A Naturalist of the Genome

The Nobel Prize for Physiology or Medicine recognizes the prescient work of a geneticist whose proposals contradicted the prevailing dogma

The Karolinska Institute's announcement of this year's Nobel Prize in Physiology or Medicine is unusually terse: ". . . to Barbara McClintock, for her discovery of 'mobile genetic elements'," reads the citation. This short phrase is pregnant with hidden import.

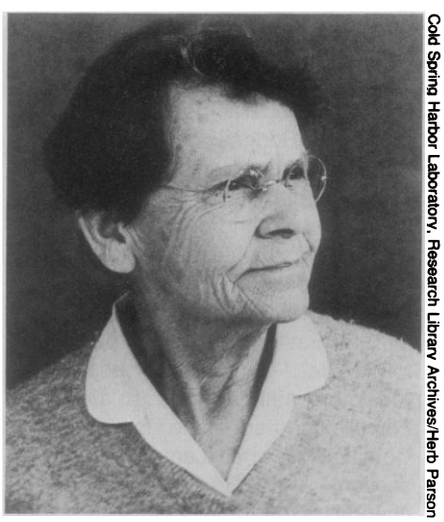
First, not only did McClintock make the entirely unexpected discovery that genes and other genetic elements can move around the genome, but she also had the courage to insist that she was correct when few wanted to hear what she had to say. Now, 30 years after her incisive insights, everyone knows she was right.

Second, McClintock has inferred from the temporal pattern of the movement of genetic elements in maize that they represent an important, if not central, influence in the embryological development of this organism and, by extrapolation, all organisms. She also suspects that jumping genes are key to certain evolutionary events, particularly to rapid speciation. In these two respects she is more or less a lone voice—perhaps, once again, ahead of her time.

In this modern age of the confident specificity of molecular biology, McClintock displays an unmatched genius for combining hardheaded, rigorous experimentation with a deep appreciation of the larger biological context of it all. A lifelong immersion in the questions of embryological development has ensured that her discernment of detail is constantly matched with and integrated into the broader picture. She is something of a naturalist of the genome: she is constantly observing, and probing, always on the alert for things out of the ordinary. Above all, she has an awe of complexities and mysteries of life and a humility for our ignorance about them.

In this latter respect, McClintock describes herself as something of a mystic, a designation that many take to imply—wrongly, according to those who know her well—that she is vague and fuzzy. "McClintock's experiments are formidable, clear and detailed," says Nina Fedoroff, of the Carnegie Institution of Washington's Department of Embryology in Baltimore. "They are beautifully done and extremely rigorous."

"McClintock's knowledge about the biological world is enormous," notes James Shapiro of the University of Chicago. "By comparison most molecular biologists are exceedingly ignorant about the way organisms operate. And when they talk to her they don't understand what she has to say and so they tell stories about how fuzzy and mystical she is. They don't appreciate that underneath the naturalist there is very sharp and rigorous analysis." McClintock's so-called "mysticism" is the product of an unusual marriage of a mind open to any possibility, to one that insists on cogent tests of hypotheses that are to be promulgated. She does not speculate loosely.



Cold Spring Harbor Laboratory, Research Library Archives/Herb Parson

Barbara McClintock, 81

McClintock embarked upon her pursuit of mobile genetic elements in the early 1940's, soon after beginning her virtually career-long association with the Carnegie Institution of Washington's genetics laboratory at Cold Spring Harbor, New York. Even by that time she had established herself as a major figure in cytogenetics. She had been associated with Rollins Emerson's famous maize genetics group at Cornell University between 1924 and 1931 and later spent brief periods at the California Institute of Technology, the University of Missouri, and again at Cornell. According to Marcus Rhoades, another member of the Cornell group, "She established maize cytogenetics as a science." George Beadle, also at Cornell and a close associate of McClintock's, was later to share the 1958 Nobel Prize for medicine for his work on the "one gene–one enzyme" hypothesis. "Two Nobel Prizes from one small group is pretty good, you have to admit," remarks Rhoades.

