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BOOK REVIEWS

The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control by Nathaniel C. Comfort. Cambridge, Mass., USA, and London, England: Harvard University Press, 2001. 352 pp. $39.95. ISBN 0674004566.

Think "Fluid Genome" and most scientists with a memory of recent molecular genetics think "Barbara McClintock". She is the grandmother of the field of genetic transposons or mobile genetic elements (Shapiro, 1995), and this biography documents her extraordinary scientific life and achievements.

A testimony to her legacy is the ubiquity of "retrotransposition". Such reverse transcriptase-mediated events have had an enormous impact on shaping the genomic DNA sequence landscape and regulating gene expression during development (eg, coat color in mice, see Morgan et al., 1999). Indeed, the molecular record shows that at least 40% of the mammalian genome has overtly accumulated DNA sequences via an RNA intermediate over evolutionary time (Kazazian, 2000) and a significant fraction of this load constitutes intronless functional genes, such as those encoding olfactory receptors (Brosius, 1999). Evidence from our laboratory suggests that covert and targeted soma-to-germline retrotransposition has played a key role in the evolution of the variable (V) gene families of the vertebrate immune system (Steele & Blanden, 2000; Steele et al., 2002). Moreover, mouse spermatozoa are endowed with retrotransposon-encoded reverse transcriptase activity, enabling sperm cells to reverse transcribe exogenous RNA molecules into cDNA copies that can be delivered to embryos during fertilization (Giordano et al., 2000). More recently, Patrick Fogarty of Tosk Inc. (Santa Cruz, CA) has established that Weismann's 'Barrier'—the 19th century 'law' protecting the soma from the germline (Steele, 1979; Steele et al., 1998)—can be readily penetrated in mice and targeted to specific loci using novel DNA transposon-based gene delivery vectors (Fogarty, 2002).

A new paradigm is therefore emerging to replace the traditional static neo-Darwinian view, allowing us to now confidently embrace Shapiro's conclusion that transposable genetic elements will be a key plank in our understanding of evolution as the 21st century unfolds (Shapiro, 2000). Indeed, horizontal gene transfer has been a common and dominant feature of genomic evolution from bacteria to man (Gogarten, 2003), and transposable elements are now considered a key factor in the evolution of eukaryotic complexity (Bowen & Jordan, 2002).

In the space of 50 years—since McClintock (1950) first published her results on mobile controlling elements in maize—the old view of evolution has been changed beyond recognition. James A. Shapiro, a key player in establishing the reality of mobile genetic elements in bacteria during the 1960s and 1970s, has aptly summed up the current situation as follows:

. . . The conceptual changes in biology are comparable in magnitude to the transition from classical physics to relativistic and quantum physics . . .. How all this modularity, complexity, and integration arose and changed during the history of life on earth is a central evolutionary question. Localized random mutation, selection operating "one gene at a time" (John Maynard Smith's formulation), gradual modification of individual functions are unable to provide satisfactory explanation for the molecular data, no matter how much time for change is assumed. There are simply too many potential degrees of freedom for random variability and too many interconnections to account for . . .. (Shapiro, 1997, pp. 32)

In this book, Nathaniel C. Comfort, an historian of 'recent science', has written an impressive and detailed scientific biography of Barbara McClintock's life and genetic discoveries. His aim is to debunk and overturn popular misconceptions by focusing on the scientific themes and problems that consumed McClintock's long life, mainly at the Cold Spring Harbor Laboratory on Long Island, New York. The book is a useful antidote to Evelyn Fox Keller's biography (published earlier in 1983 just before she won the Nobel prize at the age of 81).

McClintock's key attributes mark her out as a unique individual. She displayed a range of character traits instructive to the current generation of scientists—great courage and integrity, tenacity, hard physical work, creative analytical ability, powerful scientific memory and intuitive vision. Nathaniel Comfort documents all of these in an absorbing story with great taste and sensitivity. This is, after all, a biographical history of 'recent science'.

It is of interest that McClintock never had an intimate relationship. This fact certainly underlines the reasonable conclusion 'that she dedicated her life to science'—with all the religious overtones akin to the life and work of Mother Teresa. But what made her special, particularly to James Shapiro, who knew her well, was "her complete intellectual freedom" (Shapiro, 1995). She was open to new ideas both within and beyond science and prepared to give them a hearing when her peers at the time displayed intellectual intolerance (eg, controversy surrounding the ideas of Immanuel Velikovsky).

In my opinion, she was very lucky to win the Nobel prize (despite her clear achievements) as she had to wait almost 20 years after the clear demonstrations of insertion sequences, transposons, etc. by Shapiro and others. An early death or other unavoidable career twist could have robbed her of deserved recognition. I venture this despite the important fact of her 'central' scientific location at Cold Spring Harbor. Her 'spinsterhood' and idiosyncratic scientific dedication would have constituted a powerful emotional barrier with her more socially mobile and intellectually fashionable, genetic 'peers'. Here I agree with Fox Keller's imputation that the rise of modern activist feminism in the 1970s helped break down some of the non-scientific barriers to her gaining appropriate recognition.

The Nobel committee can delay appropriate recognition or get it plain wrong (Lawrence, 2002). Peyton Rous (Nobel, 1966) was a very old man when he was awarded the prize for his 1911 discovery of tumor viruses. With respect to the field of immunology, my own discipline, most were thoroughly deserved, yet there have been notable recent omissions. For example, Melvin Cohn should have shared the prize with Niels Jerne and/or Susumu Tonegawa for contributions to our understanding of the genesis and diversity of immune recognition, and indeed it is still curious why the man who discovered the central immunological role of the thymus, Jacques Miller, has still not been recognised given that the sequelae of his fundamental discoveries have been awarded the Nobel (genetics of the MHC, MHC-restricted T cell recognition).

