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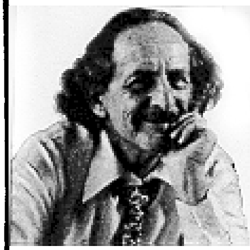

Current Comments®

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The 1983 Nobel Prizes. Part 2. Myth or Reality: Premature Discovery Is Not the Same as Being Ignored! Barbara McClintock and the Prize in Medicine

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We recently discussed the Nobel Prize-winning work of Subrahmanyan Chandrasekhar, University of Chicago, Illinois, and William A. Fowler, the 1983 laureates in physics, and that of chemistry prizewinner Henry Taube.[1] We will now review the award in physiology or medicine to Barbara McClintock. The next and final portion of the essay will focus on the winners in economics and literature.

We have discussed the work of each laureate since 1979. Our purpose in doing so is not only to discover whether or not citation analysis verifies the selections of the Nobel committee. We are also interested in emphasizing the role of scientific literature in understanding the discovery process. To help us demonstrate more concretely the impact of the prizewinners' research, we include ISI®'s unique research-front data. In our discussion of the fronts influenced by Chandrasekhar, cited above, we inadvertently included a paper by his cousin, Sivaramakrishna Chandrasekhar, of the Raman Research Institute, Bangalore, India. A correction notice appears at the end of this essay.

Since we began work on this essay, the 1984 Nobel Prizes have been announced. The award in physiology or medicine was shared by Cesar Milstein, Medical Research Council, Cambridge, England, and Georges J.F. Köhler and Neils K. Jerne, both of the Basel Institute of Immunology, Switzerland.[2] They received the award for their work on monoclonal antibodies. The impact of their classic papers will be discussed later this year.

The 1983 Nobel Prize in physiology or medicine was awarded to Barbara McClintock, Carnegie Institution of Washington's genetics laboratory at Cold Spring Harbor, Long Island, New York. The Nobel committee of the Karolinska Institute, Stockholm, selected McClintock for her "...discovery of mobile genetic elements" more than 30 years ago.[3] As quoted by *Science News* staff writer J.A. Miller, the committee said that her discovery "...is of profound importance for our understanding of the organization and function of genes. She carried out this research alone and at a time when her contemporaries were not yet able to realize the generality and significance of her findings."[4]

McClintock is the seventh woman to receive a Nobel Prize for science. Moreover, only two other women have been sole recipients of a science award since its inception in 1901: physicist Marie Curie in 1911 for her work with radium and polonium and crystallographer Dorothy Crowfoot Hodgkin in 1964 for her research determining the molecular structure of penicillin. However, McClintock is the first woman to receive the award alone in the physiology or medicine category,[5] the only category that is appropriate for her work.

There was some doubt that she would ever receive a Nobel Prize. Traditionally, awards in this group have been for research in medicine, animal biology, or microbiology. As Eugene Fox, ARCO Plant Cell Research Institute, Dublin, California, noted in an interview, "I think this is the first Nobel Prize given for work originally done in higher plants."[4] Fox added, however, that McClintock received the prize only after it became obvious to the scientific community that her findings were not restricted to plants.[4]

McClintock was born on June 16, 1902, in Hartford, Connecticut. She enrolled at Cornell University, Ithaca, New York, as a biology major in the College of Agriculture in 1919, receiving her BS degree in 1923. Registering as a graduate student in Cornell's botany department, she earned her MA degree in cytology in 1925, and her PhD in 1927.[6] According to biologists Benjamin and Frances A. Burr, Brookhaven National Laboratory, Upton, New York, McClintock started her life-long work in genetics—a new field at that time—at Cornell, where she joined a group involved in plant breeding research.[7] Working with maize, or Indian corn, her first discovery was that individual chromosomes could be distinguished under a microscope by their characteristic morphologies.[8]

