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BARBARA MCCLINTOCK

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A Biographical Memoir by

NINA V. FEDEROFF

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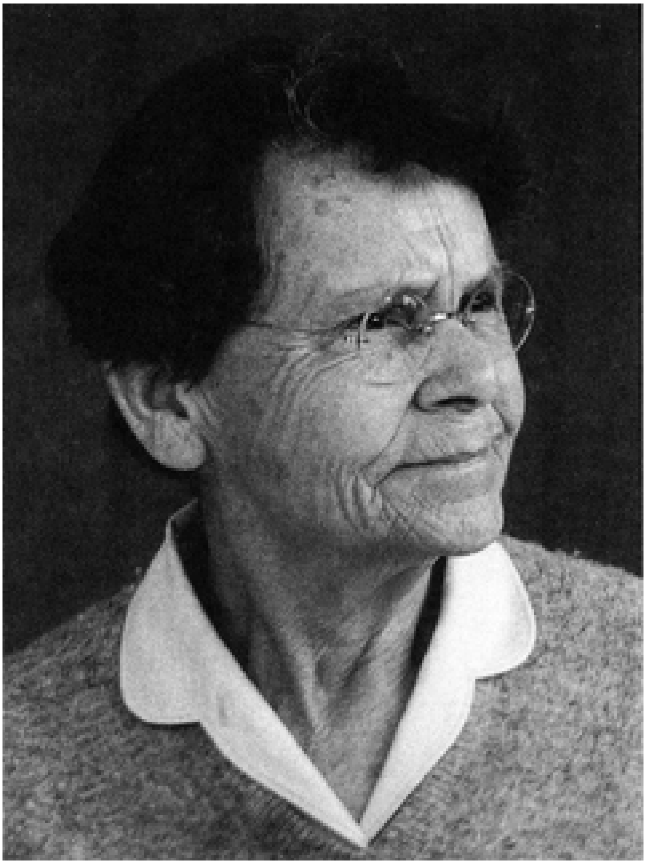

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Barbara McClintock

BARBARA McCLINTOCK

June 16, 1902–September 2, 1992

BY NINA V. FEDOROFF

BARBARA McCLINTOCK'S remarkable life spanned the history of genetics in the twentieth century. Though technically rooted in Mendel's experiments carried out decades earlier, the science of genetics began with the rediscovery of his work at the turn of the century. In 1902, the year of McClintock's birth, William Bateson wrote prophetically that "an exact determination of the laws of heredity will probably work more change in man's outlook on the world, and in his power over nature, than any other advance in natural knowledge that can be clearly foreseen." And indeed, the science of genetics, to which McClintock made seminal contributions both experimental and conceptual, has come to dominate all of the biological sciences, from molecular biology, through cell and developmental biology, to medicine and agriculture. Bateson's immodest guess was arguably an underestimate of the impact of genetic knowledge on humankind.

The chromosomal basis of heredity was already well established by the time McClintock began her graduate training in the Botany Department at Cornell University. McClintock made her first significant contribution as a graduate student, developing cytological techniques that allowed her to identify each of the ten maize chromosomes. These early experiments laid the groundwork for a remarkable series of cytogenetic discoveries by the Cornell maize genetics group between 1929 and 1935. By all accounts, McClintock was the intellectual driving force of this talented group and either contributed substantially to or was exclusively responsible for many of the discoveries. These include identification of maize linkage groups with individual chromosomes, the well-known cytological proof of genetic crossing-over, evidence of chromatid crossing-over, cytological determination of the physical location of genes within chromosomes, identification of the genetic consequences of nonhomologous pairing, establishment of the causal relationship between the instability of ring-shaped chromosomes and phenotypic variegation, discovery that the centromere is divisible, and identification of a chromosomal site essential for the formation of the nucleolus.

In the years following completion of her doctoral work, McClintock continued her maize cytogenetic studies, eventually becoming interested in chromosome breakage, making important observations on the behavior of chromosomes lacking telomeres. Using knowledge gained from these studies, McClintock developed a method for using broken chromosomes to generate new mutations. Among the progeny of plants that had received a broken chromosome from each parent, she observed unstable mutations at an unexpectedly high frequency, as well as a unique mutation that defined a regular site of chromosome breakage. These observations so intrigued her that she began an intensive investigation of the chromosome-breaking locus. Within several years she had learned enough to reach the conclusion, published in 1948, that the chromosome-breaking locus did something hitherto unknown for any genetic locus: it moved from one chromosomal location to another, a phenomenon she called transposition. The study of transposable genetic elements and transposition became the central theme of her genetic experiments from the mid-1940s until the end of her active research career.

