Barbara McClintock and the Discovery of Jumping Genes

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Barbara McClintock's life shows us how important it is to nurture original and unconventional thinking in science if we are to get out of the rut of ordinariness. After a long period of relative neglect, she was awarded the Nobel Prize in 1983 for her work on genetic instability (transposition).

The history of modern genetics begins with the experiments of Gregor Mendel (1822-1884). Mendel found that when hereditary traits were followed through successive generations of hybridisation, the numbers of offspring that resembled parental types were in simple numerical ratios relative to one another – 1:1, or 3:1, or 9:3:3:1, and so on. The most straightforward explanation of these numbers was that the traits were associated with discrete, indivisible entities, later to be called genes. Mendel's observations languished in obscurity for 34 years until their rediscovery in 1900. Following this, rapidly accumulating data enabled genes to be mapped. Genes were found to be organised into distinct groups that were arranged in a linear order. This, along with other information, suggested that genes kept company with the thread-like structures called chromosomes that existed inside the cell's nucleus. Over a period of about 50 years biologists dealt with genes and built up a successful predictive science of genetics. All the same, no one knew for sure what genes were made of (a situation that has interesting parallels to the development of the atomic theory). An understanding of the nature of the gene had to await the identification of DNA as the genetic material.

The final piece of evidence for a physical model of genes emerged from two independent experiments whose results were published in 1931. Harriet Creighton and Barbara McClintock, working in the U.S.A. with maize, and Curt Stern, working in Germany with the fruit fly *Drosophila*, finally proved that genes were associated with chromosomes. Their conclusion was based on the observation that when genes appeared to 'cross over' from one genetic neighbourhood to another, so did the chromosomal material. Immediately acclaimed as a landmark in classical genetics, the finding made McClintock famous. Having thereby endowed genes with a measure of solidity, so to speak, she next went on to do just the opposite. She developed the unsettling idea that genes could be unstable, an insight that ought to have caused a sensation. Instead, it aroused indifference. This state of affairs lasted for some 30 years. Then a rush of independent discoveries brought genetic instability, and with it McClintock, back into the limelight.

Born in 1902 as the third of four children, Barbara McClintock was a fun-loving but solitary child as she grew up in New York. She had unconventional parents to whom what their daughter *could* be was more important than what she *should* be. Parental support and understanding continued in the face of evident oddities: it was apparent that young Barbara was not cut out to be part of the mainstream. Her pursuits were scholarly but at the same time individualistic. She joined Cornell University in 1918 after finishing high school and, in a step that would prove momentous for the future, became interested in the chromosomal organization and genetics of maize while still an undergraduate. Her first major contribution to the field was to identify each of the 10 chromosomes that maize has. Later she was to order several maize genes using a method now known as deletion mapping. Along with parallel work by others on *Drosophila*, this was an exciting development. McClintock became the intellectual driving force of an extraordinarily talented maize genetics group that was assembled at Cornell by R Emerson; among others the group included George Beadle who was also to win a Nobel prize later. A PhD degree in 1927 was followed by the famous paper with Creighton which provided a materialistic grounding to

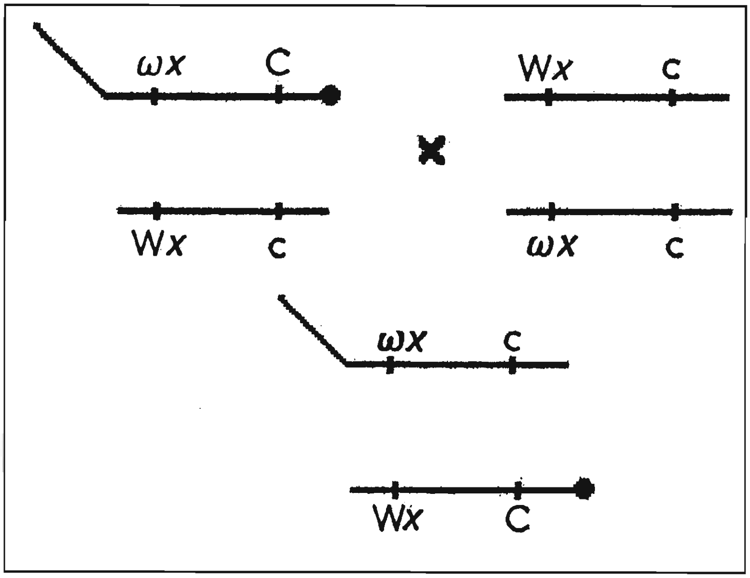

Figure 1 Creighton and McClintock made use of two genetic markers on chromosome number 9 of maize. One gene affected seed coat colour (C coloured, c colourless) and the other affected the composition of the food reserve (Wx = starchy, wx = waxy). C and Wx are dominant, meaning that they exert their effects in single doses; c and wx are recessive and have to be present in two doses in order to be perceived. A plant having the chromosomal combination (wx C/Wx c), with a knob on the chromosome containing C, was crossed with one having no knobs, two copies of c and one each of Wx and wx. Different types of progeny were produced; some possessed the coloured character in combination with starchy. As indicated in the lower portion of the figure, this was invariably associated with the exchange of that part of the chromosome containing the knob. (The bent portion is a fragment from another chromosome, also a visible marker like the knob.)

what had been, until then, the formal concept of a gene.