McClintock's early successes, it is easy to forget, were achieved at a time when the rediscovery of Mendel's work was just two decades into history; the demonstration that chromosomes carried the hereditary factors was only a decade old; the concept of the gene was still just that, a concept and a contentious one at that; and the discovery of DNA as the chemical basis of genes, the helical structure of DNA, and the genetic code were all way into the future.

Between 1910 and 1920 T. H. Morgan and his illustrious colleagues at Columbia University—A. H. Sturtevant, H. J. Muller, and C. B. Bridges—were laying the foundations of modern genetics with their detailed studies on *Drosophila*. At Cornell, meanwhile, Emerson was exploiting the readily recognizable physical characteristics of maize—such as pigmentation patterns of kernels and leaves—in elegant genetic investigations of his own. Compared with the *Drosophila* geneticists, however, he was hampered in his work, in part by the longer generation time of corn—one generation a year as against one every 10 days—but chiefly by the absence of the good direct imagery of the chromosomes that had been achieved in the fruit fly research.

It was McClintock who developed the required cytological techniques for visualizing, identifying, and characterizing maize chromosomes. She opened a window on a new world, and she and her colleagues explored it with great excitement. "She published few papers on her work," says Rhoades, "but each one was a milestone in the science." One outstanding achievement, which she published with Harriet Creighton in 1931, was the demonstration of the transfer of genetic information following the crossing over of chromosomes during the formation of sex cells. Another was her discovery of the still somewhat enigmatic nucleolar organizer region.

"These were the golden days of cytogenetics," recalls Rhoades. He is not alone when he suggests that McClintock's cytogenetics work was deserving of a Nobel Prize in itself. This, however, was not to be, though her achievements did receive recognition in circles less public, although almost as professionally rewarding, than The Big Prize. In 1939 she was elected vice president of the Genetics Society of America and served as president in 1944. And the following year she was elected as a member of the National Academy of Sciences, only the third woman to be raised to that prestigious status at the time.

Although the classical genetics community never underestimated or overlooked McClintock, the molecular geneticists and molecular biologists were very, very slow to catch up, and it was only when evidence of mobile genetic elements began to emerge from their own endeavors in other organisms that their recognition was bestowed on her. Two years ago, just when the Nobel Prize committee was beginning to consider seriously her nomination, she received two other major awards. Early in October 1981 she shared the Wolfe Prize in Medicine, and a month later she won the Lasker Award, both for the discovery of mobile genetic elements. At the same time the John D. and Catherine T. MacArthur Foundation made her its first Prize Fellow Laureate. And she has recently been the subject of biography.* As a very private person—some describe her as a loner—McClintock has found all this attention diverting and even distressing.

By working for so long without a research group McClintock was reflecting her scientific approach rather than just a solitary personality. "She wanted to be on top of her research. She wanted to be very close to her research material," says Rhoades. Drawing on the title of the recent biography, he adds, "She has a feeling for the organism."

When McClintock first went to work at the Carnegie laboratory at Cold Spring Harbor she was continuing a long tradition in genetics research in studying the basis of variegation of kernel and leaf pigmentation in maize. The most intriguing aspect to this phenomenon was its genetic instability. Although the pattern of pigmentation would generally be passed faithfully from generation to generation, there would be occasional exceptions. These exceptions were the clue to something interesting in the organism's genetics. Both germ line and so-

* *A Feeling for the Organism*, by Evelyn Fox Keller (Freeman, San Francisco, 1983).

Carbon May Break Octet Rule

To anyone who has been exposed to elementary organic chemistry, the octet rule is an immutable doctrine: elements in the first row of the periodic table prefer to be surrounded with eight electrons. This means that oxygen, for example, tends to bond to two other atoms, while carbon bonds to four.

This rule may not be as immutable as was previously believed. John A. Pople of Carnegie–Mellon University and Paul von Ragué Schleyer, Ernst-Ulrich Würthwein, and their colleagues at Friedrich Alexander University in West Germany report in the most recent issue of the *Journal of the American Chemical Society* [**105**, 5930 (1983)] that five or six lithium atoms can bond stably to one carbon atom. Says Pople: "We have to modify some of our old concepts about valency."

