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Prime mover: an obituary of Barbara McClintock

Barbara McClintock, a peerless plant cytogeneticist and the discoverer of mobile genetic elements, passed away recently at the age of 90 years.

The significance of McClintock's work for biological science is such that we need to keep reminding ourselves of the context within which it was made. Gregor Mendel's paper (published in 1866) on the laws of inheritance of unit characters in the pea plant lay forgotten till similar results were obtained by three other Europeans at the turn of the century. In the English-speaking countries, Mendel's discovery of discrete, nonblending units of inheritance, later termed genes (a term introduced by W Johannsen in 1909), was popularized by William Bateson, who even made an early discovery of linkage in inheritance of two traits but did not believe that genes were located on chromosomes. For all practical purposes, this was the work of Thomas Hunt Morgan and his group, initially at Bryn Mawr College (Bryn Mawr, Pennsylvania) but later at Columbia University and California Institute of Technology. Morgan's group showed that not only are genes located on chromosomes but they occupy fixed loci (locations). Genetic, or gene-linkage, maps, first constructed for the fruit fly *Drosophila melanogaster*, showed genes arrayed on chromosomes in a linear fashion.

By the mid-thirties, Rollins Emerson at Cornell University, following Morgan's lead, had produced linkage maps of maize. Barbara McClintock, together with George Beadle and Marcus Rhoades, worked with Emerson. The period was one that saw a major drive to locate genes-physically on chromosomes. Genetic maps, which one obtained after recombination experiments involving identified genes, were themselves derived from crossing-over values. It was of obvious interest to examine whether this type of genetic exchange, *i.e.* recombination, was accompanied by a physical exchange (crossing over) of parts of homologous chromosomes. In a classic paper published in 1931, Harriet Creighton and Barbara McClintock showed that it was indeed so.

McClintock then concentrated on the short arm of chromosome 9 of maize, on which there are at least four conveniently linked genes expressed in the endosperm. In order to produce deletions, she constructed strains in which the short arm of chromosome 9 underwent a breakage–fusion–bridge cycle. She used a very contrived setup, namely a stock with a terminal duplicated segment in the short arm of chromosome 9. Crossovers in the duplicated segment started the breakage-fusion-bridge cycle. Daughter cells formed following breakage of the intercentromeric bridge in such a situation may contain unequal amounts of genetic information. This is because the bridge can break at any position and result in deletions and duplications. It was in the progeny of plants undergoing a breakage-fusion-bridge cycle that McClintock encountered a burst of somatic instability (mutability). She noticed, for one thing, that the kernels of such maize plants showed a variegation of colour. This was puzzling; and in the course of resolving the puzzle, for six years, from 1944 to 1950, she did not publish a single paper in a journal. All she had to show were reports published by the Carnegie Institution (where she worked, in Cold Spring Harbor). But when she did publish her results, in 1950, the scientific

world was presented with a conceptual revolution (but see below). By a leap of imagination, she had discerned the presence of mobile genetic elements from her cytogenetic data. Whereas all previous work had shown that genes occupy fixed loci on chromosomes, the 'controlling elements', as McClintock called the elements that caused somatic instability in maize, could move within the genome. And when they 'transposed' to the location of a known gene and conjoined with it, they modulated the action of that gene. It is now the stuff of history that McClintock's revolutionary ideas concerning mobile genetic elements were vindicated and their importance recognized only much later, when transposons were discovered in bacteria, and more and more transposable elements were discovered in eukaryotes. So McClintock's revolution really gathered momentum only more than two decades later.

McClintock was a cytologist *par excellence*, but even she could not see these elements under the microscope because, as it turned out, the controlling elements were submicroscopic. It is important to note that when her first paper on controlling elements appeared in 1950, it was not entirely clear that DNA was the primary genetic material. It would have been impossible to relate controlling elements to DNA. However, Alfred Hershey, whose experiments on bacteriophage with Martha Chase finally convinced everyone in 1952 that DNA was indeed the primary genetic material, was in the laboratory next door. Oswald Avery, Colin MacLeod and Maclyn McCarty had already shown by biochemical methods in 1944 that a deoxyribonucleic-acid fraction isolated from a type III pneumococcus was the substance responsible for heritable transformation of pneumococcal types. The cloning and characterization of maize transposable elements had to await the discovery of similar elements in bacteria and the remarkable techniques that flowed from the recombinant-DNA revolution.

The significance of transposable elements for the organism has always been puzzling. At first they were thought to be implicated in gene regulation. Maize elements like *Ac* (for 'Activator') have been shown to consist only of a coding region for a transposase and its regulatory gene; the enzyme imparts to the element the capacity to transpose. Thus a major *direct* role for these elements in gene regulation may be discounted. On the other hand they may have played a role in at least creating new variability. Mendel's *wrinkled* gene in pea has been shown to contain an insert analogous to a maize transposable element. Also, upon excision from a site, say within a gene, maize transposable elements leave a footprint behind, essentially an alteration in the nucleic acid sequence that may change the functioning of the gene. A number of copies of these elements may be present, and a large proportion of them may have deletions in the transposase gene region. Even intact transposable elements may generally be quiescent.

Somatic instability due to the action of controlling elements had become apparent as a burst in the wake of a breakage-fusion-bridge cycle, and McClintock came up with the hypothesis that it was genomic stress that 'activated' the quiescent elements. It seemed likely that heritable variation induced as a result of genomic stress could help the organism make long-range adjustments to the stress that triggered activity of the elements in the first place. In the light of present-day knowledge, another possibility is that such elements are a kind of selfish DNA that replicates itself as part of a chromosome but in general does not perform a function for the cell or the organism.

Applications from the discovery of transposable elements were somewhat slow in coming, but of late many novel uses have been discovered. At first, transposable elements were simply used as mutators. But then Nina Fedoroff and Oliver Nelson developed an ingenious technique of transposon tagging which enables one to clone any gene in maize. Transfer of such elements to crops like tobacco, which do not have these elements, may allow location and isolation of intractable genes like those for disease resistance. Because transposable elements generally 'walk' along the chromosome and do not take big 'jumps', Jerry Kermicle made use of this property to outline a novel *in vivo* sequential mutagenesis method.

Barbara McClintock overcame many barriers that a woman scientist of those times (not to speak of today) had to encounter. When she faced unemployment in 1942, the Carnegie Institution of Washington invited her to join their Cold Spring Harbor Laboratory on Long Island, New York, where she went on to work till the end. She was elected a member of the US National Academy of Sciences in 1944, and in 1945 she was elected President of the Genetics Society of America. It is remarkable that almost all her papers were written by her alone. In 1983 she was awarded the Nobel prize in physiology or medicine. On hearing the news she is supposed to have said, characteristically, 'Oh dear!' She seems to have been quite indifferent about awards; what primarily mattered to her was her work. On one occasion, when one of us (NKN) visited with her at Cold Spring Harbor, her advice was 'Don't leave anything out of your data because that is part of the whole story.' This brilliant and bold woman illuminated many areas of genetics. We will miss her presence.

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