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Journal of

# MEDICAL GENETICS

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**The Dynamic Genome - Barbara McClintock's Ideas in the Century of Genetics.** Ed N Fedoroff, D Botstein. (Pp 422.) New York: Cold Spring Harbor Laboratory Press. 1993.

Like Stephen Hawking, Barbara McClintock inspired as much by her existence as by what she discovered. Of course, high scientific achievement is an essential ingredient, but the details don't matter. I am sure her papers on transposable elements are much more admired than read. As the subtitle suggests, her career spanned the history of genetics. She started when Mendel's ideas were still controversial, and she worked on well into the cloning era. She made her name as a virtuoso cytogeneticist, identifying each individual maize chromosome and physically assigning linkage groups. She went on to provide a classic proof that meiotic crossing over resulted in genetic recombination. Her later work on mobile genetic elements was a solitary march into unknown territory, which eventually won her the Nobel prize in 1983. As she approached her 90th birthday, her friends and admirers put together this Festschrift to celebrate her life and career. She lived to enjoy the celebration, dying on 2 September 1992.

It was a nice idea to reproduce several of her key papers as introductions to sections of related invited contributions. The reprints include her 1931 crossing over paper, a 1952 paper on Activator and Dissociator, and two papers (1956 and 1978) recording her growing belief in the wider role of 'controlling elements' in genome organisation. And of course her Nobel Prize lecture 'The significance of responses of the genome to challenge'. Between these meaty items, guest articles range from brief reminiscences to solid reviews. An excellent history by the late Marcus Rhoades of early maize genetics is reprinted from the 1984 *Annual Review of Genetics*, and Nina Fedoroff finishes the book with a fine updating on maize transposable elements. Even now they are all cloned and sequenced, their interactions are amazingly complicated. Other articles recount early investigations of transposable elements, which really took off once bacterial transposons were discovered. Despite her reputation as a fierce and solitary person, McClintock was a valued mentor to many researchers, as we see from the fond accounts of lengthy, wide

ranging, and seminal conversations. Others came only in retrospect to appreciate McClintock's pioneering explorations and make amends here.

We often hear that McClintock's later work went unappreciated. It was 'ahead of its time'. Indeed, she did have trouble with referees, and recorded the bulk of her results in the unrefereed *Carnegie Institute of Washington Year Book*. Whether or not it was appreciated is less clear. Its experimental virtuosity and validity in maize were not in question; the problem lay with deciding its significance. This was work which did not fit into most people's mental maps, and it was not clear what to do with it. Was it an interesting but ultimately trivial feature of a few plant genes, or was it, as McClintock believed, evidence of a system parallel to the conventional genes, by which whole genomes adapted and restructured themselves, and through which evolution worked? Jumping genes have joined mainstream genetics, but I think there would still be support for McClintock's more global ideas. At the moment it looks as if reductionism is triumphing over McClintock's holism. Perhaps she is still ahead of us - several of the contributors to this book think so.

Prophet in the wilderness or not, McClintock was widely admired, indeed almost deified, as a brilliant cytogeneticist, a deeply original thinker, and above all as a role model. How we would all love to work like her! - not just the Nobel prize, but the refusal to let committee meetings and paperwork get between her and her science. She was a true free spirit. She constructed her own way of life and lived it supremely well for 90 years. Perhaps we would be less willing to make all the sacrifices which that freedom required. This handsomely produced book records the gratitude and affection of the people she influenced, and stands as a fine memorial to someone who exemplified what being a scientist is really about.

ANDREW P READ

**Cystic Fibrosis and DNA Tests: Implications of Carrier Screening.** US Congress, Office of Technology Assessment. Washington, DC: US Government Printing Office, August 1992.

Take an autosomal recessive condition with birth incidence of 1 in 4200 and a relatively predictable natural history (98% respiratory complications, over 99% pancreatic insufficiency, about 50% mortality by the age of 20). Evaluate genetic tests for the carrier state and find that sensitivity and specificity both exceed 99%, errors being the result of human factors not laboratory variation. Consider the cost-benefit equation for screening, including psychosocial costs. Why do 90% of people in the reproductive age group not respond to a letter inviting them to consider the offer of screening?

The condition is  $\Delta F508$  homozygous cystic fibrosis (CF), screening tests are based on the polymerase chain reaction, the setting is the educated UK middle class in 1992. Do the data suggest that the community is uninterested in a greater degree of individual informed choice? Or are we confused by the

presence of CF resulting from other mutations, with or without  $\Delta F508$ .

Cystic fibrosis research has burgeoned since the characterisation of the causative gene less than four years ago. That landmark, and the implications of the discovery of the major mutations, influence many in North America and Europe (there are 1.9 million carriers of  $\Delta F508$  in the UK, 16.5 million in Europe, and 14 million in North America). The importance led the US Congress to request evaluation of the "scientific, clinical, legal, economic and social considerations of widespread carrier screening for CF". The resulting report from the US Office of Technology Assessment (OTA) was published in August 1992. It is an impressive document, ranging from a brief clinical overview, to state of the art genetics and then educational, counselling, financial, and ethical issues. A brief chapter summarises CF carrier screening in the UK, based on studies funded by the Cystic Fibrosis Trust and the Medical Research Council, some of which have now been published.<sup>1-4</sup> The OTA investment was large: nine project and three administrative staff, 15 subcontractors, and over 120 advisers.

An initial summary chapter (also published separately for the lay reader) sets out the issues and examines the options open to the US Congress. No screening policy has emerged. The project director, John H Gibbons, concludes that the value of the CF carrier test is the information it provides to the individual person - "We believe that public understanding of this new knowledge and its implications is necessary for its wise and thoughtful application".

The US health care systems do not facilitate early research or service developments of carrier screening tests with such major implications. Also the US history of sickle cell carrier screening in the 1970s, which was in some states mandatory, has left painful memories which evoke thoughts of discrimination and stigmatisation. The reliance upon insurance as the vehicle for funding health care provision (often organised through employment schemes) has also inhibited any screening which might lead to the early recognition of families with high health care needs (and therefore high costs!). The OTA's glance, therefore, at the UK CF programmes and at screening elsewhere (for example, in Cyprus and Sardinia where thalassaemia carrier testing has evolved considerably) was quite essential. Where, therefore are we now?

In the UK the model for carrier screening in the antenatal clinics has been most studied in Edinburgh, where 73% of 4348 women chose to be tested, identifying 111 carriers and four partnerships which were at 1 in 4 risk of  $\Delta F508$  CF.<sup>3</sup> Screening in primary care has the advantage over pregnancy testing of providing more choice for those identified as carriers. The disadvantage of the primary care approach is that people may see no relevance until they plan pregnancies. Thus the proportion who take up screening when invited by letter (9 to 12%) and by passive opportunistic offers from the GP (17%),<sup>5</sup> are, in response terms, derisory. Active opportunistic carrier testing by the GP, with the test being available immediately, has a response of 70%, back to the pregnancy level, but are these high figures indicative of too