

Perspectives

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Two Genes, No Enzyme: A Second Look at BARBARA MCCLINTOCK and the 1951 Cold Spring Harbor Symposium

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I didn't understand a word of it, but if BARBARA said it, it must be true!" With these words, the great *Drosophila* geneticist ALFRED STURTEVANT reportedly gave his opinion of BARBARA MCCLINTOCK's first public presentation of transposable elements, at the 1951 Cold Spring Harbor Symposium (GREEN 1992). A legend has sprung up around MCCLINTOCK's presentation, according to which she gave her talk with great expectation of acceptance and interest, only to be ridiculed and ignored by her colleagues. The subtext is that MCCLINTOCK was discriminated against, whether because of her views or her sex. In her biography of MCCLINTOCK, EVELYN FOX-KELLER writes that MCCLINTOCK's talk "was met with stony silence. With one or two exceptions, no one understood. Afterward, there was mumbling—even some snickering—and outright complaints. It was impossible to understand. What was this woman up to?" (KELLER 1983, p. 139).

MEL GREEN, writing in the 1992 Festschrift for MCCLINTOCK, *The Dynamic Genome*, seeks to redress the legend: "There is a widely extant viewpoint that BARBARA's research was much unappreciated and appropriate recognition was too long delayed. . . . I believe this viewpoint to be a half-truth" (GREEN 1992, p. 117). Some of the legend springs from MCCLINTOCK's own lips. In an interview with KELLER, MCCLINTOCK said, "It was just a surprise that I couldn't communicate; it was a surprise that I was being ridiculed, or being told that I was really mad" (KELLER 1983, p. 140). Unexplained, MCCLINTOCK's cool reception supports the idea that her colleagues were obtuse in failing to see the truth and beauty of her discovery, or worse, that they refused to accept her results because MCCLINTOCK was outside the geneticists' old boys' network.

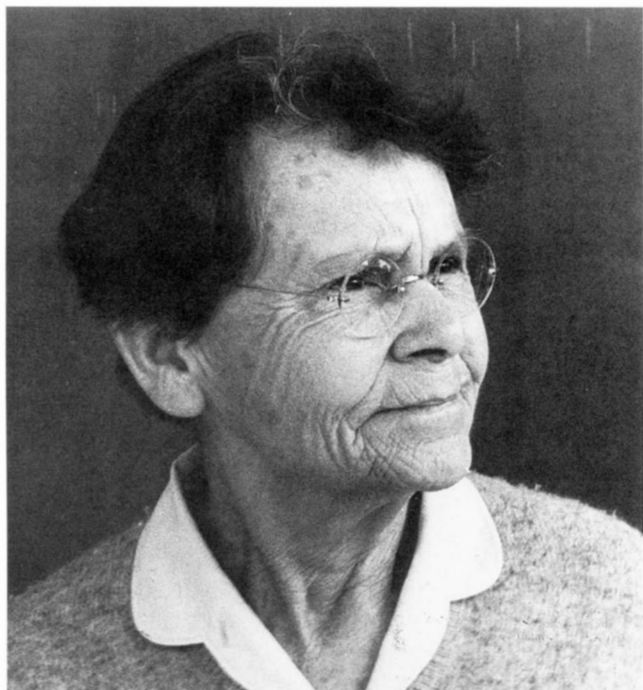
Some of the legend seems to stem from scientists wishing to squelch it. The quote at the beginning of

this essay is attributed by GREEN (1992) to ALFRED STURTEVANT, who, GREEN says, had attended the Symposium. Yet the only STURTEVANT listed as a participant in 1951 is one FRANK STURTEVANT, of Northwestern University! The error is quite excusable; while his is the only published version, this story has been repeated many times by many people, and doubtless in many versions. It is part of the legend, a mythology that continues to grow, even among demythologizers.

