

Perspectives

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STURTEVANT'S Mantle and the (Lost?) Art of Chromosome Mechanics

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... not even the most skeptical of readers can go through the *Drosophila* work unmoved by a sense of admiration for the zeal and penetration with which it has been conducted, and for the great extension of genetic knowledge to which it has led—greater far than has been made in any one line of work since Mendel's own experiments (BATESON 1916).

Drosophila is the organism of choice for this research because of the wealth of genetic information available and because of the ease with which its genome can be manipulated (generic sentence included in countless grant proposals).

IT all started, of course, in the "Fly Room" around 1910. That year, two remarkable undergraduates joined THOMAS HUNT MORGAN's laboratory at Columbia University. One of them, CALVIN BRIDGES, was beginning a brilliant if sadly brief career, the most singular highlight of which was the proof of the chromosome theory of inheritance. The other undergraduate, ALFRED STURTEVANT, would be fortunate enough to remain actively engaged in research for over half a century. BRIDGES was the first to discover autosomal linkage. He was the first to identify correctly the *X* and *Y* chromosomes in the *Drosophila melanogaster* genome and to propose that sex in this species is determined by the number of *X* chromosomes relative to the number of autosomes. He was the first to translate the discovery of the giant larval salivary gland chromosomes into a set of cytological maps. His untimely death, in 1938, prevented him from exploiting this new finding in a hoped-for collaboration with HERMAN J. MULLER, whom he had met in the early days of the Fly Room (CROW 1991).

STURTEVANT's contributions covered an amazing range of biological subjects, from the demonstration of maternal inheritance to the use of mosaicism for the study of development, from the discovery of position effect variegation to the analysis of sexual transformation. His abiding interest in evolutionary biology led to investigations of hybrid sterility, the genetic control of mutation rates, the frequency of lethal alleles in populations and, in collaboration with TH. DOBZHANSKY, the use of inversions to retrace phylogeny. Although necessarily performed in formal genetic and occasionally in classical cytological terms, STURTEVANT's experiments laid the cornerstones in many areas of modern quantitative and developmental biology;

the reader is referred to a collection of STURTEVANT's papers selected and edited by LEWIS (1961).

STURTEVANT's contribution to transmission genetics began with nothing less than the realization that differences in the strength of the linkage between genes could be used to determine their linear arrangement along a chromosome. Having invented genetic mapping, he proceeded to demonstrate that inversions are "crossover reducers"; in collaboration with GEORGE BEADLE, he suggested a simple mechanism for this effect. These discoveries led to the development of one of the most useful tools in genetic research, the balancer chromosomes. Soon, other classes of chromosomal aberrations were characterized, and each of them enabled the establishment of a fundamental concept or the development of another important tool. Translocations, for example, were used by CURT STERN (1931) and, independently, by HARRIET CREIGHTON and BARBARA MCCLINTOCK (1931) for the cytological demonstration of crossing over; deletions were used to map the physical location of genes on the polytenic chromosomes of larval salivary glands (SLIZYNSKA 1938), leading to the creation of cytological maps. The field of genetics was ready to enter the golden era of chromosome mechanics, an era that would produce an experimental corpus accurately characterized by one of STURTEVANT's students, EDWARD NOVITSKI, as "the epitome of sophistication in a rather esoteric field."

The period in question spans approximately 25 years, from the early 1940s to the late 1960s. Some of the work that was performed during this period on chromosome movement, gene function, mutagenesis, and the genetic characteristics of populations, to name a few areas, provided the framework for the subsequent or current redefinition of these phenomena in molecular, mechanistic terms. Center stage, though, was certainly occupied by genetics' first generation of engineers. Some of the special chromosomes that they discovered or constructed were useful for a variety of purposes. The discovery of the first attached-*X* chromosome by L. V. MORGAN (1922) was most propitious in that it could be used to study the relation of crossing over to meiosis, and as a tool with which one could force the transmission of normal *X* chromosomes from fathers to sons. Attached-*XY* chromosomes (STERN 1927;

NEUHAUS 1935; LINDSLEY and NOVITSKI 1959) were used to map and characterize the Y-linked fertility factors and to generate XO males. An unstable ring-X chromosome (HINTON 1955) allowed the creation of sexual mosaics or gynandromorphs. And yet, enormous amounts of creative energy, time, and effort were also spent on problems whose solution, today, could be considered an intellectual exercise carried out for its own sake.

It soon became apparent that five additional compound-X chromosomes could exist, differing from one another in the orientation of their two X chromosomes in relation to the single centromere. (MORGAN's attached-X is a reversed metacentric; the other possible combinations are the tandem metacentric, the reversed or tandem acrocentric, and the reversed or tandem compound ring.) Ingenious schemes were devised for the synthesis of all of these compound chromosomes, and laborious experiments were carried out for the purpose of studying their segregation properties and their recombination products.

Unsurpassed in skill and imagination were ED NOVITSKI, who was the original motivating force and guiding genius in this field, and his former student, LARRY SANDLER. Their laboratories and those of others, notably DAN LINDSLEY, vied with one another for the prize of being the first to synthesize a new compound combination (see NOVITSKI 1963a, b; LINDSLEY and SANDLER 1963; and references therein). Although compound-XY chromosomes, ring-X chromosomes, and ring-Y chromosomes (MULLER 1948) had been induced by exposure to ionizing radiation, no ring compound-XY chromosome existed, and the race to synthesize it was on. (As a postdoctoral fellow in NOVITSKI's laboratory from 1963 to 1965, I joined the long list of those who had an unsuccessful crack at it.) This chromosome was finally generated by a procedure involving two induced and three spontaneous consecutive recombinational events (NOVITSKI and CHILDRESS 1976). Although compound chromosomes were generated consisting of two left or two right arms of the major autosomes (RASMUSSEN 1960), the real challenge was the creation of compound autosomes with the two entire homologous elements attached to a single centromere. Better yet, why not attempt to attach both pairs of the major autosomes to each other and to a single centromere? All of these combinations were eventually synthesized by NOVITSKI, who provided an account of the wizardry needed to perform these particular feats (NOVITSKI 1963a, b; NOVITSKI *et al.* 1981).

The problems that gave birth to chromosome mechanics and were its *raison d'être*—pairing, crossing over, segregation—are no longer studied to any extent (with one or two notable exceptions) in *Drosophila*. A few of the intellectual descendants of the scions of the great dynasties of chromosome mechanics (in addition to the STURTEVANT line, those established by MULLER and DOBZHANSKY come to mind) have continued to practice the traditional craft in order to create new genetic tools. Even so, their use of chromosome mechanics is sporadic, at best, and their scientific interests are focused on gene function, cellular dif-

ferentiation, organismal development, genome organization, or the genetic basis of adaptation. The predominant techniques that they use are those of recombinant DNA, molecular cloning, and immunology. It is natural, therefore, that in looking back over that particular period in the history of genetics that is best referred to as “the age of *Drosophila* chromosome mechanics,” one cannot help wondering whether it was a crucial passage without which our current understanding of genetic mechanisms could not have been reached or whether it represents a dead end that contributed little if anything to the evolution of our field. I tend to favor the former possibility; given the relative brevity of one's professional life, the latter possibility, representing a significant waste of time, is perhaps too difficult to accept.

I had the good fortune of running into JIM PEACOCK and DAVID SUZUKI at the recent International Congress of Genetics. This encounter led to an evening of reminiscing and of recounting of the “good(?) old days”; it also provided the opportunity for JIM PEACOCK to read a draft of this *Perspectives* and to make useful suggestions for which I am grateful.

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