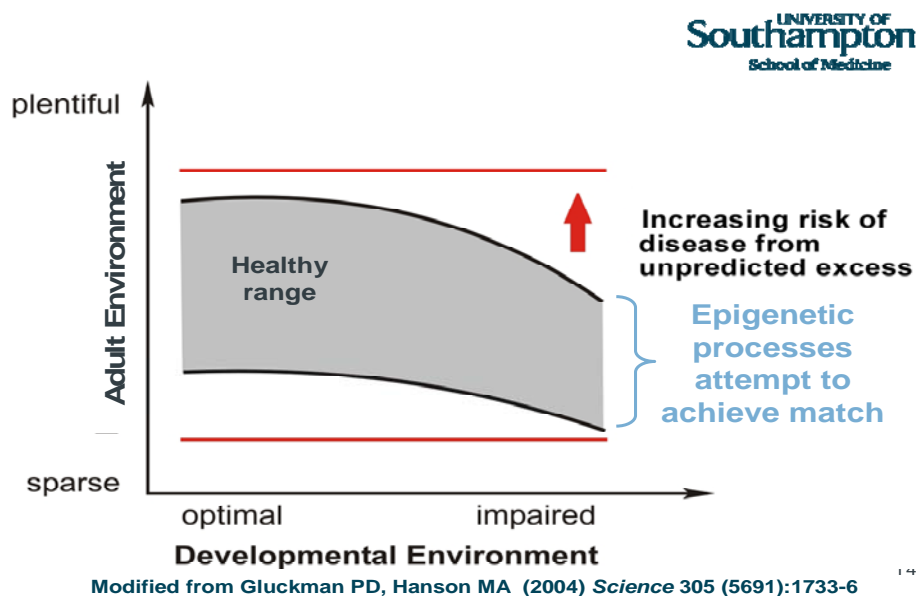


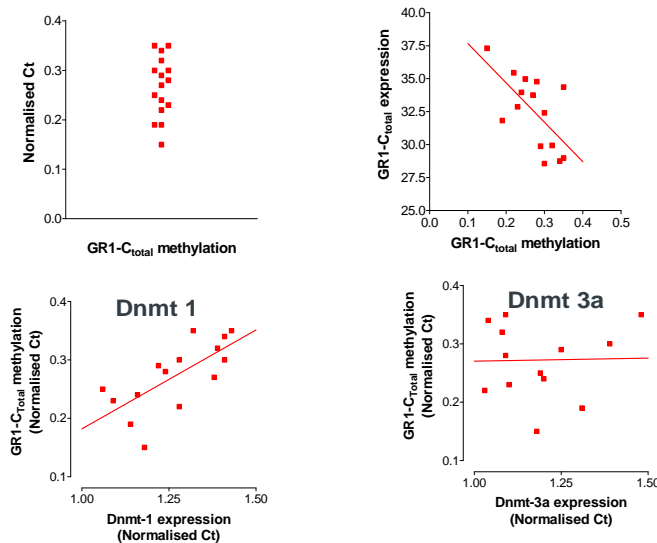
## Responses from Mark Hanson

1. There are many different types of influence on disease development, including genetic, epigenetic and environmental. Can these influences be easily distinguished, and if so, what differences are there in the way that each of these influences mediate disease susceptibility? *Epigenetic processes induce changes in DNA methylation, histone structure and, small non-coding RNAs during development. These can be measured, although the technology is still under considerable development. Epigenetic processes mediate the interaction between inherited genome and the development environment, transduced by the mother and influenced by her diet, body composition, exercise and stress levels etc. After period of developmental plasticity it is believed that epigenetic changes are fixed. Epigenetic processes are thought to affect the response of the individual to later environmental challenges, through the function of organs and systems and homeostatic control set-points. They thus affect predisposition to chronic disease (see below)*



2. Are there particular diseases for which epigenetic mechanisms have shown themselves to be particularly important and, if so, has this knowledge started to be useful for clinical practice? Is it likely that understanding of epigenetic mechanisms will lead to new diagnostic tests, or to new therapies, or to both? *Epigenetic processes ‘tune’ the phenotype of an individual to match the environmental challenges anticipated to be met in later life. Because there can therefore be a long delay between the induction (e.g. unbalanced diet in pregnancy) and the clinical manifestation of disease, epigenetic processes may be particularly important in chronic non-communicable disease such as type 2 diabetes, cardiovascular disease, osteoporosis, and perhaps some forms of neurocognitive impairment, reproductive disorders and cancer. It is very likely that new knowledge of epigenetic processes will lead to improvements in early diagnosis and prevention of such disorders, but this potential has not yet been realised. We know that epigenetically mediated changes in gene expression equivalent to those associated with pathological effects in animals, can be measured in humans at birth, but the consequences are as yet unknown.*

**Biomarkers of later risk? Expression of DNA methyl transferase Dnmt 1 and 3a, and methylation of the promoter of glucocorticoid receptor gene, and its expression, in human perinatal tissue. Inverse correlation between methylation and expression, and inverse correlation with Dnmt1, resembles animal studies**



