

Barbara McClintock's Final Years as Nobelist and Mentor: A Memoir

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September 2, 2017, marks the 25th year after the passing of Dr. Barbara McClintock, geneticist and recipient of the 1983 Nobel Prize in Physiology or Medicine for her discovery of transposable elements in maize. This memoir focuses on the last years of her life—after the prize—and includes personal recollections of how she mentored young scientists and inspired the age of genetics, epigenetics, and genomics.

Early each morning for what seemed to be an eternity, a smallish figure walked along Bungtown Road at the Cold Spring Harbor Laboratory (CSHL). Hands clasped behind her back, wearing khaki pants and a crisp white shirt, holding a plaid bag, Dr. Barbara McClintock moved from her apartment to her laboratory with an intense pace and purpose. She was well known on the CSHL grounds, and people would often stop to chat. When they did, they were frequently met with a pleasant conversation encompassing anything from local news to the latest scientific findings. If she had a meeting, Dr. McClintock was always direct but polite in indicating her need to be somewhere else. There have been many accounts and writings regarding McClintock's intense focus, her solitude in the pursuit of scientific questions, and her wish for privacy. While her intensity and scientific focus were not exaggerated, Barbara McClintock was also well known as a generous mentor to many, particularly to graduate students, postdocs, and new investigators, and especially women in the sciences. McClintock discovered the movement of DNA transposable elements and investigated their properties for more than half of her long career and was awarded the Nobel Prize in Physiology or Medicine in 1983 (McClintock, 1984). It has been 25 years since her passing on September 2nd, 1992. This memoir is to thank her not only for the extraordinary advances she gave to science, but also for the personal mentoring she gave to younger scientists like us, particularly in the last 10 years of her life.

It was the early 1980s, and plant genetics at CSHL had waxed and waned over the years, culminating with the closure of the Carnegie Institute of Genetics in the early 1970s, and McClintock's corn field making way for the library parking lot. But McClintock continued her work, and following the discovery of bacterial transposable elements, she began discussions with Ben and Frances Burr at Brookhaven National Laboratory and with Nina Fedoroff at the Carnegie Institute of Embryology in Baltimore regarding the molecular isolation of transposons in maize. Barbara had advanced the study of mobile elements as far as she could, and it was time to understand mechanisms at the molecular level. To regenerate her stocks, she planted her seeds at Brookhaven in the late 1970s.

Under the tutelage of McClintock, Ben and Frances Burr cloned the first *Ds* element (Burr and Burr, 1982), and Susan Wessler and Nina Fedoroff cloned the controlling *Ac* element (Fedoroff et al., 1983). This was accomplished by first purifying the waxy protein, which encodes an enzyme for starch biosynthesis, and then using Barbara's waxy mutable (*wx-m*) alleles (McClintock, 1948) to map and clone the transposons inserted within the corresponding gene. Barbara told Sue that she had a cold room flood early on and lost many of her strains. This included *wx-m1* through *wx-m5*. Lost for good were unique alleles designated *wx-m2* through *m4*; however, Drew Schwartz, a maize geneticist trained by Marcus Rhoades (McClintock's colleague), acquired some of McClintock's stocks

earlier. He had *wx-m1* and a sole *wx-m5* seed, which was adhered to a wooden block, where it had been scraped and stained with iodine-potassium iodide for display purposes. McClintock showed Sue her crossing records, where she used that one seed to grow a plant and make over 150 crosses (her plants were bred for numerous tillers and large tassels, the male flowers at the top of the plant, for maximum fecundity). She then proceeded to climb up on a countertop, stood up, reached into a cabinet, and pulled out the block with the missing seed. Sue remembers being petrified that she would fall. She had just won the Nobel Prize and Sue was imagining the headline: "Nobel Laureate falls and breaks neck while clueless young scientist watches in horror!" But Barbara was more eager to congratulate the young scientist on her *Cell* paper on cloning *Ac* than on winning the Nobel Prize herself.

