BOOKS: GENETICS

McClintock at 100—Reason to Celebrate

Susan R. Wessler

In her crowded office at Cold Spring Harbor, Barbara McClintock surrounded herself with stacks of reprints. Significant contributions were distinguished by the single word "important" in red ink. *The Tangled Field* is the first comprehensive biography of the life, work, and times of McClintock. I have little doubt that most geneticists who read it will conclude, as I have, that Nathaniel Comfort's book represents an important contribution to the history of genetics.

The Tangled Field
Barbara McClintock's Search for the Patterns of Genetic Control
by Nathaniel C. Comfort
Harvard University Press, Cambridge, MA, 2001. 357 pp. $37.50, £25.95. ISBN 0-674-00456-6.

McClintock's life spanned that history. She was born in 1902, two years after the rediscovery of Mendel's laws by Correns and de Vries. She died in 1992, two years after the start of the Human Genome Project. As a working scientist at Cold Spring Harbor Laboratory for the last fifty years of her life, McClintock was at the best possible location to influence and be influenced by the leaders in the field. As the world's premier cytologist and the discoverer of transposable elements, it is inconceivable that she would not be an active participant in this history.

Yet the McClintock one gleans from most written accounts of her life was a loner—a fiercely independent, intuitive scientist who was respected but misunderstood and even ignored by her peers. As the story goes, her discovery of movable genetic elements in maize flew in the face of the prevailing dogma of a stable genome. However, unlike Mendel, who died unrecognized, she lived long enough to witness the discovery of transposable elements in other organisms and to receive all of the glory, including the Nobel Prize in Medicine and Physiology in 1983.

Hiding from fame and fortune. By 1986, McClintock sometimes attended lab funtions incognito.

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The author, director of the Center for History of Recent Science at George Washington University, characterizes this story of her life as a myth that was created largely by McClintock and perpetuated by a sympathetic and receptive public. Through exhaustive research, including examination of voluminous notes and letters written throughout her life that have only recently become available, Comfort demolishes most of the myth. Remarkably, the scientist that emerges is flawed but still extraordinary.

Some of the components of the myth are relatively easy to discount. Through McClintock's detailed documentation of her experimental observations and results, we see that she was not an intuitive mystic but a rigorous, deductive scientist. Yes, she might have gone off for a few hours of isolation and solved a complex problem, but these eureka moments were actually times when months and years of data were integrated.

Exposing the myth that her discovery of transposable elements was ignored and misunderstood consumes the largest part of the book and is its most important contribution. Like an investigative reporter, Comfort explores all of the angles. He sets the stage by summarizing the scientific concepts that influenced McClintock, leading the reader on a tour of the history of embryology and genetics that begins with Spemann and Weismann; passes through Muller, Goldschmidt, and Beadle and Tatum; and extends to Jacob and Monod. With this history as background, the reader is better prepared to comprehend McClintock's experiments and interpretations. Both are presented in detail and often in her own words. Comfort makes no attempt to update McClintock's observations with molecular mechanisms that have subsequently been identified. His approach serves to preserve the excitement of discovery while simultaneously making her science accessible to those not versed in the jargon of molecular genetics. The author annotates the experiments by including contemporaneous discussions with, and letters to, friends and colleagues—additions that give the reader a "you are there" experience. Comfort also describes the reception of McClintock's ideas by the genetics community, both from her point of view and from the perspectives of her contemporaries.

Complexities of corn. Reproducible patterns of color variation on maize kernels led McClintock to her discovery of controlling elements.

In the course of her studies on the behavior of ring chromosomes, McClintock identified a strain of maize where, as she stated, "the genome went wild" and gave rise to valuable genetic stocks that displayed complex unstable phenotypes. She observed reproducible patterns of spots and sectors of pigment on the surface of the kernels and deduced that these patterns resulted from the interaction of mobile genetic elements (which she called *Ac*, *Ds*, and *Spm*) with normal genes. She named the mobile elements "controlling elements" because, in part, they were able to control the expression of multiple genes. (The term "transposable elements" was coined by the maize geneticist Alexander Brink, who thought it "less interpretative.") The complexity of these interactions led her to propose that the normal role of controlling elements was to orchestrate development. In one model, she proposed that controlling elements were intergenic heterochromatin that underwent programmed transposition leading to the activation or inhibition of particular genes.

To McClintock, the significance of her discovery was not transposition, which could be accounted for by conventional mechanisms such as chromosome breakage and rejoining. Rather, she believed she had solved a fundamental problem of embryology: how one set of genes can make different tissues. This interpretation is what she stressed in her presentations and it is what her colleagues could not accept. To members of her audience, the behavior of controlling elements was random,

CREDIT: (LEFT) COLD SPRING HARBOR LABORATORY ARCHIVES; (RIGHT) BARBARA MCCLINTOCK PAPERS/AMERICAN PHILOSOPHICAL SOCIETY

stochastic, whereas development was orderly, decidedly nonrandom. Norton Zinder, a geneticist famous for his discovery of bacterial transduction, recalls, "She really didn't want to speak about transposition. She was talking about regulation and development. And that's what she was pissed off at [us about], and nobody would take that seriously. *Everybody* took seriously the transposition."