In the 1930s, McClintock developed the cytologic techniques that were necessary to see, identify, and classify maize chromosomes.[9,10] She and Harriet B. Creighton, a colleague at Cornell, published a paper in 1931 demonstrating that genetic information could be exchanged between chromosomes when they cross over early in meiosis.[11] (Meiosis is a type of cell division in which the number of chromosomes is reduced by one-half to produce gametes, or sex cells.) Evelyn Fox Keller, professor of mathematics and humanities, Massachusetts Institute of Technology, Cambridge, Massachusetts, wrote a biography of McClintock entitled, *A Feeling for the Organism*.[12] In it, Keller noted that McClintock also discovered the nucleolar organizer.[13] This organizer is a specific area on one chromosome in a cell that is responsible for the creation of a functional nucleolus, which is a small, spherical body within the nucleus that helps synthesize ribosomes, the site of protein synthesis.

McClintock's work in the 1930s and 1940s led to her major discovery in 1951 of mobile genetic material, or "jumping genes,"[14] although, as Burr and Burr point out, "...it is clear that [she] understood the basic principles by 1948."[7] These principles were embodied in a paper published in the *Carnegie Institution of Washington Year Book*.[15] Genes are discrete elements that are responsible for structural and biochemical traits. Until the early 1950s, as Keller notes,[12] genes were believed to be absolutely fixed along the chromosome in a linear arrangement, much like pearls on a string in a necklace. The historical importance of this concept of genes occupying positions that do not change from generation to generation[16] was noted by embryologist Nina V. Fedoroff, Carnegie Institution of Washington, Washington, DC, and Johns Hopkins University, Baltimore, Maryland.

But in studying the variegation of the kernel and leaf pigmentations in maize, McClintock realized that the different patterns of pigmentation that she saw were not random mutations of fixed gene sequences. Rather, there was a definite pattern of inheritance that seemed to be controlled at the molecular level where the genes appeared to be "jumping." When they relocated on the chromosome, they changed the phenotype, or visible properties, of the corn.[16]

McClintock theorized that these jumping genes are actually "controlling elements." As explained by Fedoroff,[16] there are two types of these controlling elements: the dissociator (Ds) and the activator (Ac). The Ds element causes chromosomal breakage. And, as its name suggests, the Ac activates the Ds. The Ds element jumps along the chromosome. In maize, it may move and associate with the genes that control color, thus inactivating them. When this happens, the color of the kernels will be uniformly pale. However, if the Ac interrupts the action of the Ds, the Ds will then move away from the color genes and the kernels will be variegated.

McClintock presented her jumping gene theory in 1951 at the annual Cold Spring Harbor Symposium. McClintock's biographer, Keller, offers a scenario alleging that McClintock's presentation was rebuffed and ignored by her colleagues because the idea of mobile genetic elements contradicted the then-current belief that genes were permanently fixed in their sequence along the chromosomes. Keller quotes McClintock's account of her audience's reaction: "I was...ridiculed, or...told that I was really mad."[12] (p. 140) As Keller points out, McClintock

> ...was hardly a novice in her field, and despite the many institutional difficulties she had experienced, she was accustomed to scientific success. Above all, she was accustomed to the respect and admiration of her colleagues. By 1951, she was one of the dignitaries of her field, and scientists of her stature do not expect their work to be rebuffed out of hand.[12] (p. 140)

Indeed, not all reviewers of Keller's book agree that McClintock was ignored. John R. Laughnan, Department of Genetics and Development, University of Illinois, Urbana, in a review of Keller's book in *Science*, states:

> Many readers of this book who are geneticists, especially those who have worked in maize genetics since the early 1950's, will want to challenge the basic assumption that McClintock's work was rejected. Her papers published in 1950 and 1951 on the Ds-Ac controlling elements and on associated transposition, and others published later on the same subjects, were both understood and appreciated by the community of maize geneticists. They became immediate objects of graduate seminar presentations, and the topics of controlling elements and transposition were rapidly incorporated into graduate and undergraduate courses in genetics and cytogenetics.[17] (p. 482-3)

In another review of Keller's book that appeared in the Albert Einstein alumni bulletin, molecular biologist Lucy Shapiro, director of the Division of Biological Sciences, and geneticist Susan Henry, director of the Sue Golding Graduate Division, both at Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, also dispute Keller's views. About McClintock they state,