By the 1970s and 1980s, the involvement of DNA transposition was being proposed in a number of gene regulatory mechanisms. The team of Jim Hicks, Jeff Strathern, and Amar Klar at CSHL utilized the power of yeast genetics and molecular biology to advance the DNA transposition model in yeast mating-type switching (Klar and Fogel, 1979). Klar's work on epigenetic inheritance of mating-type switching fascinated McClintock, so much so that Strathern later repeated some of Barbara's experiments in corn. It was no surprise, then, that interest in the perceived "anomaly" of DNA movement reemerged. Building on the CSHL plant course, which started

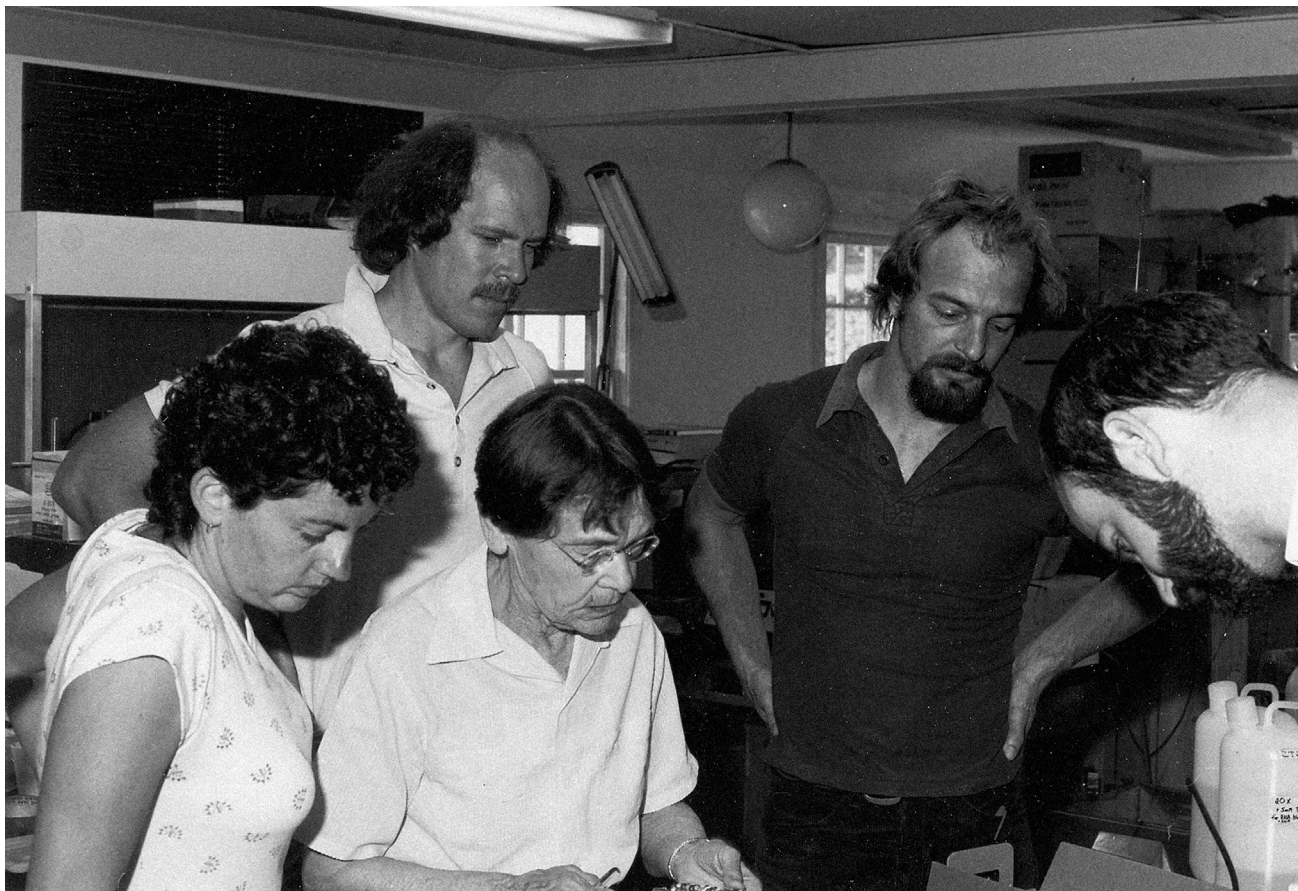


Figure 1. Barbara McClintock at the Plant Course, Cold Spring Harbor Laboratory, 1981