As with Mendel's experiments, it took decades for the generality and significance of McClintock's discovery of transposition to be appreciated. McClintock's extraordinary scientific talent and the importance of her early cytogenetic work were quickly recognized. She became a member of the National Academy of Sciences in 1944 at the young age of forty-two, only the third woman ever to have been elected. But her subsequent work on transposition led to a period of intellectual adumbration. While no one doubted her reputation for impeccable experimentation, the concept that genes could move was so at variance with the regularities of genetic transmission that permit the construction of genetic maps that its generality was doubted. But in the late 1960s evidence began to accumulate that bacteriophages and bacteria contain mobile DNA sequences. During the following two decades, it became clear that transposable elements are not only ubiquitous but are extraordinarily abundant in the genomes of many organisms. As awareness of the importance of her discovery grew, so did public recognition. Commencing with the National Medal of Science in 1970, McClintock received a number of prestigious awards, culminating in the award of an unshared Nobel Prize in Physiology or Medicine in 1983 for her discovery of transposition almost forty years earlier.

EARLY LIFE AND EDUCATION

Barbara McClintock was born in Hartford, Connecticut, to Sara Handy McClintock and Thomas Henry McClintock. Her mother was an accomplished pianist as well as a poet and painter, and her father was a physician. Barbara was the third of four children born while Dr. McClintock was struggling to establish his medical practice. By her own account, McClintock was an odd child and her relationship with her mother was difficult from the beginning. From about the age of three until she began school, Barbara lived in Massachusetts with an aunt and uncle. She accompanied her uncle, who was a fish dealer, first in a horse-drawn cart and later in his first motor truck. She reported enjoying this time and attributed her later interest in cars to watching her uncle struggle with his vehicle's frequent malfunctions.

McClintock returned home to attend school, and in 1908 the family moved to Brooklyn, New York. McClintock described herself as self-contained from a very early age, recounting her mother's report that she could entertain herself for unusually long periods even in infancy. Later, she preferred sports, as well as solitary occupations such as reading or just sitting still and thinking. Both parents were quite unconventional in their attitudes toward child rearing: they were interested in what the children would and could be, rather than what they should be. They believed that formal schooling was only a part of a child's education, of equal importance with other experiences. When, for example, Barbara showed an interest in ice skating, her parents bought her the best equipment available and let her skip school to skate when the weather was right for it.

Barbara had a very special relationship with her father, who was extremely perceptive of and responsive to her as a human being. Even as a child, McClintock had an uncanny sensitivity toward people. She recounted having a teacher who disturbed her intensely because of her perception that the teacher was spiritually repulsive. Rather than make light of her reaction to the teacher, McClintock's father took her out of school and provided her with a private tutor. And despite the strained relationship between them, McClintock's mother fully supported her daughter's unconventional life style. Barbara described an incident from childhood in which a neighbor chided her for playing boys' games in the street, telling her it was time for her to learn to do the things that girls do. Upon hearing of the incident, Barbara's mother telephoned the neighbor and firmly told her never again to speak to her daughter in that fashion.

McClintock attended Erasmus Hall High School in Brooklyn, and during her high school years it became increasingly obvious that she would not outgrow her childhood oddities and become a conventional young woman. She discovered science; she loved to learn, and most of all, to figure things out. Barbara recalled her mother's deep concern that she might become a female college professor, whom her mother viewed as creatures that really didn't belong to society and had a difficult life. During this period, Barbara too became increasingly aware that doing what she wanted to do would have painful consequences. But she knew, as well, that she had to follow her own inclinations, whatever the consequences.

At the time McClintock graduated from high school in 1918, the family situation was difficult. Although Barbara had set her heart on attending Cornell University, there was very little money and her mother was firmly opposed to further education for her daughters, believing that it made them unmarriageable. Barbara took a job at an employment agency and spent evenings continuing her education by reading in the library. Just days before the semester started and with the intervention of her father, the decision was reversed. Barbara took a train to Ithaca and began her studies at Cornell, where she would stay to earn her doctor of philosophy degree.

