Historical Perspective

From controlling elements to transposons: Barbara McClintock and the Nobel Prize

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Why did it take so long for Barbara McClintock (Fig. 1) to win the Nobel Prize? In the mid-1940s, McClintock discovered genetic transposition in maize. She published her results over several years and, in 1951, gave a famous presentation at the Cold Spring Harbor Symposium, yet it took until 1983 for her to win a Nobel Prize. The delay is widely attributed to a combination of gender bias and gendered science. McClintock's results were not accepted, the story goes, because women in science are marginalized, because the idea of transposition was too far-fetched and because her scientific style was too intuitive, too holistic and too feminine to be believed.

Most scientists I know detest this story. McClintock loathed it too. She was not scorned, biologists insist, because she was a woman nor for any other reason, she was misunderstood. The intricacy of her experiments, combined with her eccentric, elliptical style of presentation, made her science difficult to understand. Furthermore, her findings were limited to maize, and their significance was not clear until the late 1960s and early 1970s, when transposition was found to be widespread in nature and of general importance. The Nobel Prize was not late; McClintock was early, ahead of her time.

Both of these stories are myths. Both assume that, had things gone differently, the transposition prize might have been awarded sooner. Both neglect the fact that McClintock did not win the prize for what she thought was most important in her work. A closer look at how McClintock came to receive the Nobel Prize reveals that she won only after her major contribution to science was recast to fit better with current understanding of the genome.

The McClintock papers within the Nobel archive will not be accessible until 2033. However, nominators retain the rights to their nominations. Several scientists have generously made their nominations and stories of McClintock available to me; other evidence I have gleaned from interviews and archived correspondence. From these and other materials, we can reconstruct the events leading up to the 1983 prize*.

What today are known as transposable elements, McClintock called 'controlling elements'. During the years 1945–1946, at the Carnegie Dept of Genetics, Cold Spring Harbor, McClintock discovered a pair of genetic loci in maize that seemed to trigger spontaneous and reversible mutations in what had been ordinary, stable alleles. In the term of the day, they made stable alleles into 'mutable' ones. The resulting patterns in the maize leaves and kernels indicated systematic alterations in mutation rates. McClintock concluded that she had disrupted the cell's mechanism for regulating gene activity. By early 1948, difficulties in mapping the loci led her to conclude that they were not, in fact, loci – sites on the chromosomes – but chromosomal elements that moved from place to place. It soon became clear that these new elements were capable of exerting a wide range of actions upon the genes. By 1950, McClintock had developed a theory about how controlling elements orchestrated development and differentiation of the organism. The key to her theory was coordinated transposition. In each nucleus, platoons of controlling elements would transpose in concert, inhibiting and modulating the effects of the genes to execute the developmental program of the cell.

Transposition was never in doubt. Other geneticists quickly confirmed transposition in maize, but, at the time, few considered it McClintock's major claim. Although McClintock was indeed difficult to understand, all her peers grasped that her real point was control. Yet, to most scientists, transposition seemed a random process. By ~1953, once McClintock had thoroughly documented the fact of transposition, she worked hard to prevent her controlling elements from moving because their effects were difficult to study when they jumped around. She never had any inclination to pursue the biochemistry of transposition.

Current understanding of how gene activity is regulated, of course, springs from the operon, François Jacob and Jacques Monod's 1960 model of a block of structural genes under the control of an adjacent set of regulatory genes (Fig. 2). Though subsequent studies revealed sometimes baroque variations in eukaryotes, the operon remains the core theme (also the textbooks' historical starting point) of gene regulation. Immediately following publication of the operon model, McClintock wrote an article for *The American Naturalist* on the parallels between the control systems in maize and bacteria[1]. For a time, she even referred to her elements as 'operators' and 'regulators'. Jacob and Monod were not influenced by McClintock; when they referred to controlling elements, it was as extrachromosomal episomes, perhaps viral in origin, not as components of the

Barbara McClintock in the late 1940s. Photo kindly provided by the American Philosophical Society Library, Philadelphia, USA.

*A fuller account of McClintock's life and science, including the events leading up to the Nobel Prize, can be found in *The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control* by Nathaniel Comfort (Harvard University Press, 2001).