These authors reached their conclusions by performing molecular orbital calculations for the postulated species. They find, for example, that CLi_5 and CLi_6 are highly stable toward all possible dissociation reactions; that is, when one lithium atom is lost from CLi_5 or two Li atoms are lost from CLi_6, both reactions are highly endothermic. That all of the lithium atoms are bound to carbon is evident because the molecules have very high symmetry and all the C-Li bond lengths are only slightly longer than those in CH_3Li and CLi_4.

The formal charges on the carbon atoms in CLi_5 and CLi_6 are not much larger than that on CLi_4. This indicates, Pople and Schleyer say, that the carbon atom "remains content with its normal octet," and that the eight electrons are simply redistributed into five (or six) bonds rather than four. The "extra" electron or electrons contribute to lithium–lithium bonding and help to start building a metal "cage" around the central atom.

Predicted structures

Pople and Schleyer calculate that CLi_5 will have D_{3h} symmetry while CLi_6 will have O_h symmetry.

The nature of this central atom is secondary, the authors say, and hyperlithiation should be a general phenomenon for all first and second row elements. In fact, the two groups had earlier this year reported [*J. Am. Chem. Soc.* **104**, 5839 (1983)] that hyperlithiated oxygen compounds such as OLi_3 and OLi_4 are also stable. They also have some preliminary evidence that hyperlithiated nitrogen compounds are stable and that sodium can form similar hypernatriated compounds.

"Expressed colloquially," Pople and Schleyer say, "lithium is a 'sticky' element and binds to many molecules, especially if another lithium already is present. Thus, CH_4 forms only weak complexes with Li or LiH. . . . In contrast, CH_3Li binds both Li and LiH much more strongly; as a result, CH_3Li_2 and CH_4Li_2 are present, and both have pentacoordinate carbons." This tendency, however, will probably make it impossible to synthesize discrete hyperlithiated carbon compounds since adjacent molecules should interact strongly. At the University of Texas at Austin, R. J. Lagow and his colleagues have obtained a solid product, formulated as "$(CLi_4)_n$," from the reaction of carbon tetrachloride with lithium atoms. This compound probably contains hyperlithiated carbon species.

Lagow's group has also observed many hyperstoichiometric ions, such as $CH_3Li_2^+$ and CLi_5^+, that are probably derived from the neutral species. C. H. Wu and his colleagues at the University of Julich in West Germany have observed CLi_5 and CLi_6 in the gas phase; these were produced by allowing lithium atoms at high temperatures to diffuse through graphite membranes. Wu's group has also observed hyperlithiated oxygen compounds in the gas phase. The ionization potentials and energies of these hyperlithiated molecules, when they can be measured, should provide quantitative data for comparison with the computational results.—**THOMAS H. MAUGH II**

Barbara McClintock

A maize cob, each kernel the result of a separate fertilization

The kernels with deeply pigmented spots in a colorless background received Spm *from the female parent. The uniformly lightly pigmented kernels did not receive* Spm. *By counting the kernel types the number of* Spm *carried by the female parent can be deduced.*

matic mutations were occurring: the question was, what underlay them?

McClintock's studies initially revealed a series of chromosome rearrangements that appeared to be associated with this instability, and she was particularly interested in what was called the breakage-fusion-bridge cycle. Her attention on chromosome behavior became diverted, however, when she began to perceive that the pattern of mutation was by no means random and that it could best be explained by the movement of certain genetic elements. A sense of a system of control within the genome began to emerge, and it was to become a pervading theme of her work.

For 6 years McClintock pursued meticulously the genetic basis of these unstable mutations and eventually reached the point at which she felt she could not escape the conclusion that the movement of certain genetic elements—she called then controlling elements—were responsible for the shifts in phenotype she saw. So, by 1951, she was ready to describe the basis of this controlling system. Essentially, it consists of two types of elements, both of which can move—transpose—between various positions on the chromosomes, but only one of which can do so autonomously. The nonautonomous element requires the presence somewhere in the genome of the autonomous element if it is to be excised and moved.

The first system McClintock worked with was designated *Ds-Ac*. *Ds* refers to the nonautonomous element, whose presence in the chromosome might inactivate a neighboring gene. *Ac* is the autonomous element, whose insertion into a genome might cause the transposition of a *Ds* element, whereupon the affected gene might be reactivated. Movement of *Ds* can also initiate chromosome breakage, as can the transposition of *Ac*.

