

# ***More Than Molecules:***

***Barbara McClintock and the 21st Century***

Essay submitted to York University STS 3740

Dr James Elwick, Professor

Winter 2011

Bill Atkinson

YU 211 359 007

Workshop Draft 2011 March 17

Final Draft 2011 March 26

Come, slight Earth-goddess, guardian of old truth

- *My Distillate of Summer* (1)

Things too wonderful for me, which I did not understand

- *The Bible* (2)

A good scientist sees the pattern when the data are incomplete, chaotic, and confusing

- *Gerhard Herzberg* (3)

I didn't think of myself as intelligent. I just wondered why other people were so slow

- *Freeman Dyson* (4)

McClintock remains in crucial respects an outsider

- *Evelyn Fox Keller* (5)

*Horatio*: O day and night but this is wondrous strange!

*Hamlet*: And therefore as a stranger give it welcome.

There are more things in heaven and earth, Horatio,

Than are dreamt of in your philosophy.

- *William Shakespeare* (6)

## 1. Hit and Myth

Barbara McClintock [1902-1992], the 20th century cytogeneticist and one of only three women to win an unshared Nobel Prize, was enigmatic in life and remains so still. She is no more 'just McClintock' than Einstein is 'just Einstein': myth has accreted about both scientists, not only within their disciplines but in the wider world as well. Einstein is the prototype of the professorial genius whose thoughts transcend common comprehension (7). McClintock is the darling of feminists grinding an axe on the foreheads of male scientists, and of educators anxious to increase female scientific enrolment. The support of both groups (which McClintock neither sought nor valued) has made her a pop-culture icon - the brilliant woman struggling alone against the patriarchy, who after a lifetime of obscurity sees her holistic, nurturing, *womanly* viewpoint recognized.

Of course no historical portrait is static: the stocks of major personalities rise and fall. In 2001, eighteen years after her Nobel, Nathaniel Comfort, associate professor at Johns Hopkins University, published *The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control*. Comfort calls his first section *Myth*. Its keywords include:

***Brilliant young geneticist...Discovered something revolutionary...No one believed...Outright hostility...Ceased publishing...Not bound by dogma...Like Gregor Mendel, the father of genetics, whose ideas had been ignored for the last third of the nineteenth century, McClintock was rediscovered...Her ideas had at last found their milieu (8).***

My thesis is twofold. First, Comfort hits at a straw woman: the McClintock he deconstructs no longer represents the prevailing view. Second, while McClintock's ideas (like those of all scientists) are qualified by new discoveries, her *approach* remains as revolutionary as her acolytes claim. It comprises intuition based on high intellect, intense observation, and profound and sympathetic thought. For notwithstanding the claims of molecular biologists, life is more than molecules. Absent the contextual

biosystem of the cell, the most elegant molecule is doornail-dead. McClintock, unlike her mechanistic colleagues, saw this without flinching. Her work links ontogenic and embryological development (key themes c.1870-1940) with our own century's key theme: exposing the mechanisms by which cells manage their staggeringly complex existence. While McClintock did not neglect small questions she was never bound by them, and because of this she bestrides the 20th century like a colossus. Her radical approach has not been tried and found wanting. It has been found difficult and not tried (9).

## 2. Emerita

Barbara McClintock was admitted to a Ph.D. degree in botany at the Cornell University College of Agriculture in 1925. She had been captivated by cytology, the study of cells, since first encounter, and was to focus on it throughout her career. As well as cytology and cytogenetics (the study of the visible cellular genome, *viz.* the chromosomes), McClintock's academic allegiance was to another viewpoint with roots in the nineteenth century: embryology. These two disciplines, which the mid-twentieth century disparaged as much the later nineteenth century did the amateur naturalist, underlie all McClintock's achievements. McClintock, a biographer notes, "succeeded in synthesizing the uniquely twentieth-century focus on experiment with the naturalist's emphasis on observation...What for others is interpretation, or speculation, is for her a matter of trained and direct perception" (10). McClintock *saw*.

Her early experiments stand as models of elegant design. Among other things they showed that genetics can be studied not only by breeding generations of a given test species, but also by microscopically examining that species' chromosomes *in situ*. Almost singlehandedly she made her specialty species, maize, as important to genetics as *D. melanogaster*, the fruit fly made famous by T.H. Watson *et alia*.