> Her single-minded pursuit of maize cytogenetics and her valuable scientific observations led to her early recognition as a leading geneticist. McClintock's studies were read and understood by other geneticists. It is simply not true that no one understood her experiments or her method, or that the validity of her observations was questioned.... Keller does a disservice to both McClintock and other scientists by presenting McClintock's statements without an in-depth investigation or analysis of the myriad contributing factors inherent in any type of thought process, whether it relates to genetics or politics.[18] (p. 4)

McClintock's work was also quickly incorporated into scientific books and textbooks. As early as 1951, McClintock's work was mentioned in an essay that appeared in the book *Genetics in the 20th Century*,[19] by Torbjorn Caspersson, medical director, Nobel Institute for Medical Research, and Wallenberg Laboratory for Experimental Cell Research, Stockholm, and Jack Schultz, Institute for Cancer Research, and Lankenau Hospital Research Institute, Philadelphia, Pennsylvania. These authors pointed to

> ...the recent spectacular analysis by McClintock (1950) of the variegation in maize [that] has presented the problem in that material in terms similar in principle to those found useful in...*Drosophila*.[20] (p. 168)

In the same collection of essays, Nobel Prize-winning geneticist George W. Beadle, then of the Division of Biology, California Institute of Technology (Caltech), Pasadena, co-author of a paper with McClintock,[21] wrote that

> [a] direction in which progress in understanding gene action seems highly probable is represented by the recent work of McClintock...in which a striking relation is shown between gene function and proximity to heterochromatin as well as between heterochromatin and gene mutation.[22] (p. 235)

In a textbook on genetics and metabolism published in 1955, Robert P. Wagner, Department of Zoology, University of Texas, Austin, and Herschel K. Mitchell, Division of Biology, Caltech, also mention McClintock's work:

> Perhaps the most interesting examples of genetic control of the mutation rate have come from the investigations of Rhoades...and McClintock...on maize. These studies not only have confirmed the earlier finding from the work on *Drosophila* that the rate of mutation of some genes is under the control of other genes but have also provided further data supplemented by cytological observations which may eventually lead to an understanding of the phenomenon of spontaneous mutation.[23] (p. 48)

In his review of Keller's book, zoologist Stephen Jay Gould, Harvard University, puts the McClintock story into perspective. Gould appears to agree with Keller's presentation of McClintock's story:

> The strength of Keller's fine book lies in her successful attempt to avoid the myths and capture the subtleties, thereby providing a rare and deep understanding of a troubling, fascinating, and general tale in the history of science—initial rejection (or, more frustratingly, simple incomprehension) of great insights.[24] (p. 3)

But he offers this evaluation of the stories that are being told now about McClintock:

> Such heroic tales are the stuff of simplistic mythology, and McClintock's catapult into public recognition has fostered vulgar versions of what she did, thereby obscuring a more subtle story and, in a perverse if unintended way, degrading McClintock's formidable achievements. The vulgarized accounts try to use her as an exemplar for one of two archetypical stories in the sociology of science, either (1) the woman in science, a brilliant mind rejected by prejudice against the color or sex of the body housing it, or (2) the maverick genius who, despite heroic efforts, obtains no hearing because colleagues simply cannot hear a different drummer. The story is never so simple, never a clear-cut contrast of unblemished individual genius and benighted establishment. Just as McClintock's work helped to break the central dogma and establish interaction between code and product, so must the complex tale of her long rejection be cast as an interplay between her own idiosyncrasies and the reactions of her colleagues.[24] (p. 3)

Citation Information

Although the full significance of McClintock's discoveries concerning jumping genes would not be realized for several decades, it cannot be said that the main body of McClintock's work was ignored. Let's examine the data available from the *Science Citation Index*® (*SCI*®). From 1955 to the present, McClintock's publications have been explicitly cited at least 3,000 times (the *SCI* covers 1955-1984).