A re-examination of the 1951 Symposium can help replace the myth with a more rational explanation of the reaction to MCCLINTOCK's paper. It also shows how data and scientific theory are intertwined with the culture of science. MCCLINTOCK was not a passive recipient of her colleagues' judgments. She defiantly and deliberately challenged the paradigm view of the gene—a gutsy move, but one that brought upon herself some of the confusion that so distressed her.

It is certainly true that MCCLINTOCK's work was highly respected by the time she presented her data on transposable elements. Since the 1920s she had published paper after important paper on maize cytogenetics. With HARRIET CREIGHTON at Cornell, MCCLINTOCK produced the first visual evidence of crossing-over, just barely beating out CURT STERN's similar work on *Drosophila*. Subsequent work took her ever deeper into genomic instability and chromosome structure. First she showed the existence of ring chromosomes. Then she showed that ring chromosomes were a special case of broken chromosomes, one in which the ends became "sticky" and fused to each other. In 1936 MCCLINTOCK moved to the University of Missouri, where she was hired by LEWIS STADLER, who with R. A. EMERSON, MCCLINTOCK's mentor at Cornell, was one of the reigning lions of maize genetics. At Missouri, MCCLINTOCK discovered the "breakage-fusion-bridge" cycle, a further extension of her observations of chromosomal instability. The breakage-fusion-bridge cycle led MCCLINTOCK to two important conclusions, one a prediction

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and the other her most profound discovery. The observation of the “stickiness” of the broken ends of chromosomes led MCCLINTOCK to the prediction of special structures on the ends of chromosomes needed to maintain the stability lost when the chromosomes broke. She called them telomeres, the study of which today is undergoing rapid growth. When MCCLINTOCK left Missouri for Cold Spring Harbor in 1941, she took with her strains of maize that underwent the breakage-fusion-bridge cycle. From them MCCLINTOCK deduced the existence of transposable elements. The first set of experiments in which she observed transposition were done in 1944 (MCCLINTOCK 1984). She spent the next six years pursuing, confirming and verifying her results.

By 1951 MCCLINTOCK was among the best-respected cytogeneticists in the country. Even ten years earlier, when the director of the Carnegie Department, MILISLAV DEMEREC, told staff scientist E. CARLETON MACDOWELL that he had succeeded in hiring MCCLINTOCK, MACDOWELL “jumped up in the air and said, ‘We should mark today’s date with red letters in the Department calendar!’ That expresses the feeling that is general among our members” (DEMEREC 1942). In 1939 she was elected vice-president, and in 1945 president, of the Genetics Society of America. By 1951 she had received the Achievement Award of the Association of University Women, been awarded two honorary degrees, and been a member of the National Academy of Sciences for seven years. “The influence of her early work is greater than that of any of her peers, with the possible exception of ALFRED STURTEVANT,” wrote NINA FEDOROFF and DAVID BOTSTEIN. “Had she done no



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more [before transposons], MCCLINTOCK would have become a major figure in the history of genetics” (FEDOROFF and BOTSTEIN 1992).

The 1951 Symposium took place in the years between OSWALD AVERY’s demonstration that the transforming principle in *Pneumococcus* was DNA, and the double revelations of ALFRED HERSHEY and MARTHA CHASE’s “blender experiment” and WATSON AND CRICK’s model of the DNA double helix. The nature of the gene was the central question in many biologists’ minds. Bacteriophage and bacteria were the model systems of choice, with *Neurospora* and *Drosophila* close behind. Scientists working with these organisms were heavily invested in the classical T. H. MORGAN model of the gene. MORGAN’s group had shown the enormous intellectual productivity of viewing genes as unitary, particulate structures, arranged linearly and statically along the chromosomes. BEADLE AND TATUM’s one-gene one-enzyme hypothesis, first developed in the early 1940s, lay atop this foundation. It confirmed that genes were unitary by showing they had unitary effects on metabolic pathways. MILISLAV DEMEREC, director of the Cold Spring Harbor Biological Laboratory and organizer of the 1951 Symposium, acknowledged that the gene concept had been unraveling in recent years. Genes, DEMEREC said, “are regarded as much more loosely defined parts of an aggregate, the chromosome, which in itself is a unit and reacts readily to certain changes in the environment” (DEMEREC 1951). Whatever the gene’s precise molecular nature, the working model of the gene was of a unitary entity that acted independently to produce a physiologically active molecule. While many at the time recognized that it was an oversimplification, the view of the genome as a static, linear series of partic-

ulate, independently acting genes proved so successful in explaining genetic observations and generating new experiments that few had cause to doubt it.