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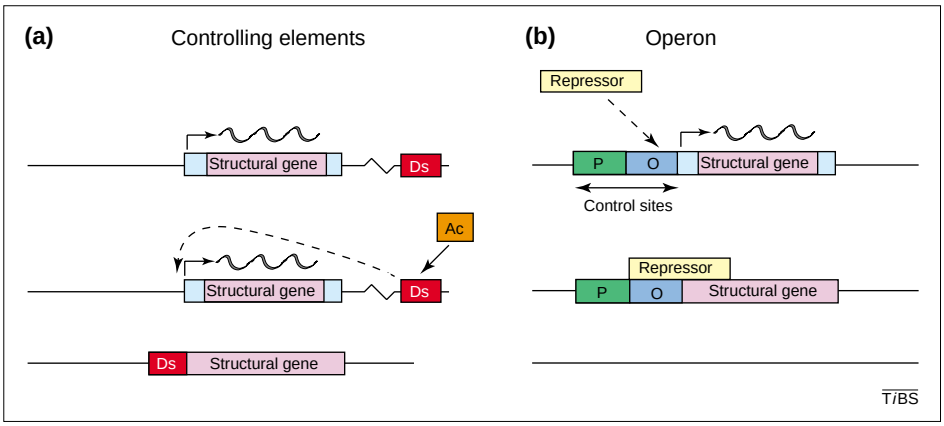

Fig. 2. Both McClintock's controlling elements (a) and Jacob and Monod's operon (b) modeled gene regulation by the action of elements outside the structural gene. In McClintock's model, the regulatory elements (Ac and Ds) acted by transposing into or next to the structural gene. Here, Ac activates Ds, causing Ds to transpose to a new position next to a structural gene. Insertion of the Ds element inhibits transcription of the gene. In the operon model, each set of structural genes had its own adjacent regulatory elements [O (operator) and P (promoter)]. In this diagram, binding of repressor to an operator sequence silences gene transcription. Figure is adapted, with permission, from *The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control*, Harvard University Press.

cell's normal regulatory machinery. McClintock, however, saw her work as the conceptual predecessor of the operon.

Seven years later, in 1967, McClintock won the Kimber Medal, which was awarded to distinguished geneticists by the National Academy of Sciences each year from 1955 until 1970. McClintock had been on the short list since at least 1964. When the award was to be announced, Marcus Rhoades, the award committee chairman and McClintock's closest colleague, asked geneticist Tracy Sonneborn, the geneticist best known for his investigations of cytoplasmic inheritance in Paramecium, to review the proposed press release. Sonneborn, familiar with McClintock's interpretation, suggested inserting 'that her studies of controlling systems of gene action were the precursors of the famous regulator–operon theory that won the Nobel Prize for its promulgators and that their thinking was probably much influenced by Barbara's notion of two-member interacting controls'[2]. Although Rhoades had reservations about McClintock's developmental-regulation theory (though not about transposition), he inserted the text.

That same year, James Shapiro, then at the Postgraduate Medical School of London, and Sankhar Adhya, at the University of Wisconsin, published their discovery of insertion sequence (IS) elements in bacteria. IS elements were discovered because of their ability to produce strongly polar mutations in known operons. Subsequent characterization showed distinctive features that enabled these elements to remove themselves from and reinsert into the bacterial chromosome. Sequencing and biochemistry revealed the existence of unique base sequences – inverted repeats – at either end of the elements that would be recognized by the enzymes responsible for excision and ligation. By the mid-1970s, IS elements had been found in other organisms and shown to function in a wide variety of ways. The rapid spread of antibiotic-resistance genes was perhaps the most spectacular, but work on phage mu, yeast mating-type switching and other areas of research, all contributed to a rapidly developing view that the movement of genetic elements within and between genomes was a mechanism of major importance.

The new transposition workers quickly discovered that McClintock had described transposition, in strictly genetic terms, long before. McClintock, then in her late sixties, experienced a scientific renaissance. In 1973, her friend Ernst Caspari, a geneticist at the University of Rochester, wrote to her, 'I completely see that you are going to have many calls for many activities. You are, after all, very famous now, and it is rather astonishing how your fame has increased at a time of life where in most people it is on the way down'[3].

In 1976, McClintock was nominated for the Nobel Prize by Judson van Wyk, an endocrinologist at the University of North Carolina, Chapel Hill. Van Wyk had nominating privileges as a result of having spent the previous four years at the Karolinska Institute in Stockholm. He nominated McClintock jointly with Seymour Benzer, best known for his work on the fine structure of the gene. The nomination form contained a box labelled 'The nomination is based on the discovery of'. In this box, van Wyk entered 'the organization and function of the genome in higher organisms'[4]. The summary description of McClintock's work stated that it had led to 'the first clear enunciation of the distinction between structural and regulatory genetic elements.' An accompanying detailed description informed by Gordon Sato, a friend of van Wyk's and a regular summer visitor at Cold Spring Harbor, stated that McClintock had 'laid the conceptual groundwork for the historic achievements recognized in the honour conferred on Jacob and Monod by the Nobel Committee in Physiology or Medicine.' After initial review, the nomination was turned down.