There are other Nobel anomalies. Frank MacFarlane Burnet shared it with Peter Medawar for immunological "self vs non-self", but Burnet's greatest achievement was undoubtedly *The Clonal Selection Theory of Acquired Immunity* published mainly as a book in 1959—it is a cornerstone to understanding diversity of structure and function during both somatic and germline evolution of the immune system (Steele, 1979; Steele et al., 1998).

Late in her career, McClintock considered genetic control in the context of an organism's integrated genomic response to the environment. This view has been articulated particularly by Shapiro (1991, 1995), who posits:

> In order for the integrated mosaic genome to make evolutionary sense, there must exist mechanism for large-scale, rapid reorganization of diverse sequence elements into new configurations. By analogy with computer-based systems, evolution could be envisaged as involving changes from one system architecture to another. (Shapiro, 1995, p. 11)

The rider here is that such massive genomic reorganisation must itself be tested for survival value by Darwinian natural selection. How rare would such successful events be, say, in higher vertebrates?

I thoroughly recommend this book. It is well written and in a style reminiscent of Horace Freeland Judson's earlier and absorbing *Eighth Day of Creation* (1980). The case can be made that McClintock's seminal work was effectively sidelined by the Watson-Crick, Jacob-Monod discoveries and the rise of modern molecular biology during the 1950s and 1960s. This may have been a scientific necessity opening the way for Shapiro and others to then fully characterize mobile genetic elements in bacteria and other higher organisms (Shapiro, 1995). In this reviewer's opinion, we now await a thoroughly researched biography of that other titan and visionary of 20th century genetics, retrovirologist Howard M Temin.

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References

Bowen, N. J., & Jordan, I. K. (2002). Transposable elements and the evolution of eukaryotic complexity. *Current Issues in Molecular Biology, 4,* 65–76.

Brosius, J. (1999). Many G-protein-coupled receptors are encoded by retrogenes. *Trends in Genetics, 15,* 304–305.

Burnet, F. M. (1959). *The Clonal Selection Theory of Acquired Immunity.* London and New York: Cambridge University Press.

Fogarty, P. (2002). Optimizing the production of animal models for target and lead validation. *TARGETS, 1,* 109–66.

Giordano, R., Magnano, A. R., Zaccagnini, G., Pittoggi, C., Moscufo, N., Lorenzini, R., & Spadafora, C. (2000). Reverse transcriptase activity in mature spermatozoa of mouse. *Journal of Cell Biology, 148,* 1107–1113.

Gogarten, J. P. (2003). Gene transfer: Gene swapping craze reaches eukaryotes. *Current Biology, 13,* R53–R54.

Judson, H. F. (1980). *Eighth Day of Creation: The Makers of the Revolution in Biology.* New York: Touchstone Books.

Kazazian, H. H. (2000). L1 retrotransposons shape the mammalian genome. *Science, 289,* 1152–1153.

Keller, E. F. (1983). *A Feeling for the Organism: The Life and Work of Barbara McClintock.* New York: W.H. Freeman.

Lawrence, P. A. (2002). Rank injustice—The misallocation of credit is endemic in science. *Nature, 415,* 835–836.

McClintock, B. (1950). The origin and behavior of mutable loci in maize. *Proceedings of the National Academy of Sciences of the United States of America, 36,* 344–345.

Morgan, H. D., Sutherland, H. G. E., Martin, D. I. K., & Whitelaw, E. (1999). Epigenetic inheritance at the agouti locus in the mouse. *Nature Genetics, 23,* 314–318.

Shapiro, J. A. (1991). Genomes as smart systems. *Genetica, 84,* 3.

Shapiro, J. A. (1995) The discovery and significance of mobile genetic elements. In Sherratt, D. J. (Ed.), *Mobile Genetic Elements—Frontiers in Molecular Biology* (pp. 1–17). IRL Press at Oxford University Press.

Shapiro, J. A. (1997). A third way. *Boston Review, 22*(1), 32–33.

Shapiro, J. A. (2000) Transposable elements as the key to a 21st century view of evolution. *Genetica, 107,* 171–179.

Steele, E. J. (1979). *Somatic Selection and Adaptive Evolution: On the Inheritance of Acquired Characters.* Toronto: Williams-Wallace (2nd ed., Chicago: University of Chicago Press, 1981).

Steele, E. J., & Blanden, R. V. (2000). Lamarck and antibody genes. *Science, 288,* 2318–2319.

Steele, E. J., Hapel, A. J., & Blanden, R. V. (2002). How can DNA patterns of somatically acquired immunity be imprinted on the germline of immunoglobulin variable (V) genes? *IUBMB Life, 54*, 305–307.

Steele, E. J., Lindley, R. A., & Blanden, R. V. (1998) *Lamarck's Signature: How Retrogenes Are Changing Darwin's Natural Selection Paradigm.* Reading, MA: Perseus Books.

Acquiring Genomes by Lynn Margulis and Dorion Sagan. New York: Basic Books, 2002. xvi + 240pp. $28.00 (hardcover). ISBN 0465043917.

The immense complexity of the biosphere cries out for an explanation. In light of the tendency of inanimate objects to wind down over time, biologists have been searching for the origin of order in living forms (Kuppers, 1990; Weber et al., 1988). While the notion that a significant degree of organization can be obtained "for free" due to emergent properties implicit in complex systems (Kauffman, 1993) and the laws of physics and chemistry (Antonelli, 1985; Thompson & Whyte, 1942), the theory which gets the most press is Neo-