In the early years of the plant course, Barbara would demonstrate maize transposon genetics using demonstration ears and kernels she had saved (Figure 3). Courtesy of Cold Spring Harbor Laboratory Archives.

some years earlier (Figure 1), Jim Watson held a meeting at the Banbury Conference center in 1984, attended by many prominent plant scientists—and, of course, Barbara herself—to relaunch plant genetics research at CSHL. A strong interest in McClintock's transposons emerged from a new postdoc, Stephen Dellaporta, in Jim Hick's lab. Paul joined soon after as Dellaporta's first graduate student (when Stephen was promoted to the faculty) studying genetic and epigenetic changes to maize transposable elements. Dr. McClintock became a member of his thesis committee. Jim Hicks recalls how the transition was made from yeast to plants. "After cloning the mating-type genes and validating our model for transposable gene regulation, we, with a certain amount of hubris, turned to Barbara for insight into how we could clone, in particular, the *R1* (red) gene from maize.

This locus held such interest because a number of genetic phenomena, including compound gene structure, epigenetic control (paramutation), and intragenic crossing over, were already genetically defined for this easily scored plant- and kernel-color-controlling gene. This led to innumerable conversations with Barbara, which she welcomed. However, since our first step would always be to make a model, for example the structure of the *R* locus, she would stop abruptly and firmly say, 'No, that is not the way;' 'You must understand the whole organism;' 'The structure will reveal itself step by step.'

Many of McClintock's insights came from the identification of novel patterns, mutants, from the expected behavior of gene action. One of the key observations came in the early 1940s, when she was studying the behavior of broken chromo-

somes (breakage-fusion-bridge cycle). By setting up an elegant use of a chromosome duplication/deletion along with genetic markers on chromosome 9, McClintock could induce random chromosome breakage along the short arm with each mitotic division (McClintock, 1941). In the progeny of crosses in which broken chromosomes were passed from both parents, she identified an unusual occurrence: the loss of chromosome markers was occurring at only one location, generating a reoccurring unique color pattern in the kernels. This pattern was heritable, reappearing consistently in the progeny from this one kernel. Recombination studies localized the breakage (dissociation) proximal to the *Waxy* locus on chromosome 9S, yet it had the ability to move and be localized to a different chromosome position in a heritable manner (McClintock, 1951).

During these studies from 1946–1949, additional changes, termed mutable loci, could be attributed to this *Ds* element, where the kernel color gene, *C1*, was restored upon excision, resulting in sectors of colored aleurone cells on a field of colorless cells (McClintock, 1948). Segregation data revealed that both chromosome dissociation (breakage) and gene control required the presence of a second unlinked locus. This locus could also change its chromosomal position on occasion. McClintock logically concluded that the chromosome “Dissociation” factor could both move and control gene expression (McClintock’s “gene action”), hence the discovery of mobile controlling elements, appropriately named *Ds* (*Dissociation*) and *Ac* (*Activator*).