As time passed, McClintock became obsessed with mechanisms of cellular control. Instructions for a cell's manufacture of proteins lay in the genome, fine. But how did those data spark and maintain a living, breathing cell? What were the ways and means? McClintock's investigation into these issues culminated with her discovery - without electron, atomic-force, or scanning tunneling microscopes, using only her trusty binocular Zeiss and her own perspicuity - that the cellular genome, till then and for years afterward conceptualized as fixed, was in reality a busy switching centre. Genetic elements (genes, gene fragments, other entities) constantly hopped among chromosomal locus (11).

Or so said McClintock; others disagreed, and brought the fight to her. McClintock's home lab at Cold Spring Harbor NY was the site of one of modern biology's key papers: the 1954 announcement by James Watson and Francis Crick of the mechanical structure of deoxyribonucleic acid. This molecule, (except in a retrovirus, *e.g.* HIV) constitutes genes. DNA is a double helix, a twisted ladder whose sequence of rungs - each of which one of four simple chemicals called nucleotides - encodes ribosomic protein synthesis when read in codons or consecutive groups of three.

Suddenly all the money was on the new kid on the block. Asking *how* cells used genetic data to control their chemistry, development, nutrition, and respiration, was deemed old-fashioned; the concept of control, when regarded at all, was sloughed off to emeritae like McClintock. Let embryology worry about such trivia; molecular biology had bigger - well, tinier - fish to fry.

As the 1950s moved into the 60s and 70s, McClintock continued to work at Cold Spring Harbor and was treated, mostly if not universally, with respect - "but in a distant, detached way, as though she were no longer relevant" (12).

### **3. Cold Comfort**

In some ways, Comfort's take on McClintock is scrupulously fair. He admits her brilliance, often gives her the benefit of the doubt, and documents the misogyny she overcame (13). His deconstruction is

less demolition than elucidation: Comfort does not knock McClintock off her pedestal so much as he scrubs away the film of feminist oversimplification. For this he deserves full credit.

Admittedly, much of McClintock's marginalization was her own doing: hers was a prickly personality, bitterly jealous of her personal and academic freedom (14). More tellingly, she was famous for her opaque explanations of her hypotheses, data, and interpretations. To the end of her life McClintock mystified and even annoyed her friends almost as much as her enemies.

On the whole, McClintock's viewpoint is that of the classical cytologist. While she welcomed new proofs of her findings [particularly transposons] from the new field of molecular biology, she never adopted its language and to the end of her days remained a cytogeneticist with embryological training. Nor were her tools the new techniques of 'wet nanotech', *e.g.* site-specific mutagenesis or polymerase chain reactions (15). They comprised a half-acre maize plot, optical microscopes, and her own eyes and brain. She and Mendel shared a garden.

Yet this was enough for McClintock to resist the new orthodoxy of molecular biology, which went otherwise largely unchallenged for the two decades ending c.1975. In this consensus, which Watson termed the central dogma, each cellular genome was as invariant as a set of blueprints. Information flowed from it, never into it: environmental conditions could not affect the genes. Genomic influence was possible only indirectly, via Darwinian selection: genes conferring selective advantage let their bearers survive and reproduce, thus raising the genes' prominence in various gene pools.

As the central dogma gained traction, 'McClintockian science' - an epithet coined anonymously by dismissive molecular biologists - grew steadily more marginalized. It was pursued by no one but McClintock and a handful of supporters, who themselves seldom fully understood her.

As a *grande dame* of science, she was unquestionably respected. The part of Comfort's *mythos* that depicts her as beyond the pale of contemporary biology emerged after the fact and is, as he

demonstrates, flat wrong. Even during her publication hiatus in the 1960s, when molecular biology rode roughshod over traditional cytology, embryology, and cytogenetics, McClintock was continually consulted by peers to discuss problems and critique unpublished papers.

Yet according to Comfort, the respect accorded McClintock was not for her new work: it came from the same nostalgic well that ultimately won her a Nobel - in other words, the sentimentalism of the lifetime achievement award (16). From 1950-75 McClintock was consulted for her mind, experience, focus, and achievements, not because she dwelt at the cutting edge of biological research. From age sixty, friends and foes alike saw her as an emerita - as the old jape had it, outstanding in her field.

Certainly McClintock herself was puzzled by her own discoveries. If we accept Einstein's dictum that scientists understand nothing they cannot clarify to a four-year-old, McClintock's murky attempts to explain her work suggest that she herself was frequently as baffled as anyone (17). That she was brilliant no one questions; that her brilliance led to lasting insights into biological processes remains in dispute. The number of those who dispute her importance is, however, steadily shrinking.