PROFESSIONAL HISTORY

McClintock flourished at Cornell, both socially and intellectually. She loved learning and she was well liked—so much so that she was elected president of the women's freshmen class. But the decisions she made during her university years were consistent with her adamant individuality and self-containment. She enjoyed her social life, but she knew that none of her relationships would last. Her comfort with solitude and the tremendous joy that she experienced in knowing, learning, and understanding were to be the defining themes of her life. In her junior year, after a particularly exciting course in genetics, her professor invited her to take a graduate course in genetics. After that, she was treated much like a graduate student, and by the time she had finished her undergraduate coursework, there was no question in her mind: she had to continue her studies of genetics.

But while Cornell had a group of outstanding geneticists, genetics was taught in the plant breeding department, which did not take female graduate students. So McClintock registered in the botany department with a major in cytology and a minor in genetics and zoology. She began to work as a paid assistant to Lowell Randolph, a cytologist who had been appointed to a position at Cornell supported by the U.S. Department of Agriculture to complement the work of the maize geneticists and, it was hoped, strengthen the maize plant breeding efforts. McClintock and Randolph did not get along well and soon dissolved their working relationship, but as her colleague and lifelong friend Marcus Rhoades later wrote: "Their brief association was momentous because it led to the birth of maize cytogenetics." The initial task of reliably identifying each of the ten maize chromosomes had not yet been accomplished. Progress was limited by the inadequacy of the existing staining techniques, as well as the fact that the chromosomes in the root tip material generally used for such studies could not be reliably distinguished. McClintock solved both problems. As Rhoades related it:

It was McClintock who capitalized on the use of Belling's new acetocarmine smear technique. In the course of her triploid studies, she had discovered that the metaphase or late prophase chromosomes in the first microspore mitosis were far better for cytological discrimination than were root tip chromosomes in paraffin sections. In a few weeks' time she had prepared an idiogram of the maize chromosomes, which she published in *Science*.

This was McClintock's first major contribution to maize genetics and laid the groundwork for a veritable explosion of discoveries that connected the behavior of chromosomes with the genetic properties of the organism, defining the new field of cytogenetics. McClintock was awarded the doctor of philosophy degree in 1927 and appointed an instructor. She had no thought of leaving Cornell and she knew exactly what needed to be done next: the maize genetic linkage groups had to be assigned to chromosomes. Again in Rhoades's words: "The years at Cornell from 1928 to 1935 were ones of intense cytogenetical activity. Progress was rapid, the air electric." The group was small, including Professor R. A. Emerson, the founder of maize genetics, McClintock, Beadle, Burnham, Rhoades, and Randolph, together with a few graduate students. McClintock had by then discovered that the pachytene chromosomes in microsporocytes were far superior to those of microspores for cytogenetic work, and the discoveries followed each other in rapid succession. Each linkage group was soon assigned to a chromosome, and the physical correlates of their genetic behavior became the primary focus of investigation.

A new graduate student, Harriet Creighton, joined the group in 1929. McClintock took charge of organizing her program of graduate study, persuading her to major in cytology and genetics. In the spring of the following year, McClintock suggested that Creighton take on the work of establishing a correlation between genetic recombination and the chromosomal crossovers that could be observed cytologically. McClintock provided stocks that had the appropriate genetic and cytological markers and guided the work, which showed for the first time that the genetic recombination was a reflection of the physical exchange of chromosome segments. The work, authored by Creighton and McClintock, was published in the *Proceedings of the National Academy of Sciences* in 1931 and was perhaps McClintock's first seminal contribution to the science of genetics, many more of which were to follow. Among the most important of her discoveries during the next few years, sometimes made alone, sometimes together with others, were that sister chromatids also exhibit genetic and cytological crossing-over, that genes can be physically localized on the chromosomes, that nonhomologous chromosome pairing has genetic consequences, that the formation of ring-shaped chromosomes accounts for certain types of phenotypic variegation, that the centromere is divisible, that broken chromosomes can undergo repeated cycles of fusion and breakage, and that a particular chromosomal site, the nucleolus organizer region (NOR), is essential to the development of the nucleolus.

