COMMENTARY/

by Bernard Dixon

McCLINTOCK'S REMARKABLE TRANSPOSABLE ELEMENTS—THIRTY YEARS LATER

A cabal of biotechnologists and molecular biologists, gathered to mull over the future implications of their pioneering work, is hardly likely to become equally excited about studies carried out three decades ago by someone now in their eighties. But that is what happened recently at COGENE's latest conference, held in Cologne (see also p. 309). The subject of interest was American geneticist Barbara McClintock, who was born on June 16, 1902, and the research concerned her discovery of transposable elements in maize during the late 1940s. If ever a major breakthrough happened way ahead of its time, this was it.

McClintock's work at Cold Spring Harbor was brought up during the COGENE meeting by Peter Starlinger of the University of Cologne. He urged today's new breed of plant breeders to go back to her unstable, mobile elements and study their biochemistry. He gave several reasons for his plea. One was that these neglected fragments of nucleic acid are "interesting." Another was that they might well be exploited as vectors for moving genes in the interests of innovation in biotechnology. And a third was that, because they can be related to low dose ionizing radiation, their investigation could provide valuable information to help resolve the continuing controversy over the biological effects of low level radiation.

A sober re-examination of Barbara McClintock's premature discovery of what we now term transposition certainly provokes a few puzzling questions. Here is someone with a high reputation in classical genetics, yet whose major achievement was either ignored or else treated with polite perplexity for a long time. That achievement had two arms: her recognition, over ten years prior to Francois Jacob and Jacques Monod's discovery of genetic regulation in bacteria, controlling elements in addition to structural genes; and her demonstration of so-called jumping genes more than twenty years before they hit the headlines in the mid-1970s.

The most plausible reason why advances of this calibre were ignored (despite their presentation in the conventional way through seminars and journals) is that they came *before* work that was essential for biologists to comprehend the mechanisms underlying such bizarre behavior. McClintock's efforts even preceded the revelation of the DNA double helix in 1953 and the subsequent unravelling of the genetic code. We now have exquisitely precise sequencing techniques which allow detailed surveillance over gene movements and manipulations. In contrast, she had to tell her story in terms of classical crosses and marker genes. And nobody seemed to understand.

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Generations of students have learned that Barbara McClintock's 1931 paper with Harriet Creighton (Proc. Nat. Acad. Sci. USA **17**:492) became a cornerstone of modern biology in correlating cytological and genetic crossing over in *Zea mays.* But it was more than a decade later when she discerned the extraordinary, repeated rounds of chromosome breakage and fusion in corn plants that were to lead her to describe a previously unsuspected basis for genetic variation. The first case concerned an intriguing pattern of pigmentation on some kernels which implied genetic instability—but an instability that was under some form of control.

Not until 1951, however, at a Cold Spring Harbor Symposium, did McClintock announce her conclusions about the hereditary machinery responsible for the changes she had observed. In short, they amounted to a remarkably prescient picture of transposition as we now know it. To a classical structural gene she added an adjacent controlling element which turned the gene on and off but which was itself regulated by a second element some distance away, possibly on a different chromosome. And she envisaged that the controlling elements did not occupy a fixed locus. They jumped around. Far from being permanent partners to a particular structural gene, they could move to a new position, and thus control a new gene.

But the world of genetics, still quaintly wedded to the view that genes were immutable, was not ready for such a radical reassessment. Even by the late 1960s, with the first discoveries of transposable elements in bacteria, biologists scarcely hurried to re-examine McClintock's ideas. It was only during the next decade, as examples came to light of transposition, not only among prokaryotes but also among eukaryotes, that the stage was set for a real revolution in our understanding of the richness of gene traffic. Although, ironically, Barbara McClintock's name did not appear on the programme for the 1980 Cold Spring Harbor Symposium devoted to movable genetic elements, it was becoming clear by then that her now historic investigations could have enormous significance for modern molecular biology.

I certainly do not intend to devote this column regularly to items of science history, but the McClintock case really is rather special. As discussed elsewhere in this issue of BIO/TECHNOLOGY (p. 309), the very latest episode in the story indicates that Peter Starlinger's theory is correct: those prematurely described DNA elements could well be the basis for a whole new industry founded on the genetic manipulation of monocoty-

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ledonous plants. The first step has already been taken in Australia by Jim Peacock, who has isolated, cloned, and begun to use a transposable Ds element from maize.

In addition to Peacock and Starlinger, who has cloned the DNA from a Ds-induced mutant of the so-called *shrunken* locus of maize studied by McClintock, several other research groups are in hot pursuit. At the Carnegie Institute of Washington Nina Fedoroff and her colleagues have reported a long (2500 base pair) insert in the *waxy* locus. And Frances and Benjamin Burr, working at Brookhaven National Laboratory, are scrutinizing other lengthy inserts in the *shrunken* locus.

As yet, there is nothing resembling unanimity of opinion about how these mobile elements operate. At the same time, there is no dissent from the view that they are of quite absorbing interest, as well as having exciting practical potential for the future. Barbara McClintock, who reaches the grand old age of 81 this month, will no doubt allow herself a modest *frisson* of pride over the attention her jumping genes are now receiving—and over their utility in the years ahead.