One who did doubt it was RICHARD GOLDSCHMIDT. For decades, GOLDSCHMIDT had been a gadfly to the genetics community. Brilliant and cantankerous, GOLDSCHMIDT delighted in challenging assumptions and pointing out logical inconsistencies in the evolving genetic theory. Since 1938, GOLDSCHMIDT had been arguing against the theory of the gene. His observations of *Bar eye* in *Drosophila* led him to conclude that the chromosome, not the gene, was the unitary element of heredity (GOLDSCHMIDT 1938; DUNN 1965). GOLDSCHMIDT argued from translocation data that the position of a locus on the chromosome determined its function. When a locus moved to a different site, its function changed. GOLDSCHMIDT argued in 1938 that "the whole conception of the gene" was "obsolete." GOLDSCHMIDT and BEADLE took up opposing sides in a debate that lasted over a decade. GOLDSCHMIDT's was a dynamic genome, not a static one. By playing the devil's advocate, GOLDSCHMIDT forced geneticists to reconsider their assumptions. Though his style was combative and his views extreme, position effects have been supported by molecular analyses. To be sure, GOLDSCHMIDT seemed to set up a straw man; his notion of the prevailing gene concept seemed to be a globular molecule situated on the chromosome, an almost literal "bead on a string." This caricature doubtless made it easier for him to ridicule the gene theory, but it also made his alternative impossible for most geneticists to accept.

For all his crotchetyness, GOLDSCHMIDT was and is an important figure in genetics. DEMEREC gave GOLDSCHMIDT the honor of presenting the opening talk of the 1951 Symposium in a special session entitled "Theory of the Gene." The session was filled out by MCCLINTOCK herself, LEWIS J. STADLER, who also critiqued the gene model, but in a way less infuriating to geneticists, and N. H. HOROWITZ and URS LEUPOLD, speaking on new evidence for and implications of the one-gene one-enzyme theory. The "Theory of the Gene" session thus had three scientists critical of the standard model and one supportive of it. Much of the rest of the meeting was given over to the microbial geneticists. Three sessions were devoted entirely to bacteriophage and bacteria, with many more papers on microbial genetics sprinkled throughout the remaining sessions. Most of the remainder concerned *Drosophila* or *Neurospora*. On both sides of the podium, discussion was dominated by classical genetics, microorganisms, and the one-gene one-enzyme vision of genetic function.

In the opening paper of the Symposium, GOLDSCHMIDT revisited the arguments many had heard before. He had new evidence to support it, however. He took on BEADLE's model early on, accusing BEADLE of "extrapolation from the mutant action to the existence

of the original gene" (GOLDSCHMIDT 1951, p. 1). Though he cited examples drawn from work on mutable genes in *Drosophila* and other organisms, prominent among GOLDSCHMIDT's remarks are several glowing mentions of MCCLINTOCK's description of the *Ac/Ds* system in maize. For GOLDSCHMIDT, transposable elements provided a shining example of position effects and a dynamic genome. He referred to transposable elements as "invisible" (*i.e.*, submicroscopic) rearrangements and position effects. To his full satisfaction, MCCLINTOCK had proved that in *Zea*, "mutable loci are actually position effects produced by genetically controlled and repeating transpositions and translocations" (GOLDSCHMIDT 1951, p. 4). GOLDSCHMIDT waxed poetic in his analogy for how genetic function derived from position: "If the A-string on a violin is stopped an inch from the end the tone C is produced. Something has been done to a locus in the string, it has been changed in regard to its function. But nobody would conclude that there is a C-body at that point" (GOLDSCHMIDT 1951, p. 7). MCCLINTOCK's data must have seemed a godsend to GOLDSCHMIDT, an example tailor-made to support his attack on the gene concept.