#### ***4. Cellula Cogitans***

Dismissing Barbara McClintock as a relic, what one young biologist called "the old bag of Cold Springs Harbor", nonetheless misses a point more fundamental than the intricacy of her explanations. One may grant Comfort's list of McClintock's shortcomings - reading them into evidence without defence objection, so to speak - and still uphold her as a great biologist: equal to not just Lederberg and Watson but also to Pasteur, Mendel, and even Darwin.

Consider the *argumentum ad auctoritatem*. Marcus Rhoades: "I've known a lot of famous scientists. But the only one I thought really was a genius was McClintock" (18). Joshua Lederberg: "By God, that woman is either crazy or a genius!" (19). Evelyn Witkin: "She could *see* genes turning on and

off" (20). Rollin Hotchkiss: "[She was] an expert microscopist...she also had an inner 'viewing lens' that mentally portrayed a far bigger map - a panorama of the whole cellular and anatomical display - spreading over into the fourth, or time dimension" (21).

McClintock's approach was ahead of its time by at least half a century. How is this? A scientist interviews nature; bad questions - myopic, timid, poorly phrased - elicit bad answers. Starting c.1950 a new generation of biologists asked a set of small precise queries, and learned things that were equally precise and small. Essentially they sketched the shapes of molecules. By contrast, McClintock dared the heaven-storming questions that haunt the great biologists: *What is life? How does it function? What makes inanimate matter live? How does life direct itself?* And this, mere months ago:

***What do they [cells] sense? How do they respond? What is important to them? These are difficult questions and, like the subject of protozoa behavior itself, extremely unfashionable. Indeed, there seems to be an unwritten convention or law that one should not even raise these issues in a scientific context. Contemporary biologists have an amazing ability to visualize and record what happens in cells...But you will be hard put to discover, in all this amazingly rich resource, anyone prepared to ask [the larger issues] (22).***

Because of their molecular focus, most biologists for the three decades ending 1980 merit McClintock's tart dismissal: "Right and left, they miss what's going on" (23). Or as a poet put it, they tell you "everything about the wasp, except why" (24).

Barbara McClintock asked why. Her ability to infer profound nanoscale truths from macroscale observations was and is astounding. By all accounts she could *project herself* into cells: identifying with them, conceptually fusing with them. "The main thing about it is you forget yourself," she said - an approach she followed so perfectly that once when writing an exam, she forgot her own name (25). McClintock's intense focus let her dare to address the big issues that most biologists ignored for decades and that many still avoid.

## 5. Crack of the Bat

Molecular biology's elucidation of the physical genome, useful as it is, answers only part of life's riddle. Still unanswered: How do a cell's genomic data go from a sequence of nucleotide triplets to a working entity, complex as a metropolis, that senses and reacts to internal and external environments many times a second? What are a cell's precise mechanisms of construction, organization, feedback, and control? Are environmental data truly excluded forever from the genome?

McClintock never lost sight of these larger questions. "A goal for the future," she said in accepting her Nobel, "would be to determine the extent of knowledge that a cell has of itself and how it utilizes this knowledge in a 'thoughtful' manner when challenged" (26).

McClintock's uncompromising quest, her gaze fixed on the titanic idea of the 'thoughtful cell', long kept her on the margins. At times she seems more artist than scientist: her vision was intuitive, even aesthetic. 'Seeing genes turn on and off' seems less like the logical formulation of a testable hypothesis than like a baseball player's lightning-fast extrapolation of where a ball will fall at the crack of the bat. An outfielder racing to a rendezvous with a fly ball based on c.150 milliseconds of aural information cannot explain his methodology; nonetheless he makes the catch. Certainly, Comfort could tell the outfielder why his intuition is unscientific. Equally certainly, he'd never make the out.

Comfort's dismissal of McClintock's approach as "unscientific" is similar. Just as sound data are by definition reproducible, so ideal methodology is amenable to lucid presentation. In other words, an experimental approach that cannot be clearly conveyed to the wider community smacks of prescientific mysticism. Yet Comfort's classical analysis conveniently ignores a central aspect of all science that has always existed above the plane of linear logic: the origin of hypotheses themselves. Anyone can test an idea; no one can say where it came from. "Fools give you reasons, wise men never try" (27).

## 6. Rage for the Machine

While I have largely left untouched the issue of gender bias, one thing seems clear: without realizing it, Comfort embodies what the feminists correctly pin on patriarchal science - its cold, emotionless, *uber*-logical analysis; its assumed superiority; its thinly veiled contempt for any different approach. Comfort exhibits neither a "feeling for the organism" nor an empathy for those who do (28).

