Commentary: Reflections on: Jablonka E, Lamb MJ.
The inheritance of acquired epigenetic variations

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We were first drawn to the subject of epigenetic inheritance in 1986, when we were trying to make evolutionary sense of the changes in the activity and conformation of sex chromosomes during gametogenesis, and the related problems of dosage compensation and genomic imprinting.1 At the time, one of us (EJ) was involved in experimental investigations into the role of DNA methylation in X-chromosome inactivation in female mammals, and the other (MJL) was a Drosophila geneticist using fruit-flies to study mutagenesis and ageing. Our complementary and overlapping research interests meant that we were familiar with the old work showing that genomic imprinting was widespread, playing an important role in the life cycle of some insects as well as mammals, and with the recent work implicating DNA methylation and chromatin modifications in the establishment and inheritance of determined and differentiated states in cell lineages. Because by training and inclination we both used an evolutionary framework when thinking about biological problems, and had been deeply influenced by the evolutionary-developmental approach of CH Waddington, we were also aware of the buzz generated by Leo Buss’s recent theoretical work.2 He had reminded the evolution community that a long-cherished assumption of the Modern Synthesis, Weismann’s doctrine that there was an early and irreversible separation of the germ line from the soma, did not hold for most organisms, including all protists, plants, fungi and many invertebrate phyla, and that this had significant consequences for prevailing evolutionary theory. Among other things, it meant that in these organisms genetic variations that arose in somatic cells could be transmitted to future generations.

By early 1988 the pieces of a jigsaw had clicked into place, and we began to argue that DNA modifications and other chromatin marks provided a mechanism through...
which spontaneous or induced changes in gene activity could be transmitted to future generations. As we saw it, this meant that ‘acquired characters’ could be inherited and therefore have evolutionary consequences, something that was contrary to the beliefs of most biologists. Our thinking was influenced by Robin Holliday, who in the mid 1970s had been one of the first people to speculate that cytosine methylation and other DNA modifications might be the molecular basis of the inheritance of different states of gene activity in cell lineages. In late 1987 he went further, suggesting that as well as being involved in carcinogenesis and ageing, ‘The inheritance of epigenetic defects’ (as he titled his paper) might also be responsible for various strange patterns of non-Mendelian inheritance and other genetic oddities. He framed his argument in terms of mistakes and abnormalities (epimutations) that were not purged by repair mechanisms operating during meiosis, but we took the argument beyond this, suggesting that the transmission of induced or accidental epigenetic modification might be adaptive, and that it could also be very important in the origin of species. When we began writing our paper, the only molecular evidence for transgenerational transmission of methylation variants that we were aware of came from studies of imprinting, and these showed that, with one exception that involved a transgene, chromatin marks were reversed when they passed through the germ line of the opposite sex. The direct experimental support for sustained epigenetic inheritance was therefore weak, although when we scoured the literature we found much indirect evidence. However, when our paper was near completion, Silva and White published work demonstrating that allele-specific methylation variants were transmitted in human families. We saw this as molecular support for our assumption that some epigenetic variants could be transmitted through multiple generations.

After asking some colleagues to review our completed manuscript, we submitted it for publication in November 1988. We had high hopes that it would be accepted, because its subject matter was topical: not only were people thinking about Holliday’s ideas about the importance of epimutations in health and disease, but John Cairns, a leading microbiologist, had recently created a stir by producing experimental evidence suggesting that in bacteria, contrary to accepted dogma, some mutations were not random in origin, but occurred as a direct adaptive response to environmental conditions. We thought our article would be a contribution to the resulting debate about the occurrence and significance of induced heritable changes.