Although McClintock's fame was growing, she had no permanent position. Cornell was hospitable to women students, but it had no women professors in fields other than home economics. Between 1931 and 1933, McClintock was supported by a fellowship from the National Research Council and worked at the California Institute of Technology and the University of Missouri, as well as Cornell. Lewis Stadler invited her to examine the chromosomes of X-irradiated plants that showed various abnormalities. She found that the irradiation had caused a variety of structural changes in the chromosomes, including translocation, inversions, deletions, and the formation of ring chromosomes. Coming to Cal Tech at T. H. Morgan's invitation, McClintock began to study the point at which the nucleolus attached to the chromosome. This led to her identification of the NOR (McClintock rued the grammatical error she made initially in naming this site the "nucleolar organizing body") and a description of its properties. She used stocks in which a translocation had broken the NOR into two segments, and her main conclusion was that each part of the NOR could organize an independent nucleolus and thus the NOR was genetically subdivisible. Describing the effect of McClintock's NOR publication, cell biologist Joseph Gall has written:

> Out of the hundreds of papers we have each read, a half dozen or so stick in our minds because of their beautiful logic, their clarification of an otherwise obscure set of data, or simply their technical elegance. . . . For me, one of Barbara McClintock's early cytogenetic papers falls in this category—her analysis of the nucleolus of maize published in 1934 in the *Zeitschrift für Zellforschung und Mikroskopische Anatomie* under the title, "The relation of a particular chromosomal element to the development of the nucleoli in *Zea mays.*"

In 1933 McClintock received a Guggenheim Fellowship to go to Germany. McClintock was utterly unprepared for what she encountered in prewar Germany, and she returned to Cornell before the year had elapsed. Her prospects were dismal. She had completed graduate school seven years earlier and had already attained international recognition, but as a woman she had little hope of securing a permanent academic position at a major research university. Emerson obtained a grant from the Rockefeller Foundation to support her work for two years. Nominally paid as Emerson's assistant, she continued to work independently. McClintock was discouraged and resentful of the disparity between her prospects and those of her male counterparts. Her extraordinary talents and accomplishments were widely appreciated, but she was also seen as "difficult" by many of her colleagues, in large part because of her quick mind and intolerance of second-rate work and thinking. And while a number of prominent colleagues sought to help secure her an appropriate academic position, the fact remained that few positions commensurate with her accomplishments were open to women.

Finally, in 1936 Lewis Stadler was able to convince the University of Missouri to offer her an assistant professorship. She accepted the position and began to follow the behavior of maize chromosomes that had been broken by X-irradiation. She learned that the ends of newly broken chromosomes tend to fuse with each other, creating dicentric chromosomes that break again when a cell divides and chromosomes are distributed to the daughter cells. She also described conditions under which broken chromosomes "healed" or were repaired in some way so that they could function normally. She reported briefly in a paper published in *Genetics* in 1944 that in a certain stock a broken chromosome end that would normally "heal" during development of the embryo failed to do so. This implied that the addition of chromosome ends, termed telomeres, was an active genetic process and that the responsible gene in the stock had been inactivated by mutation. Elizabeth Blackburn, who discovered the enzyme that adds telomeres to chromosomes, wrote that "this information was in my mind when I made the decision to look for an enzymatic activity that adds telomeric DNA to DNA ends."

Though McClintock's reputation continued to grow (she was elected vice-president of the Genetics Society in 1939), her position at Missouri remained tenuous. She understood soon after her arrival that hers was a special appointment. She found herself excluded from regular academic activities, including faculty meetings, and eventually came to the realization that she was not only unlikely to be promoted but that her continued employment depended on Stadler's presence. In 1941 she took a leave of absence from Missouri and departed with no intention of returning. She wrote her friend Marcus Rhoades, who had just taken a position at Columbia University, asking where he was going to grow his corn. He was planning to go to Cold Spring Harbor for the summer. An invitation for McClintock was arranged through Milislav Demerec, who was a member of the Genetics Department of the Carnegie Institution of Washington, then the dominant research laboratory at Cold Spring Harbor. Demerec became the department's director late that year and offered McClintock a year's research appointment. Though hesitant to commit herself, McClintock accepted. When Demerec proposed making the appointment permanent, McClintock was quite reluctant but agreed to fly to Washington to speak with Vannevar Bush, then president of the Carnegie Institution. McClintock recalled that they took to each other immediately and that both enjoyed the visit immensely. Bush supported Demerec's wish to appoint McClintock as a permanent member of the research staff. McClintock accepted, still unsure whether she would stay.