Meanwhile, transposable elements were being reframed in molecular terms. In June 1976, at a Cold Spring Harbor meeting organized by Shapiro, Adhya and muologist Ahmad Bukhari, transposable genetic elements or 'transposons' were defined simply as pieces of DNA that can move from one place to another. By 1980, transposons had become so important that James Watson introduced the proceedings of a Cold Spring Harbor Symposium on mobile genetic elements by writing that such a meeting had become 'virtually unavoidable'[5]. By now, mobile elements were mainly a subfield of microbial genetics. Papers at Cold Spring Harbor that summer touched on infectious disease, cancer, immunology and recombinant DNA. However, one area that was not discussed, was developmental regulation.

In 1981, McClintock was besieged with awards. In June, she was made an honorary member of the Society for Developmental Biology and was awarded the Thomas Hunt Morgan Medal of the Genetics Society of America. In October, the Wolf Foundation, based in Israel, awarded McClintock their $50 000 prize in medicine. On 17 November, the John D. and Catherine T. MacArthur Foundation named her their first MacArthur Laureate, a now discontinued plum for senior scholars, which awarded McClintock $60 000 a year for life, tax free. The next day, she won the Albert Lasker Basic Medical Research Award. She had also been nominated for the Nobel

Prize once again, this time by Stanley N. Cohen and Howard Temin. But the 1981 prize went to neurobiologists Roger Sperry, David Hubel and Torsten Wiesel.

Meanwhile, Nobel nominations continued to roll in. Herschel Roman, a geneticist who had been a graduate student at the University of Missouri in the late 1930s when McClintock was there, and who was now at the University of Washington, began to canvass for her. In September, apparently unaware of the previous nominations, he wrote to Marcus Rhoades that 'It seems to several of us that Barbara McClintock should get or share in the Nobel Prize, now that transposons have been shown to be so widespread and so important. I just had a letter from Beets [George Beadle] and he agrees and would support a nomination. He suggests that you lead the charge'[6]. Rhoades suggested Jim Watson as a Nobel-laureate sponsor but Watson demurred, saying he was already supporting another candidate. Joshua Lederberg, however, assented happily to Roman's request: 'Barbara for Nobel is of course an excellent idea although my own view is that Ac/Ds [her first controlling element] was not even her most important work. I would be glad to endorse and forward a nomination that you and Marcus prepared.' Other affirmations of support came in from Nobelists Salvador Luria, Alfred Hershey and Francis Crick[7].

Lederberg's nomination, informed by Rhoades' summary appraisal of McClintock's research, noted the importance of 'her work on the mechanism of control of gene action in maize, involving the action and interaction of two independent loci. This system was the forerunner of the regulator–operon theory of Jacob and Monod'[8]. When I interviewed Lederberg in the late 1990s, he did not believe McClintock's work was the forerunner of the operon theory and did not recall having said it was[9]. Indeed, it is doubtful that he believed it in 1981; the words are probably those of Marcus Rhoades. A busy man, Lederberg probably wrote a gloss on Rhoades' evaluation and sent it off, rightfully pleased to have done a good deed for a deserving colleague.

In another nomination letter for 1982, Heinz Saedler, a bacterial geneticist in Cologne working on insertion elements, wrote perceptively that McClintock's contribution 'lay in the introduction of a completely new concept. In it, chromosomes are no longer rigid structures, but show flexibility and thereby allow reorganization of the genetic material.' Shifting to a discussion of transposable elements in bacteria, Saedler continued, 'Such a reorganization of the ordering of genes is catalyzed by transposable elements. These genetic units not only jump from one place in the genome to another, they can also influence the expression of other genes; because of this McClintock at first named them "controlling elements". … The "controlling elements" were the first model system for the control of gene activity'[10].

Saedler's letter accomplished several things. It represented McClintock's work reasonably accurately, describing transposition, influence on gene action and McClintock's recent emphasis on genomic rearrangements. It also placed her work in the context of contemporary transposon research. Yet it retained the idea of genetic control. McClintock's year was not to be 1982.

The next year, a nomination by Ira Herskowitz and Bruce Alberts reflected a change in strategy. Both Alberts and Herskowitz were in the biochemistry faculty at the University of California at San Francisco. Herskowitz led the laboratory group that developed the cassette model of yeast mating-type switching; Alberts, today head of the National Academy of Sciences, used bacteriophage to study the mechanism of DNA replication. In the box 'The nomination concerns the discovery of,' Herskowitz and Alberts entered simply, 'Transposable genetic elements'[11]. The nomination began, 'Barbara McClintock discovered that discrete pieces of genetic information are capable of movement from one chromosomal location to another and that this movement of 'transposable elements' can lead to major alterations in gene expression.' Nothing is mentioned about gene regulation or the control of development and differentiation. Herskowitz and Alberts mentioned recent work that had 'shown that transposable genetic elements are present in essentially all organisms.' In addition, they went on to note the implications of transposition for cancer research, yeast genetics and genome evolution. In short, the nomination presented genetic transposition as universal, of basic importance to organisms and of great significance to medicine. It had little in common with what McClintock herself had been arguing for decades.

