Epigenetics for dummies

John Launer

In the last few years, epigenetics has seized the public imagination. Magazines like *New Scientist* are publishing articles with titles such as "How to change your genes by changing your lifestyle".[1] A book called "The Epigenetic Revolution" has become a bestseller.[2] The popular press regularly reports epigenetic research, including a recent study purporting to show that severe psychological trauma can be passed down through one's genes.[3] Overall, it would be easy for anyone nowadays to form the impression that the genetic destiny of future generations is entirely in our own hands, DNA is highly malleable, and Darwin and Mendel have been thoroughly discredited. In this article, I want to try and bring epigenetics back down to earth, with a simple account of what it is and is not, and what epigenetic research has and has not shown so far.

Epigenetics is best defined as the study of changes in organisms brought about by modification of gene expression, rather than by alteration of the genetic code in the form of DNA. The term "epigenetic" was originally coined in the 1950s, and used to denote the way that genes interact with the environment, in order to produce each individual phenotype. To describe this process at its simplest: you may be born with a capacity to be tall and confident, but if you are undernourished and abused as a child, you are likely to turn into a stunted and fearful adult instead. There is nothing very remarkable about the way genes interact with the environment in this way. Concepts like gene expression and plasticity have been commonplace in biology for a long time, and indeed form the basis of all modern biological thinking.

Since genes alone do not determine phenotypes, mechanisms have to exist at the molecular level in order to mediate gene-environment interactions. As soon as some of these mechanisms were discovered, the term "epigenetics" came to be applied to them as well. The best known of these is methylation, where a methyl group binds to cytosine on a stretch of DNA, and renders it less active. The mechanisms themselves are very common in nature, quite aside from environmental influences, and they govern gene expression in all kinds of ways, including turning a stem cell into a liver or a skin cell, or a bee larva into a worker or a queen bee. One hypomethylating agent, decitabine, is an established treatment for myelodysplastic disorders.

The question then arises: do environmental effects have to happen anew in each generation, or could they ever be passed down from one generation to the next? The French biologist Larmarck argued a long time ago that acquired characteristics could be transmitted. Indeed, he believed quite wrongly that this was the sole basis of inheritance. More surprisingly, Darwin also thought it could sometimes happen. As well as his theory of evolution, based on random genetic variation followed by natural selection, he also suggested that lifetime experiences could create "gemmules" which attached themselves to eggs and sperm, and affected offspring as a direct result.[4] It seemed an interesting idea at the time, but after Mendel's discovery of the principal laws of inheritance, biologists lost interest in this possibility.

TRANSGENERATIONAL EPIGENETICS

The first hints that acquired characteristics might be transmissible after all were rather prosaic. In the 1950s, a plant geneticist named RA Brink showed that crossing a dark form of maize with a mottled form appeared to render the dark alleles permanently inactive.[5] This alteration persisted for hundreds of generations – a process aptly called "paramutation". We now know that this and similar forms of non-Mendelian inheritance are brought about by substances that pass down in the gametes, alongside DNA. These are mainly RNA proteins, but also include prions and histones.[6] Similar effects have been shown in animal experiments, although they are not nearly as frequent or dramatic as you might believe, and their significance in natural conditions is far from clear.[7] For example, when pregnant mice are fed with Bisphenol A, a toxic ingredient of plastics, the resulting adverse effects appear not only in their offspring but also in the following generation.[8] These include obesity, diabetes, an increased frequency of cancer, and yellow fur instead of brown. In another much quoted experiment, researchers claimed to show that mice bred from fathers who had been trained to become afraid of a particular smell also showed avoidance of the same smell – although it is hard to understand how such a specific outcome could be achieved through known molecular mechanisms.[9]

As far as human beings are concerned, everyone has known for a long time that maternal behaviour during pregnancy affects the growing fetus, with lifelong effects. The most familiar example is probably foetal alcohol syndrome, where a mother's addiction can lead to irreparable damage to her infant. Although this probably happens through epigenetic mechanisms, there is no evidence that effects like these are transmitted to a further generation without repeated environmental influences as well. For a while, it was believed that prolonged maternal starvation could lead to long term transgenerational effects, but this has now been called into question.[10]

One epidemiological study has shown that fathers who smoked before adolescence were more likely to have sons with a higher body mass index.[11] However, no similar result has been shown in daughters, there is no molecular evidence to support the finding, and social effects may also have played a part. There are a few very rare inheritable conditions, where the underlying defect in some individuals may lie with methylation rather than DNA, but these are highly exceptional and hard to interpret.[12] The more spectacular findings that reach the headlines often appear to confuse correlation with causation, make claims that bear little relation to the evidence, are based on samples too small to reach statistical significance, or report results selectively.[13] There may still be some exciting findings ahead of us in the epigenetics, beyond what happens to laboratory mice in extremely unusual tests, but we aren't there yet.