The demonstration of crossing over could not have been simpler (*Figure 1*). Chromosome number 9 in maize had a variant form with a knob-like visible bulge at one end. Gene locations had already been mapped on the chromosome using conventional techniques. Creighton and McClintock carried out matings of the knobbed stock with the standard variety. In the resulting progeny the presence of the gene that mapped closest to the knob invariably was associated with the knob itself, an observation that made it compelling to think of genes as things on chromosomes. McClintock's reputation continued to grow thereafter but her career did not prosper. It did not prosper in the manner it might have, had she been more easygoing, more conventional and less forthcoming in displaying her intelligence. Getting accepted in the male world of science was not easy either. The awe and respect in which she was held by her peers contrasts starkly with her inability to make it in academia.

Eventually she left Cornell University: her position there was always tenuous and she was never made a member of the faculty. She went on to join the University of Missouri as an assistant professor (1936-1941). Scientifically, this phase of her life was marked by the observation that broken ends of maize chromosomes behaved in unusual ways and that repairing the breaks required genetic activity. This observation was to come into its own much later, initially in connection with McClintock's work on transposable elements and more recently with the study of chromosome ends (telomeres). The turning point in a hitherto uncertain life came in 1941 with the offer of a research appointment to the Cold Spring Harbor Laboratory (in New York) of the Carnegie Institution of Washington. McClintock remained at Cold Spring Harbor for the rest of her life. (She died in 1992.) Here she was to be free from the imposition of applying for grants, free to pursue her inclinations and free to follow the unexpected.

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The work on genetic instability — or, to put it more correctly, genetic transposition, — for which she was to be honoured in 1983 with a Nobel Prize, dates from her early days in Cold Spring Harbor (*Figure 2*). Considering that this was a major scientific dicovery, the fact that she was already in her 40s when she made it is unusual. There are other noteworthy aspects to it too. For one thing, it was not merely that she found something new, but that what she found turned conventional thinking upside down. (It should be remembered that gene mutations were known and accepted, so genetic instability as such was not the issue. The surprise was that certain genes could move from place to place thousands of times more frequently than the rate at which mutations were known to occur.) Secondly, as indicated at the beginning, the response to her announcement was a mixture of bafflement and silence. The more perceptive geneticists realized that something startling had emerged. But because it flew in the face of supposedly proven facts, transposition was relegated to the status of a brilliant discovery that was simultaneously a bizarre curiosity.

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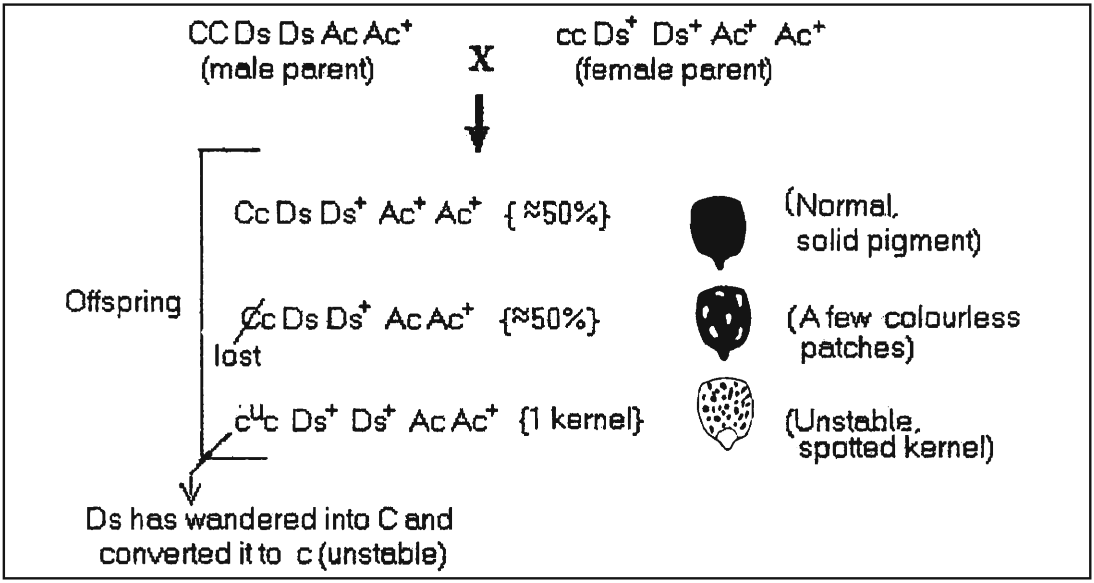