Her constant focus on unique patterns was always reinforced during discussions of the maize plant. One day while visiting her laboratory, Paul was handed a few envelopes containing single seeds. A hand written note across the front asked: “what is different about this kernel?” Scientific discussions with Dr. McClintock were rarely brief, particularly when visiting her laboratory and office. The lab was a modest-size open room, with tables usually neatly displaying a few ears of corn or packets of seed. Her low-power dissecting scope was always on the east-side table, and her microscope—the instrument she used to describe the structure of all 10 chromosomes of maize—was also available. Two large filing cabinets held her pedigree information and field notes, the “database” that carried the core information about all the studies. Dr. McClintock would access this database with incredible efficiency during a discussion. Off the lab was her office containing a large desk, surrounded by books and publications along with a cot for naps. A door led to the seed storage room, a very small temperature- and humidity-controlled area. Discussions often started with a greeting at her door followed by a simple question or the presentation of a new observation. Hours would pass as Dr. McClintock pulled out ears and kernels from the storage room and observation notes and pedigree examples from the filing cabinets to explain the “simple” question or show how her extensive work would or would not bolster an observation. No less than 3 hours would pass before

coming up for air. As Paul recalls, “just when my blood sugar was low and my brain was filled, Dr. McClintock would stop the discussion and observe how exhausted I looked.” She would reach into the cabinet and pull out a jar of freshly baked brownies with black walnuts. Tea time accompanied this delicacy as she herself collected and prepared the nuts and baked the dessert. Cracking open the tough black walnut fruit was always a sight. McClintock would lay them out across her driveway and roll her Honda Accord over them. The time spent with a single graduate student was astounding, as was the extent of influence she would have on the approach to scientific investigation that she instilled on all of us.

Days before one of these genetics lessons, Paul decided to bring Dr. McClintock a bouquet of beautiful variegated red carnations to show his appreciation. Paul was feeling a bit unsure that this innocent act would be taken as an appropriate gesture, but what could be more innocent than a young graduate student giving his 82-year-old professor a bunch of flowers?

Walking into her lab, he handed the bouquet over and waited; she looked intently at the flowers and commented about their variegated pattern. She then proceeded to take them over to the bench, where she drew a scalpel and dissected the flower to reveal the developmental nature of the variegated pattern. It was a wonderful lesson in plant development revealed by clonal sectors, as she had famously described for plants with unstable ring chromosomes (McClintock, 1938). This led to accessing her plant notes, kernel photos, publications, and eventually brownies and tea. Clearly not the outcome Paul was expecting at the time, but looking back, he should have expected nothing less or more.

During this time, CSHL leased land from the nearby nature conservancy to grow the first genetics field since McClintock planted her last on the grounds in 1968. Studies with her material had already been underway at other locations with Nina Fedoroff and Ben and Francis Burr. Many of those long discussions had also occurred throughout the fall and winter between McClintock and Dellaporta. As the spring neared and planting preparation was upon us, discussions switched to the

more practical needs of field preparation and planting. McClintock had very particular, tried-and-true methods in field, plant, and seed care. She meticulously taught us her methods down to the brands of card, stapler, and paper clip used in the field. Getting ready to plant involved setting up cards, setting up experiments by organizing the field with tester stocks in one place, planting straight rows with a string, measuring seed to seed distance with a marked wooden board, and poking seed holes with a stick. Dellaporta and Chomet were on hands and knees, and McClintock right beside them with the stick, orchestrating the entire planting. As the plants grew, it was not unusual to find Dr. McClintock in the field at 6:30 a.m., weeding the rows before pollinations began. Walking through the field each day, it was clear that she had bred her plants with multiple tillers and shorter stature—she designed them for her needs.

Along with the National Science Foundation, the seed company Pioneer Hi-bred began funding the CSHL plant group infrastructure, culminating with the arrival of Steve Briggs, a young Pioneer scientist to join the new plant group. By the mid to late 1980s, the group had expanded, and Venkatesan Sundaresan (she called his circular *Mutator* transposons “rings”), Eric Richards, and Tom Peterson were treated to brownies, jelly beans, and tea, as well as to planting advice: how to deal with crows (“they talk to each other”), deer, and raccoons. But they were also treated to inspiration in their research into transposons, telomeres, and plant reproduction. Carol Greider was a Cold Spring Harbor fellow at the time, in the same cozy building (Delbruck) that housed the plant and yeast groups, and was well aware of Barbara’s early work on telomeres, including the first description of a potential mutant in maize that could not “heal” broken chromosomes (McClintock, 1941). Carol went on to win the Nobel Prize herself in 2009 for her earlier discovery with Elizabeth Blackburn of telomerase and telomerase RNA.