But what about the earlier years? Many years ago, with NIH support, we compiled the *Genetics Citation Index* (*GCI*)—*1958-1962*. This publication was distributed to over 1,000 geneticists. The *GCI 1958-1962* section contained over 105,000 citations taken from 6,000 source articles published in 38 genetics journals between 1958 and 1962 and contained over 225 citations to McClintock's work.

In addition, the *GCI* also contains a separate section covering 1949-1963. It includes 35,000 citations taken from 2,000 source articles published in three key genetics journals: the *American Journal of Human Genetics*, the *Annals of Human Genetics*, and *Genetics*. In the *GCI* for 1949-1963, McClintock's work was cited in about 105 additional unique citations.

The overlapping citations between these two *GCI* packages have been eliminated. However, these smaller counts have been included in the *SCI* totals mentioned earlier. In fact, the last and largest section of the *GCI* was derived from the 1961 *SCI*. It included over 1.4 million citations.

While the Nobel committee was quite slow in recognizing the importance of the discovery, McClintock's most-cited paper is probably "Chromosome organization and genic expression,"[14] published in 1951 in the *Cold Spring Harbor Symposia on Quantitative Biology*. The paper describes her theory of jumping genes. It was cited in over 335 publications between 1951-1984. Interestingly, this and two other highly cited McClintock papers,[25,26] are core to two current research fronts.

The 1956 paper, "Controlling elements and the gene,"[25] was cited explicitly at least 310 times—the 1965 paper, "The control of gene action in maize,"[26] about 190 times. The latter paper describes her discovery of the suppressor-mutator system (Spm), which is different from the Ds-Ac system and also much more complex. It is important to note that citations to these papers appeared long before we began identifying so-called "research fronts." In the recently published *SCI* cumulation for 1955-1964, there are about 730 citations to McClintock's work; in particular, her 1951 paper[14] was cited about 95 times. The bar graph in Figure 1 shows the year-by-year citations to this paper from 1955 to 1984. The bar graph in Figure 2 shows year-by-year citations to all of her works on which she was first author from 1955 to 1984.

Research Front Data

These key papers by McClintock comprise three of the five core papers of the *ISI/BIOMED*® research front #82-1799. Twenty-nine papers were published on "Characterization of maize controlling elements and *Zea mays* transposons" in 1982. Of the other two, one was by J.R.S. Fincham, University of Edinburgh, Scotland, and G.R.K. Sastry, University of Leeds, England, and was published in 1974 in the *Annual Review of Genetics*.[27] The other, by Burr and Burr, appeared in *Genetics* in 1981.[28] This paper and the three others by McClintock[14,25,26] carried over to identify the core for the *SCI* research front #82-2065, "Transposable controlling elements in maize and other eukaryotes," on which about 62 papers were published in 1982 alone. There were 27 citing papers from 1982 in research front #82-1799.

Another, much earlier paper by McClintock, "The relation of a particular chromosomal element to the development of the nucleoli in *Zea mays*,"[13] published in 1934, received about 340 citations between 1955 and 1984. This article describes her early work involving the nucleolus, which was part of the basis of her jumping-gene theory 17 years later. We won't know

Figure 1: Chronological distribution of articles citing Barbara McClintock's 1951 *Cold Spring Harbor Symposium* paper for the period 1955-1984.