McClintock did stay. She was a staff member of the Carnegie Institution of Washington's Genetics Department until 1967, whereupon she became distinguished service member of the Carnegie Institution, remaining at Cold Spring Harbor until her death in 1992. Carnegie gave her the freedom to do her work unfettered by teaching and other academic duties. McClintock's dislike of making commitments was a given: she always wanted to be free—free to do exactly what she wanted to do, when she wanted to do it. Indeed, she insisted that she would never have become a scientist in today's world of grants because she could not have committed herself to a written research plan. It was the unexpected that fascinated her, and she was always ready to pursue an observation that didn't fit.

Settling in at Carnegie, McClintock continued her studies on the behavior of broken chromosomes, devising a method of using them to produce mutations on the short arm of chromosome 9. In 1944 and 1945, the years she was elected to the National Academy of Sciences and the presidency of the Genetics Society, respectively, McClintock reported in the *Yearbook* of the Carnegie Institution of Washington on her analysis of progeny grown from self-pollinated plants obtained by crossing parents, each of which bore a broken chromosome 9. She detected many mutations among these progeny, including the expected terminal deficiencies, some internal deficiencies of various sizes, and some "provocative" mutants that showed variegation from the recessive to the dominant phenotype. She further reported observing "an interesting type of chromosomal behavior" involving the repeated loss of one of the broken chromosomes from cells during development. What struck her as odd in the light of her previous studies on broken chromosomes was that in this particular stock it was always chromosome 9 that broke and it always broke at the same place. McClintock called the labile chromosome site *Dissociation* or *Ds* because "the most readily recognizable consequence of its actions is this dissociation." She quickly established that the *Ds* locus would "undergo dissociation mutations only when a particular dominant factor is present." She named this factor *Activator* (*Ac*) because it activated chromosome breakage at *Ds*. By the time she wrote her report for the Carnegie *Yearbook* published in 1948, she had reached some extraordinary conclusions about these loci. *Ac* was not only required for *Ds*-mediated chromosome breakage but could destabilize previously stable mutations, much as her friend Marcus Rhoades had described several years earlier for a pair of interacting loci, one of which was an allele of the maize *a* locus. But more than that, and unprecedented, the chromosome-breaking *Ds* locus could "change its position in the chromosome"; it could *transpose*. Moreover, she had evidence that the *Ac* locus was required for transposition of *Ds* and that, like the *Ds* locus, the *Ac* locus was also mobile.

Within several years, McClintock had established beyond any doubt that both the *Ac* and *Ds* loci were not only capable of changing their positions on the genetic map but also of inserting into loci to cause unstable mutations of a type initially studied by R. A. Emerson at the P locus of maize. By the time she prepared her paper for the Cold Spring Harbor Symposium of 1951, McClintock had isolated unstable alleles of at least four different genes. Some were caused by the insertion of the *Ds* element and so required the presence of *Ac* for instability. Others were caused by insertion of the *Ac* element itself and were inherently unstable. She had determined that the instability of such mutations, which had long fascinated geneticists and horticulturists, was attributable to the frequent departure of the inserted genetic element from the gene during development, restoring normal function and, concomitantly, the wildtype phenotype. She had also identified different noninteracting "systems" of mutability, later renamed transposable element "families."

McClintock recounted that the reaction to her symposium presentation ranged from perplexed to hostile. Later, she published several papers in refereed journals and from the paucity of reprint requests, inferred an equally cool reaction on the part of the larger biological community to the astonishing news that genes could move. After that, McClintock tended to write up her results *as if* for publication and file them, publishing little more than concise summaries of her results in the annual *Yearbook* of the Carnegie Institution and occasional overviews for symposia. McClintock continued her analysis of the *Ac-Ds* transposable element family and began the study of a new element that she called *Suppressor-mutator* or *Spm*. This element, which also came in versions that could transpose autonomously and versions that could not, had many of the characteristics of the *Ac-Ds* family but exhibited an even more complex behavior. Some insertion mutations, for example, did not completely suppress expression of the affected gene, except when the fully functional *Spm* element was present in the same genome, implying that the element could produce a substance that affected expression of the mutant gene.

