Something old, something new, something false but much that’s true

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We are grateful to Christopher Kuzawa, not only for reading our book carefully and setting its messages in a broad context, but also for drawing attention to the implications of evolutionary biology for medicine. This is an area in which we are both deeply interested, but we did not present it as a major feature of our book. We are glad that Kuzawa makes an issue of it in his review. He points out that the comparative approach encouraged by evolutionary biology should make biomedical scientists rather more careful than has often
been the case when they generalize from mice to humans. He notes that humans are more buffered during their uterine life than the animals commonly used in experimental studies and links this to the longevity of humans compared with rodents. In short, it is a real pleasure for us to have the book read by somebody who has so clearly understood what we were trying to express.

In contrast, we are surprised by Jonathan Wells' review of our book. He has taken one very small part of the book and used it to advance one particular position. Admittedly, we have been sharply critical of his hypotheses in the past\textsuperscript{1,2} and he has used this opportunity to respond. We do not think this justifies such a singular review of a book that had quite a different purpose from what he suggests. Our central purpose, as Kuzawa notes, was to clarify some of the muddles that have grown up around the nature-nurture debate and confusion in understandings of developmental processes in the evolutionary context and to show the integration of mechanisms that generate robust outcomes in development and those that generate plasticity. We also were setting out to integrate important concepts that pre-dated molecular discoveries with the new understandings arising from epigenetics. Against that background, the developmental response of the mammalian fetus to the condition of its mother is only a small part of the many ways in which humans, like other animals, adapt their phenotypes to local conditions. Wells' critique calls for a longer response than we have time or space for here and we have made it elsewhere. Even so, we shall respond briefly to his attempts to defend his own position. If an offspring responds adaptively to the condition of the mother, then a mismatch between the prediction and reality should be true not only when the offspring ends up in more favourable conditions than that of the mother but also when the conditions are worse. That is the 'acid test' and is supported by the evidence. Wells tries to mitigate the force of this evidence by arguing that the effect occurs when the offspring are still under the care of the mother. The relevance of his comment to what is after all a functional argument is not obvious. In any event, he ignores the point that if a large-bodied girl develops rickets in a famine her reproductive success is severely reduced.

Wells argues that a forecast is unlikely to be correct in such a long-lived species as humans. Most obviously the greatest fitness effects are those relating to survival to reproductive age and there are considerable data on prenatal influences of this type on childhood physiology. More generally, members of the hominin lineage have manifestly been migratory, travelling into vastly different climatic regions of the globe. Natural selection would have led to genetic differences in populations living in different climates for any length of time, but any mechanism that can protect individuals from relatively short-term changes in living conditions that differ from those in which previous generations lived will also be highly advantageous. If a mother can transmit to her unborn offspring cues that will affect its stature, metabolism and a host of life-history characteristics, she will be at an advantage in fitness terms over a mother who cannot. Here again Wells' response is unconvincing. He suggests correctly that the mother will tend to dampen the immediate effect of a change in the environment, but her offspring still has to cope with this new environment as a relatively self-sufficient child and later as a totally self-sufficient adult.

Much of Wells' position is based on Robert Trivers'\textsuperscript{3} proposals about parent-offspring conflict. Not a bad place to start because the ideas have much going for them, particularly in the hands of somebody like David Haig,\textsuperscript{4} provided that one does not fall into the metaphorical trap of confusing genetic conflict with the folk concept of conflict leading to damage and disadvantage. In the event, the evolutionary concept of conflict underplayed the extent of parent-offspring cooperation, whereby the mother responds sensitively to the condition of her offspring and the offspring responds sensitively to the mother's condition.\textsuperscript{5} A better acquaintance with this literature would help interpretation. Also, we would urge him to consider the book in its entirety.

George Davey Smith's review is especially useful in the context of the present symposium because he shows how the ideas presented in our book relate to those of epidemiologists. We are grateful for that and, indeed, learned a lot from him. We also enjoyed his wry account of fashions in science. Indeed, if you look at how many times 'epigenetic' occurs in the titles of papers, it rose from 478 papers in 2001 to 3833 a decade later. At one level, though, we think he is wrong. He writes about our critique of broad sense heritability as applied to populations: 'The early dismissal of 'heritability'' and all it entails in PRDE [Plasticity, Robustness, Development and Evolution] is something epidemiologists may want to ignore.' We think that he may be confusing the technical meaning of broad sense heritability with other meanings of heritability that include how much the similarity of a phenotypic likeness between individuals relates to their genetic similarity. We have no quarrel with that latter non-technical usage. We do, however, think that the pseudo-quantification of a ratio of genetic sources of variance to total sources of variance in the population is deeply misleading. To take a striking case, the genetic variation in 5-HTT gene, which affects how well the brain uses serotonin, interacts strongly with parenting quality.\textsuperscript{6,7} Children who are homozygous for the short version of the gene are highly sensitive to the way they are treated by their parents. With poor parenting they are very easily upset by trauma and with good parenting are highly resilient. In contrast, those who are homozygous for the long version and those who are heterozygous at
the locus are unaffected by the quality of parenting. In such a case, a heritability estimate is meaningless.

Gene–environment interaction may be used too freely these days as is gene–gene interaction or epistasis. Indeed, as we pointed out, the term gene is not easy to define and has different and not necessarily compatible meanings. Even so, once epistasis is recognized as important in the developmental process, the factors influencing phenotypic characters are less profitably thought about in terms of the genes as coding units, but in terms of the factors that are generated downstream. Even in the simplest case the interactions are not strictly between segments of DNA but between the products of genes. Of the three great figures who started the formalization of population genetics, Sewall Wright was much more sensitive to epistasis than R.A. Fisher or J.B.S. Haldane. It was an omission on our part that we did not mention him in our book. Wright believed that selection for single genes was far less effective than the selection of interacting systems. Fisher, by contrast, was keen to isolate the non-additive effects in his equations so that he could deal with the much more tractable additive effects. However, such mathematical brilliance has arguably got in the way of understanding the biological phenomena.

The point can be illustrated made by looking at the details of an example provided by people with the Kallmann syndrome. The main behavioural consequence of the Kallmann syndrome in men is a lack of sexual interest in members of either sex. The syndrome is generally associated with a mutation at a specific genetic locus. The syndrome was classically described as sex linked but other genetic abnormalities have been found to produce the same syndrome, which are autosomal. Cells that are specialized to produce the neurohormone, gonadotropin-releasing hormone (GnRH), are formed initially in the nasal region of the fetus. Normally the GnRH-producing cells would migrate into the hypothalamus. As a result of the mutation, however, their surface properties are changed and the cells remain in the nose. The GnRH cells, not being in the right place, do not deliver their hormone into the hypothalamic-pituitary vascular network that is necessary for the pituitary gland to secrete the appropriate levels of two other chemical messengers, luteinizing hormone and follicle stimulating hormone. Without these hormones, the testes do not produce normal levels of the testosterone. Without normal levels of testosterone, the man shows little sign of normal adult male sexual behaviour. Even in this relatively straightforward example, the pathway from gene to behaviour is long, complicated and indirect. Each step along the causal pathway requires the products of many genes and has ramifying effects, some of which may be apparent and some not. Indeed, such considerations are at the heart of the new discipline of systems biology.

Davey Smith ends with a nice point, namely ‘The shock of the new should not, however, obscure the fact that we still have much to learn from the old biology….’ As old warriors ourselves, we can only agree.

References

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