McClintock won the prize that year, solo, although the suggestion had been floated that she share it with Susumu Tonegawa, whose brilliant experiments demonstrated genomic rearrangement among antibody genes. (Tonegawa won in 1987.) One cannot yet know whether the Herskowitz–Alberts letter was the determining document; Nobel campaigns often acquire a momentum and other, independent nominations might well have been submitted. But, regardless of whether it defined or represented the shift, the Herskowitz–Alberts nomination expressed beautifully McClintock's contribution to science as being the discovery of genetic transposition, not genetic control. This is the standard view of her work today.

McClintock seems to have been bittersweet about the Nobel Prize. Though, of course, she was glad of the scientific recognition, Jim Shapiro believes she was pained by the fact that the recognition missed her central point. In 1999, he said, 'She told me she wasn't interested in transposition. She was interested in regulation'[12]. McClintock herself expressed this opinion in interviews throughout the 1970s and early 1980s.

Barbara McClintock could not possibly have won a Nobel Prize for transposition before 1976. Until then, her work since 1944 had been understood as she had wished: a theory about development and differentiation. That theory had never been widely accepted and, by the 1970s, it had been solidly refuted. Between 1976 and 1983, her Nobel nominations gradually overcame a quarter-century of inertia, as transposition was reframed as the basis of genomic rearrangement. Any delay for her award seems to be a consequence of residues of that old developmental framework clinging to her nominations.

This view in no way diminishes either McClintock or the prize. The reframing of great discoveries could, in fact, be common, and might sometimes happen repeatedly: recently, in some circles, dogmatic opposition to transposon-mediated gene regulation has softened (for examples, see Refs 13–17). What does seem rare is for a scientist to live to see her work take on new meaning. McClintock

was fortunate in earning the admiration of junior colleagues who, within her lifetime, rewrote history to ensure due, but not overdue, credit to one of the century's great geneticists.

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Book Review

Going everywhere: molecular transport in eukaryotic cells

Essays in Biochemistry: Molecular Trafficking (Essays in Biochemistry, Vol. 36)
edited by Philip Bernstein
Portland Press, 2000. $24.00 (131 pages)
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This book contains ten short reviews on a variety of topics within the area of molecular trafficking in eukaryotic cells. In the preface, the editor emphasizes the timeliness of this volume, particularly as the 1999 Nobel Prize for Physiology and Medicine was awarded to Günter Blobel for the discovery that 'proteins have intrinsic signals that govern their transport and localization in the cell'. Blobel's contribution to the field is also highlighted throughout the rest of the text: many of the authors have either a direct or an indirect connection with the Blobel laboratory.

Eukaryotic cells are structurally complex and require the specific localization of many factors to function correctly. The molecular components involved are diverse and numerous, and are constantly being degraded and renewed. Because the site of synthesis is frequently different from the site of function, the components have to be targeted and transported to their destinations. This text describes some of the targeting signals and transport mechanisms that account for this relocation. In the case of proteins (the major focus of these reviews) relocation often entails transport into or across cellular membranes. Since Blobel, many scientists have tackled this area and, although much remains to be discovered, a general understanding of the mechanisms of molecular trafficking has begun to emerge. This book reviews a selection of the relevant developments.

The first two chapters discuss protein targeting and translocation to the membrane of the endoplasmic reticulum (ER), and the immunological properties of ER chaperones. Emphasis then shifts to the role of glycosylation in protein transport, and to the mechanisms of vesicular transport itself. Next come accounts of protein import into chloroplasts and mitochondria, and the last four chapters discuss transport of proteins and nucleic acids into and out of the nucleus. More specifically, these describe the nuclear pore complex, the signals and mechanisms that mediate bi-directional transport, how regulated nuclear transport controls gene expression, and how viral models are being used study RNA export from the nucleus.

Because it is a multiauthor text, there is inevitably some variation in the way material is presented and its readability, but this is only a minor limitation. Overall the reviews are concise, well-illustrated accounts that present the major findings without submerging the reader in the considerable and often very complicated experimental details that that support them. Although this text might not suit specialists working in the areas under review, it is very appropriate for the target readers: students and teachers of biochemistry and molecular cell biology. Each chapter ends with a take home message derived from a summary of the state-of-the-art literature about the particular topic. Furthermore, the authors themselves are active contributors to the areas they review, and generally write with the confidence and authority this allows.

Molecular trafficking in eukaryotic cells is a huge topic maintained by a massive research effort that has generated a correspondingly impressive bulk of literature. In such a rapidly moving field, the production time for a book of this type (or the failure of contributors to meet the editor's deadlines!) means that the material it contains is out of date by the time it appears in print. This limitation applies here to a certain extent – most of the references cited in the bibliographies appeared in 1998 or earlier – but this is not