One sees identical *hubris* in other disciplines. c.1985-2000, for example, nanotechnology was conceptually dominated by Eric Drexler, a sci-fi author posing as a reputable theorist. Drexler postulated tiny machines, molecular assemblers or 'nanobots', that would snap atoms together like Lego blocks to make objects quickly and automatically. Within decades, Drexler predicted, nanobots swimming in our bloodstreams would remove all pathogens, neoplastic cells, and atherosclerotic plaque. Other nanobots would repair genomic telomeres eroded by meiosis; still others would lie dormant in our flesh, storing hyperbaric molecular oxygen to be released in the event of a heart attack. The upshot of these interventions [so Drexler] would be immortality - not just for people alive today, but also for those who, about to die, had had their bodies dunked in liquid nitrogen. But "real nanotechnology isn't about physical immortality, or killer nanobots, or waking up dear dead Auntie Flo from her long nap in the freezer," writes a Nobel laureate. "Real nanotechnology is more amazing than any pipe dream" (29).

Compared to McClintock's approach, mainstream biology continues to exhibit a Drexlerian hubris. McClintock rages against mechanistic biology; Comfort's rage seems *for* such a thing, rejecting as irrational McClintock's awed respect for the subtle and the profound. Darwin was closer to the core of things when he contemplated the "tangled bank" of an English stream - a metaphor for life's infinite complexity. The 21st century may find another tangled bank within the cytoplasm, with proteins standing in for macroscale species. McClintock sensed this; for all his erudition, Comfort does not.

## 7. Gaea

The science that temporarily sidelined McClintock was molecular biology, whose adherents correctly saw their discipline as a mechanistic attack on McClintock's approach. She was a visionary, a mystic; they "cockily rejected the scientific tradition in the textbooks - including much of the cytogenetic tradition that McClintock had helped establish" (30). Where McClintock saw, listened, and inferred, the new brigade dictated terms to life. *God said, Let Watson be! and all was light* (31).

The 1970s brought molecular biologists a humbling realization: It Ain't That Simple. Life still had curves to throw: new investigations into the workings of cells and cellular genomes revealed vast and unexpected complexities. Giant enzymes cruised down the DNA ladder, repairing errors in nucleotide replication. Various forms of RNA, DNA's poor cousin, ferried data to ribosomic factories. Arrays of sensor proteins lay imbedded in the forward edges of cells' bilipid membranes, detecting nutrient and toxin gradients. For experimental biology, a trickle of humility crept in. At its culmination, it rediscovered McClintock's transposable genetic elements and named them transposons.

Initially this happened unwittingly, without reference to McClintock. Then Joshua Lederberg *et alia* recalled that 'Dr Barb' had posited such things years ago. The central dogma at last began to admit the McClintockian view:

- *Just as a house is more than blueprints, a cell is more than molecules*
- *Even in their mechanisms of control, cells are in constant flux*
- *Life is 1% genetic data and 99% a system of systems*
- *Life's only changeless force is change*

Scientists with viewpoints less parochial than Comfort's were the first to appreciate McClintock's unorthodoxy: Joshua Lederberg deserves a nod. A scientific advisor to eleven successive U.S.

presidencies, 'Uncle Josh' was a generation younger than McClintock but shared her extraordinary range of interests. As a Nobel laureate with nothing to prove, he could step outside academic expectation. Prions, misfolded proteins, fascinated him; so did the search for extraterrestrial intelligence. He found in McClintock a cognitive soulmate. His koan had been answered: She was brilliant, not insane (19 + 32).

The tide still flows. Stuart Kauffman: "Alone, each molecular species is dead... [only] the collective system of molecules is alive" (33). Matter is dead until it is not, and at the interface something amazing occurs; for want of a better term it is miraculous (34). McClintock saw this steadily through the long hegemony of central dogma. But then every dogma has its day.

Various disciplines support McClintock's insight. Matter needs no nanobots because atoms self-assemble in perfect order *by taking information from their immediate environment* (35). Though biology has yet to import this insight from material science, nothing prevents a similar process from moving environmental data into the genome. For example: cells routinely inhibit genetic expression by attaching the free radical CH<sub>3</sub> to a gene, a process called methylation. Central dogma asserts that meiosis scrubs away all such off-switches, giving each new cellular generation a fresh start. But recent evidence suggests that certain genes methylated in parent or germ cells due to environmental pressures remain methylated in daughter cells [bacteria, amoebas] and haploids [eukaryotic multicellular organisms].

If this be true, it slays the central dogma for all time. The environment speaks; the genome listens; acquired characteristics may indeed be inherited. Life is complex beyond description and ultimately unpredictable. It is free, it is McClintockian; it is - forgive the pun - unComfortable.