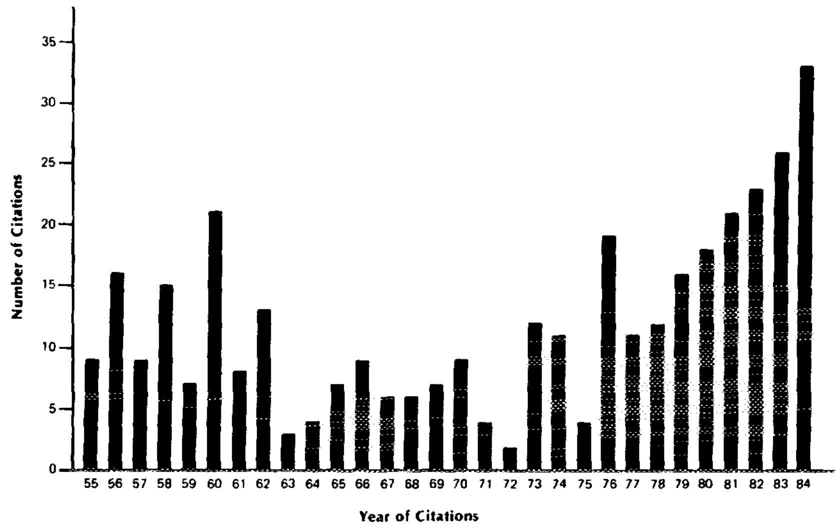
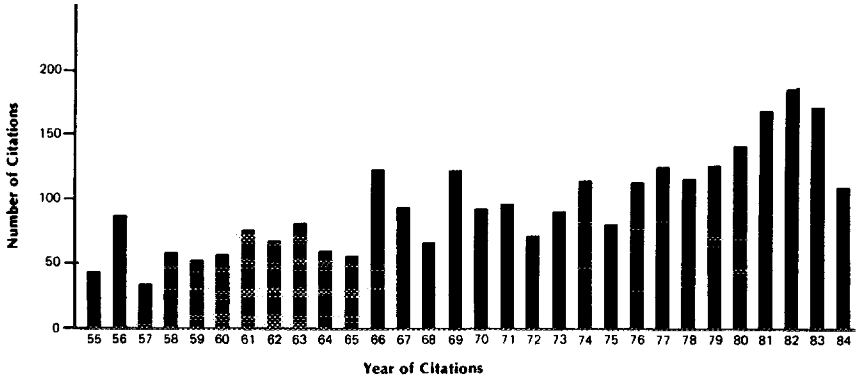


Figure 2: Chronological distribution for the period 1955-1984 of articles citing the works of Barbara McClintock on which she was first author.



until we complete the *SCI* for 1930-1954 to what extent her work was cited during those years, except as already noted for the *GCI*. This particular paper was cited only three times in the three genetics journals mentioned from 1949 through 1954.

In a recent article in the *Wall Street Journal*,[29] Hal Lancaster and Marilyn Chase, both staff reporters, wrote, "Then there's Eugene Garfield's theory of 'citedness;' the more frequently a researcher's work is mentioned in professional papers by his peers, the more likely he or she is to win a Nobel." Yet, I have often said that citation analysis *cannot* predict Nobel Prize winners. Nor is that its purpose. However, citation analysis *can* help identify those individuals who are *of Nobel class*. More importantly, it enables us to watch the growth and development of research fronts pioneered by such persons. To this extent, we can "forecast" research fronts that may eventually be acknowledged by a Nobel Prize.

In the same simplistic account of the Nobel Prize process, the head of the committee that decides the physiology or medicine award is alleged to have said that this citedness theory [*sic*!] "...doesn't work very well." He appears to have used McClintock as an example and is quoted as saying that McClintock "...published in very strange journals of plant breeding that aren't included among the commonly used publications." I suspect that "medical journals" was what he meant.

Although McClintock herself claimed that she stopped writing articles for the edification of her colleagues after her theories had been rejected,[12] she actually continued to publish in well-known scientific journals. And her work, as mentioned earlier, has been extensively cited. In particular, her work was heavily cited during the 1950s. Moreover, her controversial papers have been published in such "strange" journals as the *American Journal of Botany*, *Genetics*, and the *Proceedings of the National Academy of Sciences USA*. Even her 1934 paper[13] appeared in *Zeitschrift für Zellforschung und Mikroskopische Anatomie*, by no means an obscure journal.

So it is evident that McClintock and the main body of her work, if not her theories on jumping genes, were appreciated and recognized by geneticists—if not medical scientists—long before she received the Nobel Prize in 1983. That she was made a member of the National Academy of Sciences in 1944 is significant. And her National Medal of Science in 1970 was late, but came long before the Nobel. Table 1 provides a chronologic list of the many prestigious scientific awards received by McClintock throughout her career.

Table 1: Chronologic list of awards and honors received by Barbara McClintock before the Nobel Prize in 1983. A=year. B=name of award.