In her own paper, directly following GOLDSCHMIDT's in the Symposium volume, MCCLINTOCK returned the favor. Both implicitly and explicitly, she repeatedly aligned herself with GOLDSCHMIDT. Twenty-three pages into her paper, she said, "It will be noted that use of the term gene has been avoided in the foregoing discussion of instability" (MCCLINTOCK 1951, p. 36). She went on to say that this "does not imply a denial of the existence within chromosomes of units or elements having specific functions. The evidence for such units seems clear." But the gene concept, she said, "stems from studies of mutation." She then made the link with GOLDSCHMIDT explicit: "The author agrees with Goldschmidt that it is not possible to arrive at any clear understanding of the nature of a gene, or the nature of a change in a gene, from mutational evidence alone" (MCCLINTOCK 1951, p. 36). MCCLINTOCK invoked GOLDSCHMIDT again in her conclusion: "Evidence, derived from *Drosophila* experimentation, of the influences of various known modifiers on expression of phenotypic characters has led Goldschmidt (1949, 1951) to conclusions that are essentially similar to those given here" (MCCLINTOCK 1951, p. 46). In the battle between GOLDSCHMIDT and BEADLE, it could not have been more plain with whom MCCLINTOCK allied herself.

It is clear what appealed to MCCLINTOCK in GOLDSCHMIDT's work. Like MCCLINTOCK, GOLDSCHMIDT was arguing for a dynamic genome, a self-regulating system defined by the interactions among its parts. To both, the static concept of linear beads on a string, though it had enormous predictive value, was a vast oversimplification. Yet MCCLINTOCK undersold herself somewhat by aligning herself so closely with GOLDSCHMIDT. Her model was

considerably more sophisticated than GOLDSCHMIDT's. Unlike GOLDSCHMIDT, MCCLINTOCK believed in genes; she just didn't believe they were the entire story. Her "controlling elements" were presented as a new sort of genetic material, not genes but regulators of genes. While GOLDSCHMIDT denied the BEADLE and TATUM model, MCCLINTOCK was working outside of it.

Equally clear, however, is why MCCLINTOCK's work would have received a cool reaction from the assembled audience. The differences between MCCLINTOCK's and GOLDSCHMIDT's views would have been obscured by their obvious mutual admiration. Hadn't MCCLINTOCK avoided even the use of the term gene for the first two thirds of her talk? Hadn't she concluded by saying GOLDSCHMIDT's conclusions were essentially the same as her own? To an audience full of Neurospora, Drosophilists and phageologists, it must have seemed that they had just had to endure their second GOLDSCHMIDT talk!

Although many geneticists were relaxing their concept of the gene, all were employing it. Whatever a gene was, it was unitary and it acted independently. Eleven papers in the Symposium concerned the mutagenic effects of radiation and chemicals. Further, "mutation" and "gene" were defined in ways that were internally consistent but entirely self-contained. A mutation disrupted a gene. In his paper on pseudoallelism and crossing over, E. B. LEWIS defined the gene as a physical unit within which there is no crossing over. A static, discrete unit was inherent in his definition: "The definition of any particulate unit must be in terms of its indestructibility by some breakage or splitting process" (LEWIS 1951, p. 174). LEWIS's concept of a gene complex became a paradigm in Drosophila developmental genetics, but the regulation of the bithorax complex by chromosomal components has proved to be a key element in understanding its operation. While GOLDSCHMIDT and MCCLINTOCK's 1951 vision of genetic regulation differs from the modern conception, the parallels are in many ways more striking than the differences. MCCLINTOCK's controlling elements were non-genes, genetic particles outside the framework of one-gene one-enzyme biochemical genetics.