These descriptions of McClintock's of what proved to be the first example of an interaction between a trans-acting regulatory factor and its DNA binding site, were published well before Jacob and Monod's seminal work on the regulation of the *lac* operon in *E. coli*. McClintock immediately saw and attempted to draw attention to the parallels between these regulatory phenomena by adopting Jacob and Monod's terminology to the regulation of maize gene expression mediated by transposable elements. More fascinating yet, McClintock found that the *Spm* element could become heritably inactivated by a genetic mechanism that differs strikingly from conventional mutation by its reversibility. Indeed, although the element could be transmitted in an extremely inactive form through many plant generations, it remained capable of both transient and heritable reactivation. In particular, McClintock came to the conclusion that an active element could activate an inactive one so long as both were present in the same genome. This suggested that an active element provides a substance that activates the element, either directly or by interfering with the genetic mechanism that is responsible for inactivation.

By this time, McClintock's work had taken her far outside the scientific mainstream and in a profound sense she had lost her ability to communicate with her colleagues. There have been many attempts at explanations, all of which undoubtedly contain a measure of truth. By her own admission, McClintock had neither a gift for written exposition nor a talent for explaining complex phenomena in simple terms. But perhaps there are more important factors, since patient readers have found both her early and her later papers not only comprehensible but indeed intellectually elegant. First, the very notion that genes can move was in deep contradiction to the regular relationships among genes that underlie the construction of linkage maps and the physical mapping of genes onto chromosomes. The evidence that genes maintain their positions relative to each other was overwhelming: the concept that genetic elements can move would undoubtedly have met with resistance regardless of author and presentation. Indeed, even twenty years after McClintock's initial report, emerging evidence that mobile elements exist in bacteria was met with skepticism.

And more than that, by the time McClintock took up the study of transposition, she was not just a brilliant beginner but an accomplished, experienced, mature cytogeneticist. Her experiments were very complex and difficult to communicate even to the quickest of minds. Mel Green recounts that shortly after the 1951 Cold Spring Harbor Symposium, he and several other geneticists queried Sturtevant, arguably one of the century's leading geneticists, about what McClintock had said. Green quotes Sturtevant as saying: "I didn't understand one word she said, but if she says it is so, it must be so!" Such was the intellectual respect that McClintock commanded—and such was the strangeness of concept and complexity of her experimentation.

McClintock was deeply frustrated by her failure to communicate, but her fascination with the unfolding story of transposition was sufficient to keep her working at the highest level of physical and mental intensity she could sustain. Her work on transposition was interrupted only twice. The first interruption was a visit to Stanford in 1944 in response to an invitation from George Beadle, who thought she was precisely the person to work out the problem of identifying the chromosomes of the mold *Neurospora*, which had become a popular organism for molecular geneticists. The second occurred in the late 1950s when the National Academy of Sciences established a committee to identify and collect indigenous races of maize in Central and South America out of concern that the introduction of high-yielding agricultural hybrids would result in their disappearance. McClintock was asked to help train local cytologists to carry out the work of classifying the maize races by chromosome morphology. McClintock spent the winters of 1958 and 1960 in Central and South America, fascinated by the emerging realization that the spread of maize through the region could be tracked by the chromosome constitution of the indigenous populations. The work was summarized briefly in the *Yearbooks* of the Carnegie Institution, appearing as a full monograph in 1978.

But transposition remained McClintock's central passion. By the time of her formal retirement, she had accumulated a rich store of knowledge about the genetic behavior of two markedly different transposable element families. She was sufficiently confident of the importance of her work to carefully preserve all of the stocks with mutant elements that she accumulated along the way, perhaps in unconscious preparation for the new generation of molecular geneticists. And indeed, beginning at about the time her active fieldwork ended, transposable genetic elements began to surface in one experimental organism after another. These discoveries began in an altogether different age. In the two decades between McClintock's original genetic discovery of transposition and its rediscovery, genetics had undergone as profound a change as the cytogenetic revolution that had occurred in the second and third decades of the century. The genetic material had been identified as DNA, the manner in which information was encoded in the genes had been deciphered, and methods had been devised to isolate and study individual genes. Genes were no longer abstract entities known only by the consequences of their alteration or loss: they were real bits of nucleic acid that could be isolated, visualized, subtly altered, and reintroduced into living organisms.