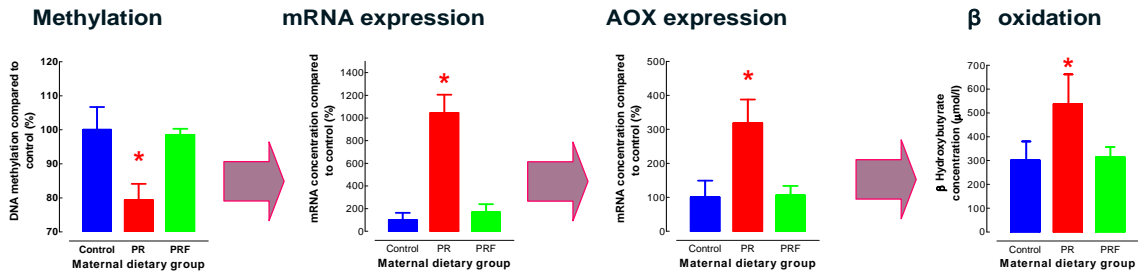
Lillycrop et al. *Br J Nutr.* 2007 Jun;97(6):1064-73

*Particular concerns relate to the sections of the population where such diseases are particularly prevalent - lower socioeconomic and educational attainment groups in developed countries, and populations in developing countries undergoing nutritional and other lifestyle transitions. The current allocation of resources to prevention of non-communicable vs. infectious diseases in many parts of the world is disproportionate to the projected burden of these diseases.*

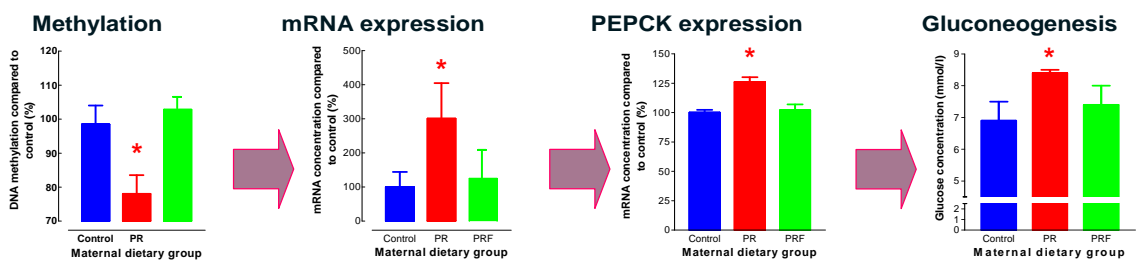
3. Predictive genetic testing and genetic diagnosis of disease states are starting to become useful in the prevention and treatment of common diseases, including management decisions about which drugs may be effective in an individual person's disease state. Can you foresee similarly useful "personalised" epigenetic tests of disease states becoming available? *Definitely. Because epigenetic changes might explain the substantial differences between individuals in risk of disease, even in genetically identical individuals in the same environment, they could have application in the prediction and management of disease on an individual basis.*
4. Epigenetic marks or imprints are not passed down strictly from generation to generation and many epigenetic marks develop early in life, often during intra-uterine life. Might management of pregnancy or treatment of diseases in early childhood be modified by knowledge of epigenetic mechanisms? *We now have evidence from experimental studies that epigenetic marks in non-imprinted genes, induced in one generation from an unbalanced diet fed to their mothers during pregnancy (Lillycrop et al *J Nutr.* 2005 135(6):1382-6.), can be passed to more than just the immediately succeeding generation (ref Burge et al). This suggests that dietary or other lifestyle interventions before and during pregnancy could be extremely valuable and again we have evidence for this (see below). Furthermore, at least in such experimental studies, the period of developmental plasticity during which epigenetic processes act extends into the early postnatal period, and a short regimen of hormonal treatment (the satiety hormone leptin) can reverse the changes induced in utero by unbalanced maternal diet (Gluckman et al *Proc Natl Acad Sci U S A.* 2007 104(31):12796-800).*

Unbalanced diet in pregnancy in rats induces epigenetic change in PPAR $\alpha$  and GR gene promoter DNA methylation, expression and that of downstream genes, and metabolic function in livers of offspring (red vs. blue bars). Supplementation of maternal diet with folate (green bars) prevents epigenetic and resulting downstream effects.

**PPAR $\alpha$**



**GR**



Lillycrop et al. *Br J Nutr.* 2007 97(6):1064-73 , Burdige et al. *Br J Nutr.* 2007 97(6):1036-46.

- Epigenetic marks or imprints are thought to be important in programming cell development from undifferentiated stem cells to mature adult tissues. How might understanding of epigenetic factors in stem cell differentiation be used to develop novel therapies and when might these start to become clinically useful? *A good example of the possibilities here concerns the activation of the 'fetal' genome in cardiac hypertrophy in later life, a process which is associated with heart failure but which could be used to repair the damaged myocardium. Activation of stem cells in the brain and other tissues provide other examples. Development of novel drugs to target epigenetic control here is probably some years away.*
- Are there any barriers in our way to understand epigenetic influences? Is there sufficient emphasis and funding in this area? What is necessary for the UK to maintain competitiveness in this field? *Because epigenetic effects can exert varied effects across many parts of the genome, e.g. at loci of action of a range of transcription factors, understanding their function may be more difficult than for mutations or haplotypes. The UK has a lead in the basic science in this area, especially in the role of epigenetic control of non-imprinted, and also possesses human cohorts well-characterised from early life. To maintain this lead has funding implications which are substantial, both in terms of the provision of analytical equipment, the need for bioinformatics and for further basic research.*