MCCLINTOCK did not go unnoticed in the Symposium. Several speakers in later sessions referred to her work, either in their papers or in the reprinted discussion that followed many of the papers. STADLER, of course, cited her graciously, though he did so nonanalytically. JACK SCHULTZ cited her 1933 work on association of nonhomologous chromosomes during prophase of meiosis and NORMAN GILES cited her seminal 1945 paper on the cytology of Neurospora. Two others referred to MCCLINTOCK's work on transposons. ALFRED MARSHAK, commenting on DAVID BONNER's paper on gene-enzyme relationships in Neurospora, cited MCCLINTOCK's work in connection with observations that nuclei

contain a pentosenucleoprotein that continually releases polynucleotide into the cytoplasm. This polynucleotide, presumably RNA, was presented in the context of the one-gene one-enzyme theory as direct evidence that unitary genes have discrete, independent effects in the cytoplasm. MARSHAK suggested that MCCLINTOCK's *Activator* was involved with the formation of nucleoproteins from raw histones and polynucleotides, much like a conventional gene. MCCLINTOCK's data, he says, are

readily explained on the basis of the hypothesis if we suppose that *Ds* and the other similar factors represent chromosome segments containing greater amounts of DNA than those which were previously associated with the locus in question. . . . If the "activator" is involved in the production of the pentosenucleoprotein[,] as for example from raw materials such as histones and polynucleotides stored in the nucleolus[,] an alteration in the amount of the substance we have assumed to govern the rate of activity of the locus will result and hence a mutated condition: or if the intensity of the activator action varies, in a mutable condition. In this connection it appears significant that the simultaneous presence in the genome of a *Ds* or *Ds*-like region together with an "activator" results in a "fusion-breakage event" which further suggests involvement of transport and utilization of nucleolar materials (MARSHAK 1951, p. 157).

In this rather convoluted passage, MARSHAK attempts to explain MCCLINTOCK's observations from a BEADLE-and-TATUM point of view. Although MCCLINTOCK emphasized that *Ac* and *Ds* were not conventional genes, MARSHAK's explanation hinges on *Ac* being involved in the production of nucleic acids—in short, acting like a gene. Significantly, MARSHAK says that "while other interpretations may seem equally plausible, this one . . . is amenable to being tested experimentally," suggesting that MCCLINTOCK's interpretation is not.

In their paper on chemically induced mutations in Neurospora, K. A. JENSEN, INGER KIRK, G. KOLMARK, and M. WESTERGAARD offer a different interpretation of MCCLINTOCK's results. They cite MCCLINTOCK's controlling elements as evidence for their theory that mutable genes might result from unstable precursors accumulating in the nucleus, the result of blocked steps in a BEADLE and TATUM-style biochemical pathway:

We know from the work on biochemical mutants of Neurospora that when a specific intermediate step in the synthesis of a vitamin or an amino acid is blocked by mutation, a precursor may accumulate in the cells. We also know that some of these precursors are highly stable and may be extracted from the mycelium, and that others are very unstable and are converted into by-products, like the purple pigment in our adenineless strain, whereas others disappear completely. We want to suggest that some of the unstable precursors may act as mutagens during the decomposition. This would be a very specific type of mutagens [sic], since, as primary gene products, they may be produced within the nucleus. It does not seem improbable that some of these precursors would be so unstable that they may only react over a very short distance, thus inducing mutations in loci only within a

short distance from the “blocked” gene. The so called unstable or mutable loci now under investigation by McClintock (1950) may be due to such an “unstable precursor” mechanism (JENSEN *et al.* 1951, p. 258).