By the time Rob arrived at Cold Spring Harbor in 1989, McClintock was frequently hosting famous scientists but still found time for junior colleagues. On one occasion, Rob was attempting to recombine chromosome translocations (“interchanges”) with normal chromosomes carrying *Activator*



Figure 2. Barbara McClintock in the Greenhouse with Rob Martienssen, 1990

McClintock was a patient mentor to young scientists at CSHL and elsewhere. Courtesy of Cold Spring Harbor Laboratory Archives (photo: Tim Mulligan).

transposons in order to recover interchromosomal *Ac* transpositions. Barbara had similarly recombined interchange chromosomes with conspicuous heterochromatic “knobs” 60 years earlier, in order to correlate genetic and cytological crossing over (Creighton and McClintock 1931). The procedure involved harvesting tassels while they were still enclosed within the stalk, and Barbara had a famous technique for recovering them without damaging the plant, akin to surgery with a scalpel, that she demonstrated one morning in the greenhouse. Farm manager Tim Mulligan witnessed the unlikely pair; Rob was fresh from postdoctoral studies at Berkeley and in appearance resembled a follower of The Grateful Dead. Tim grabbed his camera and asked permission to take a photo. Barbara said, “Oh, no, I haven’t done my hair!” Tim offered a comb, but Barbara was already laughing. The picture is now a classic representation of Barbara’s close

teaching relationship with younger scientists at Cold Spring Harbor (Figure 2).

One of her prized possessions was a Bausch and Lomb compound microscope, which she had used to generate extraordinary micrographs of chromosomes over the years: her discoveries included the physical basis for crossing over (Creighton and McClintock, 1931) and the first evidence for telomeres and ring chromosomes (McClintock, 1938; McClintock 1941). During the 1980s, even with her reduced vision, McClintock continued to give lessons in cytology using prepared slides. Paul Chomet and Steve Briggs, among others, observed meiotic spreads, chromosome knob arrangements, chromosome 9S deletions and duplications developed for studies of the breakage fusion bridge cycle. When she felt he could make better use of it, she gave her prized microscope to

Joe Gall at the Carnegie Institute but never lost her fascination with optics and imaging technology. David Spector was junior faculty at that time and brought Barbara into Cairns building at CSHL to show her the newly acquired confocal microscope—she was amazed and had many great questions. After using the microscope for a while, David brought some images to her office to show her the nuclear structures that he was studying, and she said, “just a moment,” and went to one of her file cabinets, thumbing through reprint folders, and pulled out a very old article that contained *camera lucida* drawings of various cell structures and said, “I think this is what you are seeing.”

Barbara’s 90th birthday was celebrated in spectacular style at Jim Watson’s house in June, 1992. Guests included Al Hershey, as well as David Botstein and Nina Fedoroff, who had edited a volume of scientific essays from Barbara’s



Figure 3. Ears of Maize Demonstrating Transposition and Chromosome Dissociation; 1947, 1949

Demonstration ears of corn kept by McClintock to illustrate the “standard” position of the transposable element *Ds* (*Dissociation*) after *C* (*colorless*), *Sh* (*shrunk*), and *wx* (*waxy*) on chromosome 9 (upper ear, from 1947) and the transposed position before *Sh*, *Bz* (*bronze*), and *wx* (lower ear, from 1949). Courtesy of Cold Spring Harbor Laboratory Archives (photo: Sarah Vermeylen).

colleagues. Rob and others had the daunting task of reading chapters to her over the summer, since medical problems made reading a burden. On September 2, 1992, after a gorgeous late summer day filled with long discussions with Rich Roberts at his farewell party, Dr. McClintock fell ill during the night and passed away at Huntington Hospital, NY.