Just over a month after mailing the manuscript from London (this was before the days of electronic submission), we received Science’s editorial rejection; Nature’s rejection took only two days. We probably made a strategic mistake by including ‘Lamarckian inheritance’ in the abstract and covering letter. For the previous half-century, Lamarck and the ideas about inheritance attributed to him (largely the inheritance of the giraffe’s extended neck) had generally been ridiculed, so by mentioning Lamarck we probably convinced the editors that we were part of biology’s lunatic fringe. However, we were aware of this risk and decided to take it. Avoiding Lamarck would have meant hiding behind semantics, and we believed that the anti-Lamarckian dogma needed re-evaluation in the light of epigenetics.

Fortunately, one of the people who read our paper before submission was John Maynard Smith, who had been MJL’s PhD supervisor. By chance she had bumped into him and given him the manuscript just before he left for the Institute for Advanced Study in Princeton, where he had some thinking time. On his return he told us that he thought our paper was interesting and important, and urged us to get it published. It was not that he accepted our arguments about the evolutionary significance of epigenetic inheritance—on the contrary, he thought he could show why we were wrong. So, after it was rejected by Science and Nature, at Maynard Smith’s suggestion we submitted the paper to the Journal of Theoretical Biology, although he warned us the journal was not widely read. John was a member of the editorial board, so the paper was accepted immediately and published in July 1989. In the following year Maynard Smith’s counter-arguments were published in the same journal, and later we in turn countered his arguments. Otherwise, as Maynard Smith had anticipated, there was little reaction to our paper.

We continued to think, talk and write about epigenetic inheritance over the next months, and continued to have difficulty getting some ideas published. Because of this, we decided that instead of battling with journal editors to get bits and pieces accepted, we would write a book in which we could give a broader and more complete picture of what we saw as the mechanisms and evolutionary consequences of the transmission of epigenetic variants. Thanks once again to the support of John Maynard Smith, Epigenetic Inheritance and Evolution: the Lamarckian Dimension was eventually published in 1995. By this time the field of epigenetics had grown substantially: its medical importance was quite clear, and there were commercial interests in the possibilities of cloning and transgene technology, which demanded that chromatin marks and their inheritance were better understood. Evidence of transmissible methylation and chromatin variants had therefore increased. In our book we also discussed two other routes of information transmission in cell lineages—self-maintaining metabolic patterns and structural templating.
What we could not discuss in 1995 was information transmission through small non-coding RNAs. This was not recognized until the late 1990s, when the discovery of gene regulation through RNA interference and the realization that it provided a powerful research tool gave epigenetics research an enormous boost. It soon became clear that the small RNAs that mediate gene silencing can not only be transmitted to daughter cells, but also move to more distant cells, including germ cells. Thus, another route through which epigenetic changes can affect future generations was revealed, one that might have significant effects in all species, including those with early segregation of the germ line. Weismann’s barrier was breached in a surprising way, one that was reminiscent of Darwin’s unacceptable idea that hereditary information is transmitted from body cells to the reproductive organs through small molecules called gemmules.  

Today, ‘epigenetic inheritance’ has become an umbrella term covering the many interacting ways through which variations that do not depend on DNA differences are transmitted in lineages of cells and organisms. In disciplines as diverse as animal behaviour, plant ecology and epidemiology, it is recognized that through epigenetic inheritance acquired variations can have an impact on later generations. Sadly for us, in our own field of evolutionary biology, with a few exceptions, either the significance of epigenetic inheritance is down-played or the subject is treated with hostility; many evolutionary biologists have not bothered to get acquainted with epigenetic research. We have continued to argue that epigenetic and other types of non-DNA variations must be included in evolutionary thinking. Our hope is that now that studies of heredity and development have moved away from the gene-centric approach that characterized the last half of the 20th century, the developmental system approach that is replacing it will lead to more interest in evolutionary epigenetic research and to a more widespread acceptance of the importance in evolution of the inheritance of acquired epigenetic variations.

Conflict of interest: None declared.

References


Commentary: A conceptual revolution limited by disciplinary division

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In the past decade or two we have witnessed a remarkable thaw in the long chilly relations between the biological and social sciences. For more than a century it seemed that there was only one basic way the two modes of enquiry