McClintock charted the fate of controlling elements indirectly by the effects they had on kernel and leaf pigmentation and on chromosome integrity. For instance, the early switching on of a gene involved in kernel pigmentation might produce a uniformly dark kernel, because all daughter cells would carry this new state of the gene. A similar mutation late in development would result in a small spot of pigmentation in a lighter background. The essence of McClintock's insight was that there were two types of genes: those that encoded some form of structural information; and others that controlled the activity of these structural genes. The results of countless crosses through the years has convinced McClintock that she was seeing the manifestation of a system that was central to normal developmental timing.

By now three major families of controlling elements have been found—*Ds-Ac*, and *Spm* and *Dt*—plus a series of lesser studied elements. All appear to operate on the dual system of autonomous and nonautonomous pairs. And all follow the *Ds-Ac* pattern of operation in general, but with specific variations. For instance, in the *Spm* system, the autonomous element can initiate a gene-supression activity in the nonautonomous element in addition to mobilizing it.

McClintock published a brief account of the *Ds-Ac* system in the *Proceedings of the National Academy of Sciences* in 1950, and made a major presentation at a Cold Spring Harbor symposium the following year. Her message made no impact. Some attribute the lack of communication to poor presentation of very complex material. Others counter this and point out that the same message is understood well enough now. McClintock says she faced "the dogma of the constancy of the genome."

The theory of the gene had been rationalized by this time. The New Evolutionary Synthesis, with its emphasis on population genetics, was quickly maturing and robust. And molecular biology was about to flourish, placing even greater emphasis on the study of simple rather than complex organisms. All of this combined to leave little conceptual room for jumping genes.

A few people understood what McClintock had found or simply had sufficient confidence in her science to be willing to contemplate something so at odds with the prevailing orthodoxy. And she had the willing and attentive ear of geneticist Richard Goldschmidt, whose even greater unorthodoxy included the idea of megamutations as the basis of sudden evolutionary change. "The difference between them," says Rhoades, "is that McClintock documented everything meticulously whereas Goldschmidt was just ideas." The two were, however, friends, and, says McClintock, "I was able to comfort him against the criticism he received."

There are strong intellectual links between the positions of these two great geneticists. McClintock, for instance, wrote recently that, "there is little reason to question the presence of innate systems that are able to restructure the genome." She refers to the accelerated mobilization of controlling elements following some kind of stress—she calls it genomic shock—on an organism. "Their extensive release, followed by stabilization, could give rise to new species or even new genera." Although McClintock comments occasionally in print in this vein she considers evolutionary change to be so complex a process and current ideas to be so inadequate as explanations that she prefers to stay only with what can be documented.

Although her first major attempt to tell the world of molecular genetics about mobile controlling elements failed in 1951, she continued intermittently to present her work. At another Cold Spring Harbor symposium 5 years later she said, "Controlling elements appear to reflect the presence in the nucleus of highly integrated systems operating to control gene action. . . . [It] would be surprising indeed if controlling elements were not found in other organisms." They would be found, of course, and in startling ubiquity, but not for another two decades. Before that happened the

French Nobel prizewinning molecular biologists Jacques Monod and François Jacob announced their scheme for control of gene activity in bacteria, which included specific, but nonmobile, regulatory sequences. At last, McClintock's ideas had produced an echo in the halls of the molecular biology establishment. But it was an echo with limited fidelity to the original.

The *re*discovery of mobile genetic elements occurred piecemeal, starting in the mid-1960's with certain elements in bacteria, proceeding in the mid-1970's with the discovery of bacterial transposons, which can carry drug-resistance genes, and then exploding into the 1980's with many kinds of mobile elements in all kinds of organisms, including humans. "In every genome you look, they are there," comments Gerald Fink of Massachusetts Institute of Technology. In *Drosophila*, for instance, they comprise several discrete families and constitute between 5 and 10 percent of the genome.

