Keynote Lecture XII
Perinatal Determinants of Cardiovascular Risk in Adulthood

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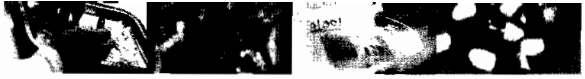
Professor Hanson has an international reputation in developmental physiology, leading for 20 years one of the few research groups investigating both pre- and postnatal physiology. This group has averaged *ca.*20 research students, visiting overseas fellows and post-doctoral workers. Its success has led to the creation of new academic posts in the universities where he has worked - Reading, UCL and Southampton. He has achieved substantial research funding from a wide range of Funding bodies. This has totalled over £19 million for his Division over the last 5 years. In 2002 he was awarded a British Heart Foundation Chair in Cardiovascular Science and in 2001 he was made a FRCOG *ad eundem.*

Professor Hanson has championed an integrative approach to developmental physiology, despite the trend towards reductionism over the last decade. As Director of Southampton's Developmental Origins of Health and Disease Centre he has developed a major initiative in gene-environment interactions in this clinically important area. He has worked extensively in the area of fetal programming, in particular to develop a large animal model for investigation of *fetal* mechanisms, and to examine the effect of mild nutritional challenges in pregnancy on cardiovascular, endocrine and metabolic development. They showed that such effects occur in the absence of reduced fetal growth. This contributes substantially to understanding the processes underlying the link between adult cardiovascular and metabolic disease and early development, which operate across the full range of birthweight and childhood growth in the population. In relation to cardiovascular disease, they showed that an unbalanced diet in pregnancy produces endothelial dysfunction in small arteries of the offspring, coupled to altered vascular gene expression and reduced nitric oxide synthesis. Apart from the associated elevated blood pressure these changes affect cardiovascular responses to a subsequent pregnancy and in turn the offspring of the second generation. This work raises fundamental questions about the nature of the heritable components of disease risk.

The international profile of his research is underlined by the basic and clinical researchers who have come to work with his group from overseas, with funding from both UK and overseas sources. Through such links he has established a worldwide network of collaborations with colleagues in New Zealand, Canada, USA, Australia, Japan, Chile, Germany, The Netherlands, Belgium, Norway and Sweden. This is fundamental to the International Society for the Developmental Origins of Health and Disease.

He has an excellent track record of fostering collaborations between clinicians and basic scientists. He has a long-standing interest in developing novel imaging techniques, including ultrasound, e.g. 3D and dynamic 3D techniques for application to the fetal heart and circulation, and near infra-red spectroscopy to measure fetal cerebral haemodynamics and metabolic status. He has extended the concepts of fetal circulatory control, which he developed in the sheep, to the human and they have shown that maternal body composition and diet before pregnancy have a marked influence on late gestation fetal blood flow distribution. Such translational research is vital to understanding the programming of cardiovascular and metabolic function.

He co-wrote 'The Fetal Matrix' which was published in 2004 and describes an important new evolutionary biological theory. This work has received much attention in the scientific media with major reviews in *Science* and many clinical journals.



More than 90% of our existence as a species was prior to the development of agriculture, with its associated cultural changes. Thus understanding our biology and our capacity to respond to the environment must take account of our evolutionary history. Moreover, knowledge about the recent past (i.e. life history approaches), particularly the environmental conditions experienced by our parents and grandparents and in our early life, provide additional insights. These elements combine into the "developmental origins of adult disease" concept (e.g. see Gluckman and Hanson 2005).

One genotype can generate a range of phenotypes through the processes of developmental plasticity. There are many examples of effects of this plasticity, sometimes called 'maternal effects' in lower vertebrates and invertebrates. In mammals, examples of developmental plasticity are complex because they involve continuous change rather than distinct and alternative phenotypes. The underlying mechanisms involve epigenetic processes, including DNA methylation (e.g. Lillycrop et al 2005), histone acetylation and perhaps small RNAs. They induce important developmental influences on the regulatory processes that control blood pressure, metabolism and hormonal responses.

In developing mammals it has been thought that any adaptive advantage conferred would be immediate, as for example, in the reduced fetal growth following maternal malnutrition. This is the basis of the 'thrifty phenotype' hypothesis. However, there is a second class of response in which the adaptive advantage is *deferred* (Gluckman and Hanson 2005). This can only have adaptive value in enabling the offspring to survive to reproduce in a future environment. This concept of *predictive adaptive responses (PARs)* suggests that developmental responses may be made in expectation of the future environment (Gluckman and Hanson 2004) and not just to protect against an adverse prenatal environment. Provided the prediction is more often right than wrong, PARs confer a survival advantage.

For the fetus, prediction of future environment depends on transplacental signals from its mother: these are mainly nutritional or hormonal in origin. If nutrient delivery from the mother is poor, the fetus will predict a deficient postnatal environment and develop its metabolic regulation accordingly. But what happens if the prediction is wrong, e.g. if the fetus predicts a deprived postnatal environment and yet the environment is rich? Then many of the adaptive changes it made in early life will turn out to be maladaptive. We have proposed that it is the degree of *mismatch* between the developmental and post-plastic environments that influences the risk of later disease.

The relationship between the maternal environment and fetal environment is not linear. Irrespective of how enriched the maternal environment is, the fetal environment is somewhat restricted by the processes of maternal constraint. This puts an upper limit on what the fetus can sense with regards to nutrition, and in doing so its capacity to predict its future environment. This would have conferred an adaptive advantage in the evolving hominid because it biased development towards the assumption of poor nutrition in postnatal life. It is now disadvantageous, especially as nutrition becomes more abundant and lifestyle more sedentary. We are paying the price of the speed of postnatal environmental change because we have evolved with developmental processes that limit our capacity to adapt to such environments.