Her distinct smile was no longer around, nor her deep insights into all aspects of biology and genetics. Yet, years prior, McClintock had begun to spread her knowledge, experience, and view of the world into the minds of many young investigators. A few months after her passing, a number of her colleagues were brought together to properly distribute and archive the contents of Dr. McClintock’s lab, office, and seed storage room. On this occasion, the time in her lab was not for learning or great scientific discussion. It was now the knowledge she passed to us that allowed us to understand the value and meaning of what was left behind.

There were no longer brownies and tea after the long days in her lab. Reprints were sorted and saved, some of her writings and notes and all her corn cards (crossing records) went to the American Philosophical Society, and others stayed at the Cold Spring Harbor archives.

We were tasked with sorting through her seed room, which was filled with invaluable but mainly nonviable seeds (as corn seed has a shelf life of about 10 years). Anything that could grow went to the Maize Genetics Cooperative Stock Center for continued growth and distribution. Some of the other material from the 1960s–1980s was shipped to the Smithsonian Museum and to the National Center for Seed Preservation (Fort Collins, CO) for future access and observations. Methodically moving through the room, we came upon a distinct stainless steel box. Inside were a number of ears of corn that were dated much earlier than all the other stocks. As we laid these ears out, one in particular caught our eye. The beautiful variegated kernels on

this 1940s relic showed the classic chromosome 9 breakage-fusion-bridge patterns, while a few kernels were missing around the ear. After checking the stock numbers, we realized that this single ear might well be from the original set of studies in which she discovered transposable elements. Additional ears from 1947 and 1949 were clearly marked with tags indicating the two different positions of *Ds* on chromosome 9 that constituted the evidence for transposition (Figure 3). She had carefully preserved these ears as demonstrations following the controversial Cold Spring Harbor Laboratory Symposium of 1951, where she had presented transposition to a mostly (but certainly not entirely) bewildered audience (McClintock, 1951). Seeing the actual material, carefully preserved, was an inspiration even after she died.

Barbara’s later reputation as something of a mystic was fueled in part by her use of terms more appropriate to physics than to biology. That is, she recognized that her “controlling elements” could undergo changes of state and changes of phase. She meant by these new but rigorously defined terms that transposons could change their genetic properties (changes of state) or epigenetic properties (changes of phase) to control gene action. It took 30 years and major advances in molecular biology to reveal that, broadly speaking, changes of state were DNA rearrangements (Weil et al., 1992), and changes of phase were changes in DNA methylation (Chomet et al., 1987). These studies led to an early explanation for the control of nearby gene expression and to the molecular nature of epialleles (Barkan and Martienssen, 1991). We were among those lucky enough to participate in these exciting discoveries, and we had the chance to discuss them with her. Dr. McClintock was even kind enough to submit Rob’s paper on epigenetic suppression of transposon induced mutations to the *Proceedings of the National Academy of Sciences*, though this led to long discussions on the meaning of the word “suppression.” It was Rob’s first paper at Cold Spring Harbor Laboratory and was among the very last that Barbara submitted to PNAS.

McClintock saw the early beginnings of the genome project, although the human and maize genomes were published

years after she died. She would have been thrilled, for example, that Hicks later found examples of copy-number variation in cancer explained by breakage fusion bridge cycles. In maize, the mechanism underlying chromosome breakage by Ds transposons was unraveled by Sue Wessler using polymerase chain reaction (PCR). Finally, epigenetic modification (“changes of phase”) of some transposons proved to involve RNA interference, the same mechanism that underlies paramutation, a silencing phenomenon discovered by Brink in the 1950s (Chandler, 2007). But perhaps most satisfying of all, it turned out that most of the human and maize genomes were composed of transposable elements, making some of Barbara’s most speculative ideas about gene control not only plausible but also demonstrable, at least with a modern understanding of the nature of the gene (Fedoroff 2012).