Thus, soon after the initial realization that mutations of a certain type that occurred in bacterial viruses might be attributable to the insertion of a foreign DNA sequence, visual evidence was obtained by electron microscopic analysis of heteroduplexes between homologous DNA sequences having and lacking the insertion. The newly inserted mobile elements appeared as unpaired loops of DNA extending from the DNA duplex. Mobile genetic elements were no longer abstract concepts. Although the study of maize transposable elements had been an active and productive field of research since Emerson's original studies on variegation at the P locus long before McClintock explicated the underlying genetic mechanisms, the recognition that mobile elements are ubiquitous and in fact extraordinarily abundant components of the genomes of many, if not all, organisms grew slowly during the 1970s and 1980s.

My first encounter with McClintock, which was to lead eventually to the molecular cloning and characterization of the maize elements, took place during a visit to the Cold Spring Harbor Laboratory in 1978. The laboratory itself was no longer the same institution that McClintock had joined almost four decades earlier. The Genetics Department had been closed by the Carnegie Institution of Washington, although a Genetics Unit consisting of McClintock and A. Hershey, both retired, had been maintained. J. D. Watson was by then the director of a vastly larger complex of laboratories at Cold Spring Harbor, all engaged in molecular biological investigations. I had been asked to give a seminar at the Cold Spring Harbor Laboratory on my postdoctoral work in Don Brown's laboratory at the Carnegie Institution of Washington's Department of Embryology in Baltimore. Although McClintock was unable to attend the lecture, I encountered her by chance in a hallway of the Demerec Laboratory, and she invited me to her spacious laboratory for a chat. We talked for several hours, and I was drawn to the clarity and depth of her discourse, no matter the subject. It was so at variance with her reputation for obscurity that I was prompted to read her papers from beginning to end upon my return to Baltimore. I was intrigued with what I found to be a marvelous genetic detective story, and when I received an unexpected offer of a permanent staff position at Carnegie's Embryology Department, I immediately decided to tackle the molecular analysis of the maize elements.

The task I had taken on proved daunting, as much because of the distance between McClintock's classical genetic approach and that of the molecular biologist as because plant molecular biology simply didn't exist yet. Our relationship began in earnest when I grew my first corn crop consisting of McClintock's transposable element stocks during the summer of 1979 at the Brookhaven National Laboratory, where we were kindly offered space and help by Ben and Frances Burr. Although McClintock was highly critical of my first efforts at maize genetics, enough of the right crosses got done despite my ignorance, so that I had the material I needed to begin the molecular cloning of first the *Ac* and *Ds* elements and, later, the *Spm* element. Our first interactions were difficult, and it took several years before we were comfortable with each other's way of thinking. But in time we both came to value deeply the intellectual as well as the personal side of our relationship.

By the time the maize elements were cloned and their molecular analysis began, the importance of McClintock's discovery of transposition was widely recognized. She received the Kimber Genetics Award in 1967, the National Medal of Science in 1970, and the Lewis S. Rosensteil Award and the Louis and Bert Freedman Foundation Award in 1978. In 1981 she was named prize fellow laureate of the MacArthur Foundation and received the Wolf Prize and the Lasker Basic Medical Research Award. In 1982 she shared the Horwitz Prize. Finally, in 1983, thirty-five years after publication of the first evidence for transposition, McClintock was awarded the Nobel Prize for Physiology or Medicine. Yet while the money attached to these prizes increased her financial security, something to which she'd given little thought in earlier years, she found the ceremonies arduous and the attendant publicity and adulation utterly repugnant. She longed for her privacy, and she was exhausted and disturbed by the endless stream of requests that only seemed to grow in volume with each award. Suddenly everyone wanted her: there were honorary degrees, keynote speeches, lectures, interviews—even autograph hunters.