Figure 2 Activator (Ac) and Dissociator (Ds) are two unstable genetic elements discovered by McClintock (plus signs indicate the absence of the corresponding elements). The gene C gives rise to coloured kernels and c (in two copies) to colourless ones. About half the progeny of the genetic cross indicated at the top are normal-looking because in the absence of Ac, Ds is stable. In the remaining half, Ds caused a chromosomal break and loss of C, resulting in some colourless patches. But in one exceptional kernel, Ds wandered into C and converted it into an unstable colourless variant. This accounts for the numerous patches.

for her intellectual powers without being understood. Nor did it help that her papers were written in a style that made them next to impossible to grasp by anyone who had not already reached her own acuteness of perception with regard to the intricacies of maize genetics and cytology. To top it all, her revolutionary finding was not reported in the standard scientific literature, but instead in the annual reports of the Carnegie Institution or in Conference Symposium volumes. Behind this odd choice seems to have been the growing feeling on the part of McClintock that she had moved so far outside accepted modes of thinking that the establishment would not have been receptive to her anyway.

Nevertheless, she felt frustrated by her lack of success in communicating the excitement that she felt. According to her biographer, the reactions that McClintock's work elicited constituted a bitter anticlimax. (An indication of the general level of indifference is that even as late as 1965, there was no mention of genetic transposition in A H Sturtevant's otherwise authoritative history of genetics. Joshua Lederberg, the co-discoverer of genetic exchange in bacteria, is said to have come back from a meeting with her and said "By God, that woman is either crazy or a genius".) On looking back at this continued neglect, one cannot help but ask disturbing questions related to the supposed impersonality, objectivity and receptivity of scientists. Other questions, also not easy to answer, have to do with science as it is practised in theory and in fact and the manner in which the scientific community reacts to deviations from accepted points of view.

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The general appreciation of her work began to change with the arrival of the molecular biology revolution in the late 1960s. Soon it became apparent that the tendency of segments of DNA to move from one location to another was, if not universal, quite common. Interest in the field grew rapidly and it became apparent that mobile genetic elements, or 'jumping genes', as they came to be popularly known, were all over the place. One fact after another started emerging regarding their behaviour; it was demonstrated that comparable elements are involved in the transfer of resistance to antibiotics, in the generation of the immune response and in the spread of certain cancers by viruses. By the end of the 1970's the story of genetic instability, when set off against the long years of neglect, endowed McClintock's persona with a whiff of romance. Her status was raised almost to that of a cult figure.

Sure enough, even in what came to be thought of as 'her' field, genetic transposition, in one essential respect she remained an outsider. The question had to do with *why* genes jumped from place to place. All along, McClintock's stand had been that when segments of DNA moved, they did so for specific reasons. Because of their demonstrated ability to regulate the functioning of other pieces of DNA in maize, she coined the phrase 'controlling elements' to describe these segments. She went to the extent of advocating that similar controlling elements might be responsible for choreographing the orderly changes in patterns of gene expression that underly the development of a fertilized egg into an adult in plants and animals. Her viewpoint attracted virtually no support then, nor does it today. If anything there is an

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increasing tendency to favour the hypothesis that transposable elements are parasitic molecules of DNA that have no purpose as such besides that of ensuring their own survival and reproduction. Other aspects of McClintock's thinking verged on the mystical, for instance her readiness to ascribe a certain kind of wisdom to cells and organisms. To be fair, this may have been no more than an overly metaphorical way of expressing a conviction that natural selection is all-pervasive, and that the demand of evolutionary adaptation has crafted living structures down to the smallest detail.

Today, the concept of mobile genetic elements is acknowledged as an essential component of what we have come to think of as the dynamic structure of DNA. To that extent McClintock's efforts have been vindicated. Her work is also a prime example of the way in which seemingly esoteric pure research can have unexpected offshoots. Her life provides a cautionary tale as well. The notion that the pursuit of knowledge for its own sake is a worthwhile enterprise inspite of its being fraught with uncertainty, is rapidly falling by the wayside. This is so even in supposed institutions of higher learning. As the years pass, it is unlikely that there will be many havens left of the sort that the Carnegie Institution provided to McClintock. If nothing else, contemporary standards of scientific assessment would have made it difficult for her to hold down a research job for any reasonable length of time. One needs only to visualise the dismay with which a committee would react to being told that someone had 30 publications in 'standard refereed journals' over half as many years, let alone over an entire career. Barbara McClintock's life shows us how important it is to nurture original and unconventional thinking in science if we are to get out of the rut of ordinariness, be it only occasionally.

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Suggested Reading

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- **Fedoroff N V. Transposable genetic elements in maize.** ***Sci. Am.*** **June, 1984.**