A	B
1933	Guggenheim Fellowship John Simon Guggenheim Memorial Foundation New York, NY
1939	Vice-President, Genetics Society of America Rockville, MD
1944	Elected to National Academy of Sciences Washington, DC
1945	President, Genetics Society of America Rockville, MD
	Listed among the 1,000 top scientists in the US by *American Men of Science*
1967	Kimber Genetics Award National Academy of Sciences Washington, DC
1970	National Medal of Science National Science Foundation Washington, DC
1978	Lewis S. Rosenstiel Award Brandeis University Waltham, MA
1981	Albert Lasker Basic Medical Research Award Albert and Mary Lasker Foundation New York, NY
	MacArthur Prize Fellow Laureate Award John D. and Catherine T. MacArthur Foundation Chicago, IL
	Wolf Prize Wolf Foundation Herzliah-Bet, Israel
1982	Prix Charles Leopold-Mayer Charles Leopold-Mayer Foundation Paris, France
	Louisa Gross Horwitz Prize Columbia University New York, NY

McClintock is not bitter about receiving the Nobel so long after her original work on transposable genetic material was published. After learning that she had won the award, she said in an interview with Lawrence K. Altman of the *New York Times*, "The prize is such an extraordinary honor. It might seem unfair, however, to reward a person for having so much pleasure, over the years, asking the maize plant to solve specific problems and then watching its response."[30] In fact, according to her biographer, Keller, even the rejection of her theories doesn't bother her anymore, although McClintock admitted that, initially, the outcome of the 1951 symposium "really knocked" her. "Later on," she recalls, "there were years when I couldn't talk to anyone about this, and I wasn't invited to give seminars either."[12] Still, she claims that, in the long run, the experience was good for her, impelling her to work even harder.

Barbara McClintock is not the only scientist whose work was not fully appreciated immediately. As you saw in Part 1 of this essay,[1] astrophysicist Subrahmanyan Chandrasekhar also was not recognized when he first presented his findings about nucleosynthesis. In the future, I will discuss delayed recognition in detail and many of the individuals involved—including these two 1983 Nobelists.

But clearly, the popular press enjoys any opportunity to note the chinks in the scientific award process. The media often help perpetuate the myth that all famous scientists of the past were unrecognized by their peers—forgetting that while their ideas remain controversial the very same peers may elect them to formal elite groups. The true martyrs of modern science, if any exist, are relatively rare. This does not mean that there are not injustices in the formal reward system of science. And that in turn may be very different from the informal reward system partially reflected in the citation history of each individual.

* * * * *

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Correction Note: Will the Real Chandrasekhar Please Stand Up?

In our discussion of astrophysicist Subrahmanyan Chandrasekhar,[1] our zeal to include information about ISI® research fronts led to an unfortunate error. On page seven of the essay, we mentioned work on liquid crystals done by "S. Chandrasekhar." This is part of the core for research fronts #81-0849 and #83-3556. However, this is the work of a cousin, Sivaramakrishna, of the Raman Research Institute, Bangalore, India. Both gentlemen are fellows of the Royal Society of London. Incidentally, they are also both nephews of the late Sir C.V. Raman.

I suppose that if their names were Smith or Cohen, we might have been more diligent in checking the possibility of a homograph. Sivaramakrishna Chandrasekhar's book, *Liquid Crystals*,[2] published by Cambridge University Press in 1977, is even more highly cited than his paper in *Pramana*.[3]

Our diligent colleague and correspondent in New Delhi, S. Arunachalam, editor of the *Indian Journal of Technology*, not only called this error to my attention, but he also correctly points out that the total citation counts for these two gentlemen were probably merged. Having re-analyzed the citation data, there is nothing significant to change in the essay, except to eliminate the confusion in research fronts #81-0849 and #83-3556. However, the counts in some earlier studies might need modification to demonstrate to what extent each of the two Chandrasekhars are well cited. Indeed, Sivaramakrishna's work on liquid crystals, mentioned above, qualifies as a *Citation Classic*™. We hope that he will honor us with a commentary on his work.

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