And still, through it all, McClintock never lost her connection with science—she never retired. She continued to live at Cold Spring Harbor, spending her last years in a spartan apartment on the ground floor of Hooper House, a women's dormitory heavily used during the summer meetings season at the laboratory. She attended every session of the annual Cold Spring Harbor Symposium, as well as seminars, the year around. She read voraciously, lamenting her failing vision. Her laboratory was filled with books on all subjects, and the tables were covered with stacks of articles copied from current journals, many with sentences carefully underlined here and there, giving evidence of careful attention. She was keenly aware of every development in the molecular and genetic analysis of the maize transposable elements as it unfolded in my laboratory and elsewhere. She took special interest in the analysis of the complex and elegant *Spm* family of elements, my own particular favorite. Not until the last few years of her life did the molecular and genetic studies on this family of elements become so complex that she began to find it difficult to follow and remember the details. Even when I visited Cold Spring Harbor in 1991 to give a course lecture on the molecular genetics of the maize transposable elements, McClintock sat through the entire session, which lasted late into the evening. Her questions were penetrating and her observations invariably widened the discussion: the students were amazed.

It was during this visit that I was approached by Jim Inglis of the Cold Spring Harbor Press to assemble a volume in honor of McClintock's ninetieth birthday the following year. I took on the project, despite qualms that Barbara would find this not a gift but another burden. David Botstein, who joined me in this effort, and I approached a number of individuals whose lives had intersected with McClintock's to write for this volume. What emerged was *The Dynamic Genome*, a collection of varied essays each reflecting the pursuits and passions ignited by the sparks and embers scattered from the fierce blaze of McClintock's intellect through the decades of this century of genetics. Many of the authors joined in the celebration of her ninetieth birthday at the home of Jim Watson, not far from her modest apartment on the laboratory grounds. She knew nothing of the book but recognized her friends—even Harriet Creighton, her first "unofficial" graduate student, had made the trek to Cold Spring Harbor. We settled Barbara on Jim's front porch and I began to read aloud the introduction and the list of authors and their essays. At first she joked a bit, discomfited by the attention. But soon her face began to glow as she perceived the depth of understanding and respect gathered around her, lovingly collected between the covers of the book. She said later it was the best party ever for her, though she admitted that it had taken a week to recover at her age. She was sure that she would die at ninety and a few months later she was gone, drifting away from life gently, as a leaf separates from an autumn tree. What Barbara McClintock was and what she left behind are eloquently expressed in a few short lines written many years earlier by her friend and champion Marcus Rhoades, whose death preceded hers by a few short months:

> One of the remarkable things about Barbara McClintock's surpassingly beautiful investigations is that they came solely from her own labors. Without technical help of any kind she has by virtue of her boundless energy, her complete devotion to science, her originality and ingenuity, and her quick and high intelligence made a series of significant discoveries unparalleled in the history of cytogenetics. A skilled experimentalist, a master at interpreting cytological detail, a brilliant theoretician, she has had an illuminating and pervasive role in the development of cytology and genetics.

THE QUOTATIONS ATTRIBUTED to McClintock are from her publications on transposition, primarily the annual reports appearing in the *Yearbooks* of the Carnegie Institution of Washington; all of these are reproduced in *The Discovery and Characterization of Transposable Elements: The Collected Papers of Barbara McClintock* (New York: Garland Publishing, 1987). All other quotations, with the exception of the first and last (Bateson and Rhoades), appear in the chapters by the individuals to whom they are attributed in *The Dynamic Genome: Barbara McClintock's Ideas in the Century of Genetics* (ed. N. Fedoroff and D. Botstein; Cold Spring Harbor: Cold Spring Harbor Press, 1992). The Bateson quotation appears in E. A. Carlson's, *The Gene: A Critical History* (Philadelphia: W. B. Saunders). The final quotation of M. M. Rhoades was taken from an undated document in the files of the Carnegie Institution of Washington titled "Barbara McClintock: Statement of Achievements," possibly prepared in support of her nomination for an award. Other than my own recollections of conversations with McClintock, my principal source of information about her early life and the chronology of later events was E. F. Keller's, *A Feeling for the Organism: The Life and Work of Barbara McClintock* (San Francisco: Freeman, 1983), as well as a copy of McClintock's curriculum vitae, given by her to me in about 1980 together with one of her two complete collections of her reprints.

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