Some mobile elements are large and complex, measuring as much as 10,000 nucleotides in length and carrying many genes, while others are simple sections of repeated DNA just a few hundred nucleotides long. Some people would classify all such elements as "junk" or "parasitic" DNA. Others strongly demur and insist that, for instance, although there is yet to be found any convincing evidence for the involvement of a limited class of elements in development in organisms other than maize, the possibility should by no means be dismissed. In any case it is clear that the mobility of certain genetic elements is essential in the generation of the huge diversity of antibodies in vertebrates and in the production of different antigenic coats in certain parasites. Jumping genes clearly represent a potentially rich source of mutation. In addition, an evolutionary link between mobile elements and retroviruses now seems incontrovertible, as does a causal relationship with certain cancers.

The list of mobile genetics elements is now long and growing fast. It is more than a catalog of interesting pieces of DNA: it is a statement that "the dogma of the constancy of the genome" has been swept away, 30 years after Barbara McClintock knew it was wrong.

—ROGER LEWIN

Spacelab: Science on the Shuttle

A new era of space science dawns with the first flight of Spacelab; but how useful will the shuttle really be for science?

On 28 November—or later if the National Aeronautics and Space Administration (NASA) cannot solve its latest problem with the space shuttle boosters in time—the space shuttle *Columbia* will lift off for the long-delayed first flight of Spacelab, the European Space Agency's (ESA's) orbital scientific laboratory. When it finally happens, it should be quite a show: to celebrate the event, ESA and NASA have given the 9-day mission at least one of everything.

On board the pressurized laboratory module, which rides in the shuttle bay like a camper in a pickup truck, and on the U-shaped pallet, which holds instruments exposed to the vacuum, there will be astronomical telescopes, solar telescopes, and an electron beam accelerator to excite the ionosphere. There will be earth observations by camera and by microwave, and motion sickness experiments on the astronauts. There will be confused sunflower seedlings trying to sprout in weightlessness. And there will be 30 experiments in materials processing, including the mixing of immiscible alloys and the convectionless growth of large, perfect crystals.

In the normal course of events, this would be the worst way conceivable to run a mission. Many of the experiments are utterly incompatible: *Columbia* will constantly be twisting down to point toward the earth, up toward the stars, and out toward the sun. No one experiment will be able to make full use of the time.

But then Spacelab 1 is not a normal mission. It is an exercise in engineering exuberance: one module, one pallet, six astronauts, three communications channels, dozens of instruments, 70 experiments, and innumerable investigators—from 14 countries—all working together for the first time.

Even more important, Spacelab 1 is a symbol—for ESA, the symbol of Europe's emerging prowess in space technology; for NASA, the symbol of a revitalized space science program, long constrained by delays and overruns on the shuttle. Indeed, the Spacelab program as a whole is seen by NASA as a major step toward the agency's most heartfelt goal, a permanent manned space station.

There is something fitting about the latter aspect, for Spacelab grew out of NASA's disappointment over its first bid for a space station in the early 1970's. *That* space station had been endorsed as a worthy successor to the Apollo moon landings by the high-level Space Task Group, chaired by then Vice President Spiro T. Agnew. A giant rotating wheel, capable of housing some 50 people full time, it would have cost some $20 billion (1970 dollars). It would have been the jumping-off point for a manned mission to Mars. And it would have been serviced by a reusable space shuttle, included in the plan almost as an afterthought as a cheap way of ferrying things up there and back.

Unfortunately for NASA, however, the euphoria of the first moon landings had proved short-lived, and Vietnam was ravaging the federal budget. Worse, the agency's attempts to lobby the skeptical Nixon White House were heavy-handed and clumsy. In the end NASA was lucky to get the shuttle.

"Once that decision was made [in 1972], a lot of us were appalled that there was nothing left in the plan for space science," recalls Robert L. Lohman, NASA's chief of Spacelab development. "So we took the idea of these RAM's [Research and Applications Modules, intended to be carried up and attached to the space station by the shuttle], and started to look at using them in the shuttle instead for 'sortie' missions."

Meanwhile, says Lohman, the Agnew commission had made a strong recommendation to internationalize the space program, and this was striking a responsive chord overseas. The Europeans were especially eager; "At one point they even wanted to build half the space shuttle orbiter in Europe," says Lohman. When the United States proved reluctant, the Europeans turned their attention to the Space Tug, a reusable booster that would ferry satellites from