Neither MARSHAK nor JENSEN *et al.* ignored MCCLINTOCK’s work; neither, however, accepted her interpretation of her data. MARSHAK and JENSEN were working within the dominant paradigm of the BEADLE and TATUM model, and attempted to jam MCCLINTOCK’s anomalous controlling elements into that prevailing and familiar conceptual framework. These examples neither illustrate cloddishness on the part of MARSHAK or JENSEN, nor demonstrate that MARSHAK and JENSEN “misunderstood” MCCLINTOCK’s work. Rather, they suggest scientists who listened to and believed MCCLINTOCK’s data but thought her interpretation overly speculative and even untestable. E. B. LEWIS had a similar reaction. He said of MCCLINTOCK, “Everybody recognized her as a great scientist. You could trust what she found out experimentally, but it was the speculation that got out of hand. This reinforced her mystical ideas. You just couldn’t fit it into the standard genetic theory” (E. B. LEWIS, personal communication). LEWIS even suggests that MCCLINTOCK and GOLDSCHMIDT may have been seen as supporting the anti-genetic stance of T. D. LYSENKO—a view MCCLINTOCK and GOLDSCHMIDT would have found absurd, but one that illustrates how far out they seemed to mainstream geneticists. MCCLINTOCK’s peers were struggling to re-interpret anomalous data into terms with which they were comfortable.

Other factors doubtless also contributed to the confusion about and lack of acceptance of MCCLINTOCK’s conclusions. Her model system may have had some alienating effect, but it would seem to have been small. True, STADLER was the only other maize geneticist on the program, yet there were several other plant geneticists and several cytologists. And although maize was becoming an unfashionable organism in genetics, it wasn’t so far out of style as to be incomprehensible. MCCLINTOCK’s presentation may have been something of a barrier, however. Non-trivial, surely, was her paper’s considerable length. It filled 35 pages in the Symposium volume and was by far the longest of any at the meeting. MCCLINTOCK presented a welter of data, with long sections of background on each important mutation and detailed descriptions of her crosses. Her talk was essentially historical in structure, rather than the more conventional format of Introduction, Results and Conclusion, so it tended to ramble. Also, she used highly unconventional language. Beyond dispensing with the word “gene,” she invented new terms to describe her new phenomena. In addition to “activators” and “dissociators”—terms that even those scientists who tackled her data handled with verbal kid gloves, such as quotation marks and “so-called”—she spoke of “altered states,” “out-of-phase timing,” and “controlling

systems.” She wrote that “it was the pattern of behavior, rather than the change in expression of the particular phenotypic character, that was obviously of importance” (MCCLINTOCK 1951, p. 43). She felt it was necessary “to consider these various widely different levels of unitary control and how they may operate in the working nucleus, and also to consider the nature of the changes that can affect their operation” (MCCLINTOCK 1951, p. 37). This was pretty cosmic stuff to a biochemical geneticist or phage group member.

The controversy between the MCCLINTOCK/GOLDSCHMIDT view of the gene and the BEADLE/TATUM view was resolved with the advent of modern molecular techniques. As is often the case, both sides were partly right. Transposition became widely accepted in the 1970s as SAEDLER, STARLINGER, SHAPIRO, BOTSTEIN, FINK, FEDOROFF and others identified transposable elements in microbial and animal systems and elucidated the mechanism of transposition. It became clear that transposable elements can encode proteins that regulate other genes. *Ac* was shown to encode transposase, which activates *Ds*. Genome instability, position effects, and genomic regulation have become hot topics as molecular techniques allow confirmation and modification of MCCLINTOCK’s ideas. MCCLINTOCK’s vision of biology needed to be filtered through the accepted methodology and language of genetics and molecular biology in order for it to significantly influence our understanding of the gene. Further, the new techniques made it possible to confirm what had seemed speculations, and to do it in multiple species.

MCCLINTOCK was universally admired as an experimentalist, but to some she seemed to be extrapolating too much from her data. Those unfamiliar with her work probably associated her paper with the one preceding it and considered MCCLINTOCK just another Goldschmidtian. MCCLINTOCK herself encouraged this perception by explicitly aligning herself with the notoriously controversial GOLDSCHMIDT. And GOLDSCHMIDT was, in fact, the closest to MCCLINTOCK in his concept of the gene. But unlike GOLDSCHMIDT, MCCLINTOCK didn’t refute the paradigm—she stepped outside it. Among those who knew and respected her, some tried to squeeze her findings into their conception of the gene, while some, like STURTEVANT—or whoever it was—didn’t understand a word of what she said.

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