EPIGENETIC HYPE

Given this state of affairs, it is worth asking why epigenetics is having such an impact on people's imagination. Part of the answer is that Darwin's theory of natural selection, with its vast time scale, immensely slow progress, and seemingly improbable consequences like the human eye, is still too challenging for many people to grasp. It is far easier to seize on an idea like the rapid alteration of genetic material, than a theory that feels counter-intuitive if you only expect to be alive for around 80 years, rather than a few

Correspondence to Dr John Launer, Faculty Development, Health Education England, Stewart House, 32 Russell Square, London WC1B 5DN, UK; john.launer@nwl.hee.nhs.uk

million. There is also a common misapprehension that modern biology strongly supports the view that "genes are destiny", however much real biologists do to debunk this.[14] People therefore reject mainstream genetics, without ever having understood it in the first place. Probably most important of all, the hype around epigenetics boosts people's sense of control: if you believe you can change your own genes, or at least those of your children, you may feel less of a prisoner to the arbitrary effects of your genome, or your own upbringing. Epigenetic hype feeds into the same rugged, individualistic vision of self-improvement as the dozens of popular books and hundreds of magazine articles on neuroscience, explaining how you can change your own brain.[15]

The irony in all of this is that the lessons being drawn in the hyped articles are usually true in their own right, even if the arguments used to support them are unsound. It certainly makes good sense to provide everyone with good nutrition, a stable upbringing, and a secure social environment, but one scarcely needs an understanding of molecular epigenetics to be convinced of this.

Twitter Follow John Launer at @JohnLauner

To cite Launer J. *Postgrad Med J* 2016;**92**:183–184.

Postgrad Med J 2016;**92**:183–184.
doi:10.1136/postgradmedj-2016-133993

REFERENCES

1 How to change your genes by changing your lifestyle. *New Scientist*, 9 Dec 2015. https://goo.gl/HgVmqV (accessed 21 Jan 2016).
2 Carey N. *The Epigenetics Revolution: How Modern Biology is Rewriting Our Understanding of Genetics, Disease and Inheritance.* London, Icon Books, 2012.
3 Rouse A. Holocaust survivors pass the genetic damage of their trauma on to their children, researchers find. *Mail Online*, 21 Aug 2015 http://www.dailymail.co.uk/sciencetech/article-3206702/Holocaust-survivors-pass-genetic-damage-trauma-children-researchers-find.html (accessed 21 Jan 2016).
4 Darwin C. *The Variation of Plants and Animals Under Domestication.* London: John Murray. 1868: 375.
5 Brink RA. Paramutation at the R locus in maize plants trisomic for chromosome 10. *Proc Natl Acad Sci 159*;45: 819–27.
6 Rando OJ. Ghosts in the genome: How one generation's experience can affect the next. *The Scientist*, 1 Dec 2015. http://goo.gl/nfldVc (accessed 21 Jan 2016)
7 Morgan DK, Whitelaw E. The case for transgenerational epigenetic inheritance in humans. *Mamm Genome* 2008;19:394–7.
8 Morgan HD, Sutherland HE, Martin DIK, *et al*. Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet* 1999;23:314–8.
9 Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nat Neurosci* 2014;17: 89–96.
10 Stein AD, Lumey LH. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. *Hum Biol* 2002;72: 641–54
11 Pembrey ME, Bygren LO, Kaati G, *et al*. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet* 2006;14:159–66.
12 Buiting K, Gross S, Lich C, *et al*. Epimutations in Prader-Willi and Angelman syndromes: a molecular study of 136 patients with an imprinting defect. *Am J Hum Genet* 2003;72:571–7
13 Mitchell K. The trouble with epigenetics (Part 2). *Wiring the Brain* [blog], 14 Jan 2013. http://www.wiringthebrain.com/2013/01/the-trouble-with-epigenetics-part-2.html (accessed 21 Jan 2016)
14 Laland K, Brown G. Sense and Nonsense: Evolutionary Perspectives on Human Behaviour, *2nd edition*. Oxford: Oxford University Press, 2011.
15 Neuroskeptic. Epigenetics: Are genes the new brains? *Discover Magazine*, 26 Sep 2013 http://blogs.discovermagazine.com/neuroskeptic/2013/09/26/the-social-life-of/ (accessed 21 Jan 2016).

Epigenetics for dummies

John Launer

*Postgrad Med J*2016 92: 183-184
doi: 10.1136/postgradmedj-2016-133993

Notes