The last word belongs to Evelyn Witkin. Barbara McClintock's ideas, she said, remain "completely unrelated to anything...[they are] *like looking into the twenty-first century*" (36).

# *Bibliography*

Atkinson, W., *Nanocosm* [New York: Amacom, 2005 (2nd edition)]. ISBN 0-8144-7277-X

Atkinson, W., *Simon Pure* [Chapel Hill NC: CreateSpace, 2011] ISBN 145-647-739-4

Bartlett, J., *Familiar Quotations* [New York: Little, Brown & Company, 1968 (Fourteenth Edition)]

The Bible [Revised Standard Version]

Bray, D., *Wetware* [New Haven: Yale University Press, 2009] ISBN 978-0-300-14173-3

Comfort, N. *The Tangled Field* [Cambridge MA: Harvard University Press, 2001] ISBN 0-674-00456-6

Dyson, F., *Infinite in All Directions* [New York: Harper & Row, 1988] ISBN 0-06-091569-2

Frickel, S. & Moore, K., ed., *The New Political Sociology of Science* [Madison WI: University of Wisconsin Press, 2006] ISBN 0-299-21330-7

Keller, E., *A Feeling for the Organism* [New York: W.H. Freeman and Company, 1983]  
ISBN 0-7167-1504-x

Thomas, D., *A Child's Christmas in Wales* [New York: Holiday House, 1985] ISBN 0-8324-0565-6

Wallace, B. & Falkinham, J., *The Study of Gene Action* [Ithaca NY: Cornell University Press, 1997]  
ISBN 0-8014-3265-0

## *Notes*

1. Atkinson, W., Unpublished sonnet, penultimate line [1979]
2. RSV Job 42: 3
3. Herzberg, G., private communication (oral). Ottawa ON, 1979 November
4. Dyson 122
5. Keller *xix*
6. *Hamlet* Scene I Act IV
7. (a) *There's a wonderful family named Stein / There's Gert and there's Ep and there's Ein /  
Gert's poems are bunk / Ep's statues are junk / And no one can understand Ein*  
(b) *Professor, what time does Grand Central Station arrive at the next train?*  
[Both quoted in Cerf, B., ed., *A Treasury of Laughter* [New York: Charles Scribner's  
Sons, Book of the Month Club Edition, 1944]
8. Comfort 2
9. Daly, J., History 2b6 lecture, McMaster University, winter term 1965. I believe this was said by C.S.  
Lewis but have been unable to trace the original quotation, which referred to religious belief
10. Keller 155
11. *Locus* is a 4th declension noun whose plural is not *loci* but *locus* with a long final vowel: *lo-coos'*
12. Watson, J. [quoted in Comfort 247]
13. e.g. Comfort 177 ["stellar intelligence...fierce honesty"]. Also 102f, 113, 175ff
14. e.g. Comfort 247: "McClintock would complain about having to do all her own typing and filing, but when she was offered a secretary, she refused"
15. Atkinson 167-193
16. Comfort Ch 9 *passim*
17. Lederberg, J., personal communication (oral). University of Western Ontario, 1980 June
18. Keller 50
19. Quoted in Keller 142. Thirty years after he framed his koan, Lederberg led the group that successfully nominated McClintock for the Nobel
20. Keller 137

21. Hotchkiss, R., in Keller *xiv* [Foreword]
  
22. Bray 4f (Italics mine)
23. Keller *xxi*
24. Thomas 25
25. Keller 36
26. McClintock, Nobel acceptance speech [Quoted in Bray, *frontispiece*]
27. Hammerstein, O., song lyric: *Some Enchanted Evening* [in musical *South Pacific*, 1949]
28. Keller, title & *passim*
29. Smalley, R. [Quoted in Atkinson, W., *Nanocosm* (2005: 2nd edition Foreword)]
30. Comfort 247
31. Alexander Pope, *Epitaph of Isaac Newton* [1739?] Quoted in Bartlett 412
32. For an informal sketch of a 55-year-old Lederberg see Atkinson, W., *Simon Pure* [Chapel Hill NC: CreateSpace Books, April 2011] 77f
33. Quoted in Bray 198
34. The Bible, Genesis 2:7: *The Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life.* I present this as a metaphor for presently unknown biomechanisms
35. Theis, T., personal communication (oral). International Nanotechnology Conference, San Diego CA, May 2003 [Quoted in Atkinson 106-115]
36. Keller 137 (Italics mine). Keller's *summa* reads in part: "Since 1983, McClintock's place in the history of modern biology has only become more secure" [Keller *op-Frontispiece*: Author's Note on the Tenth Anniversary Edition]