So, unlike Mendel, who was eventually recognized for his most important discoveries, McClintock was lauded only for her discovery of transposition, not for the contribution that she thought was really important. Although unhappy about this, McClintock exhibited a zest for living and for science till near the end of her days. Her life has served as a role model for women in science and as an example of the success that can come from unconventional thought and an independent approach. By stripping away the myth and revealing the very human scientist, Comfort has given us a more accessible role model as we begin to celebrate the centennial year of her birth.

BOOKS: MOLECULAR BIOLOGY

A Highly Personal Perspective

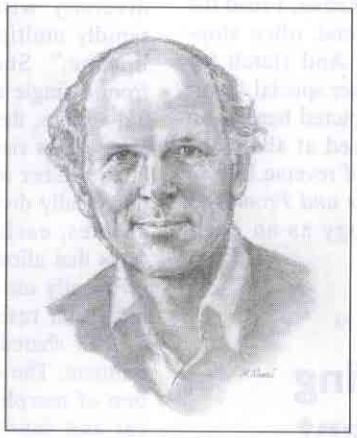
Mark Ptashne

Diagnosed with colon cancer in 1986, Harrison (Hatch) Echols, a molecular biologist at Berkeley, devoted parts of each of his last six years to writing a narrative history and textbook of his field. His unfinished project has now been edited and completed by his wife, Carol Gross, also a professor at Berkeley. The result is an absorbing and lucid survey of molecular biology and how, in many cases, it got to where it now is.

Operators and Promoters has a subplot: it is also a kind of self-portrait of Hatch. The picture emerges in bits scattered throughout the text in the form of opinions about science, scientists, and the sociology of science. He disapproves of the War on Cancer, declared some 30 years ago, saying it was "about as useful as declaring a 'War on Earthquakes.'" He resurrects his proposal, which was seriously debated at a 1970 Cold Spring Harbor meeting on phage lambda, that individuals eschew independent publication and instead gather by discipline once a year to decide what is worth telling the outside world. And so on. These and other thorny matters are not argued in detail; they tell us more about Hatch than about the issues.

Operators and Promoters
The Story of Molecular Biology and Its Creators
by Harrison Echols
Edited by Carol A. Gross
University of California Press, Berkeley, 2001. 486 pp. $65, £43. ISBN 0-520-21331-9.

Perhaps I can add to this portrait. Hatch presented himself as the archetypal Californian: tie-dyed shirt, hair in a ponytail, hesitant of speech—in short, way laidback. At a Gordon Conference, I fell for this ruse and found myself on a tennis court with him. Hatch's demeanor didn't change much, but the balls came over the net with lethal speed and precision. It was something like being a civilian taking a stroll through Jurassic Park. I took up golf.



Hatch Echols

As with Hatch himself, there's more to *Operators and Promoters* than first meets the eye. Hatch has chosen to recount the development of molecular biology by emphasizing, to a surprising degree, who did what. This approach has its dangers, but in this case it is used to fine effect. Rather than reading that such and such was done, we read that so and so (often a graduate student or postdoctoral fellow) did such and such. The active voice helps make the text flow.

Hatch also enlivens his account by telling slightly offbeat stories. For example, in describing the development of the Jacob-Monod view of the world, he describes how Mel Cohn and Annamari Torriani isolated a mutant bacterium that was unable to grow on lactose but perfectly inducible for β-galactosidase when challenged with an inducer other than lactose. That led Cohn to postulate, correctly, the existence of a lactose permease (his strain being mutant in that permease). It seems a small point, but Monod's response is revealing: "If we have to think about silly things like permeability, this field is hopeless—let's forget this mutant."

Hatch had interesting opinions about what is and is not important. My favorite is directed toward those—surely not you, gentle reader—who got a headache whenever someone started explaining the Holliday model for "the molecular basis of genetic recombination." We read an explanation of the model (accompanied, as are discussions throughout the book, by simple black-and-white drawings) and then the bracing words: "The Holliday model is one of the great ideas of modern biology."

Hatch draws attention to intellectual threads, and he searches for what made experiments possible, for what the critical insights were. Lest we forget, what Watson and Crick really learned from Pauling were the "Pauling Principles": figure out how the building blocks of the macromolecule can fit together, and the total structure may emerge. DNA replication seemed a complicated mess, too much so to ever reproduce in a test tube, until Kornberg guessed that most of that complexity was required to synthesize the building blocks, the triphosphates. Use presynthesized triphosphates, he thought, and it's a different story. The development of recombinant DNA technology might have been stuck had it not been for Mandel's discovery that calcium treatment of bacteria allowed efficient uptake of DNA. And the Brenner, Jacob, Meselson experiment that demonstrated the existence of mRNA failed until, at the last minute, Brenner surmised that they had to raise the magnesium concentration to protect the ribosomes floating in high-density cesium chloride.

There is a special emphasis on the pervasive influence of the study of phage lambda, to which Hatch made important contributions. How genes are regulated; how DNA molecules recombine at specific, widely separated sites, as during excision of the phage chromosome from the host chromososome upon induction; how that excision can produce a phage carrying a host gene, explained by the celebrated insight (nicely described here) of Allan Campbell; how certain enzymes direct so-called general recombination and others the process of repair of DNA damage; how the phenomenon of host restriction, which led to the discovery of host-restriction endonucleases, works; and how the initiation of DNA replication is controlled. All these and more, as studied with lambda, had an enormous impact on the subsequent developments, according to Hatch. And who would argue with that proposition? He illustrates the point, after expressing his enthusiasm for the development of recombinant DNA technology and its commercialization, with this paean to the virtues of basic science:

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