*, Carnegie Institution Publication no. 264 (1918); and *The North American Species of Drosophila*, *ibid*., no. 301 (1921); and *A History of Genetics* (New York, 1965). His other works include *The Mechanism of Mendelian Heredity* (New York, 1915; New York, 1972), written with T. H. Morgan, H. J. Muller, and C. B. Bridges; *The Genetics of Drosophila* (Amsterdam, 1925), written with T. H. Morgan and C. B. Bridges; and *An Introduction to Genetics* (New York, 1939), written with G. W. Beadle.

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