McClintock had collected reprints from geneticists throughout the decades, a historical treasure trove of discovery, from the early days of chromosome mapping to modern epigenetics. A reprint of her own 1929 *Science* paper (McClintock, 1929), in which she numbered the 10 maize chromosomes according to size, was annotated with hand-drawn gene names and a double arrow to switch two that she later realized were misassigned. Many of the other reprints were also annotated, in different colored inks, depending on her interpretation: we found some of our own work, as well as others, annotated in this way, a treasure to the authors in each case.

But she was never one to put herself at the center of attention. Greg Freyer was a postdoc with Rich Roberts and remembers the day the prize was announced (Monday, October 10th, 1983). He was in the lab early, as usual, when around 6 o’clock, phones all over the building starting ringing. At first, he just ignored

it, but he eventually figured out that something was going on and answered one of them. The caller identified themselves as a reporter from the *New York Times* and asked if he would like to make a statement regarding Barbara McClintock winning the Nobel Prize. Greg declined, but he called Bruce Stillman’s number, who called Jim. A little while later, he went looking for Barbara and found her on the lab grounds, picking up black walnuts with a large set of tongs. “Hi Barbara, I just wanted to congratulate you.” She gave him a puzzled look. “For what?” “You won the Nobel Prize!” She stopped for a second, smiled, and said, “That’s nice.” “I’m sure everyone is going to be looking for you.” “I guess I should go look into this,” and she turned and walked away. Later in the day, some reporters were around and found her back out picking black walnuts. She was eventually escorted to the press conference by Terri Grodzicker and Joe Sambrook, but she was wearing a Groucho mask as a disguise.

No one could reconstruct her knowledge, her experience, but she also knew that it took a team to continue discovery. In her Nobel address (McClintock, 1984), she wrote about her experience in the laboratory of Dr. Rollins Emerson. Marcus Rhoades and George Beadle were her colleagues, and she stated, “The initial association of the three of us, followed subsequently by inclusion of any interested graduate student, formed a close-knit group eager to discuss all phases of genetics, including those being revealed or suggested by our own efforts. The group was self-sustaining in all ways. For each of us, this was an extraordinary period. Credit for its success rests with Professor Emerson, who quietly ignored some of our seemingly strange behaviors. Over the years, members of this group have retained the warm personal relationship that our early asso-

ciation generated. The communal experience profoundly affected each one of us.”

Similar to the credit she gave to Emerson, there cannot be enough credit given to Dr. McClintock for advancement of genetics and genome biology and the nurturing of young scientists. We feel fortunate to have experienced a brief but life-changing relationship with such a caring and selfless individual.

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REFERENCES

- Barkan, A., and Martienssen, R.A. (1991). *Proc. Natl. Acad. Sci. USA* 88, 3502–3506.
- Burr, B., and Burr, F.A. (1982). *Cell* 29, 977–986.
- Chandler, V.L. (2007). *Cell* 128, 641–645.
- Chomet, P.S., Wessler, S., and Dellaporta, S.L. (1987). *EMBO J.* 6, 295–302.
- Creighton, H.B., and McClintock, B. (1931). *Proc. Natl. Acad. Sci. USA* 17, 492–497.
- Fedoroff, N.V. (2012). *Science* 338, 758–767.
- Fedoroff, N., Wessler, S., and Shure, M. (1983). *Cell* 35, 235–242.
- Klar, A.J.S., and Fogel, S. (1979). *Proc. Natl. Acad. Sci. USA* 76, 4539–4543.
- McClintock, B. (1929). *Science* 69, 629.
- McClintock, B. (1938). *Genetics* 23, 315–376.
- McClintock, B. (1941). *Genetics* 26, 234–282.
- McClintock, B. (1948). *Carnegie Inst. of Wash. Year Book* 47, 155–169.
- McClintock, B. (1951). *Cold Spring Harb. Symp. Quant. Biol.* 16, 13–47.
- McClintock, B. (1984). *Science* 226, 792–801.
- Weil, C.F., Marillonnet, S., Burr, B., and Wessler, S.R. (1992). *Genetics* 130, 175–185.