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Themed Issue: David Barker commemorative meeting, September 2014; the future of the science he inspired

REVIEW

The birth and future health of DOHaD

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Professor David Barker, CBE, FRS, made an enormous contribution to biomedical research, which helped to change its direction and assisted translation to clinical medicine in the area of non-communicable disease (NCD). In this paper, I briefly note some of the studies, which led to his work, and describe how the underlying mechanisms came to be investigated by fetal physiologists. This is a unique aspect of the change in scientific emphasis, from a gene-centric and adult lifestyle view of NCD to a more holistic perspective, which placed emphasis on the importance of development that took place in the late 20th century. Early this century, the DOHaD Society was formed: I discuss some aspects of the formation of the Society and note the important role it is now playing in addressing the need to find early-life interventions to reduce NCD. This forms part of the unique legacy that David Barker has left to science and medicine.

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Introduction

This review is a personal perspective on the origins and future of the DOHaD Society, as a tribute to the major contribution of Professor David Barker, CBE, FRS, towards establishing this field. It is based on my introductory presentation at the David Barker commemorative meeting held in Southampton on 18 September 2014 and, as a personal reflection, does not attempt to give a complete review of the DOHaD field.

The conception of the concept

We do not know when the concept that life before birth has such a profound impact on later health first became current, although Hippocrates in his treatise 27 on the nature of the child states 'Now it is just in the same way that the child in the womb lives from its mother, and it is on the condition of the health of the mother that the condition of the health of the child depends'. However, the long gestation of the concept seems to have been nearing full term in the 1930s when Kermack *et al.*[1] linked poor living conditions in childhood to later premature mortality. Later, in 1977, Forsdahl[2] linked such poor living conditions in childhood and adolescence as risk factors for arteriosclerotic heart disease, and he noted that this occurred even when the adult environment was not poor, making the dominance of the prenatal environment important. A range of studies were conducted by Dörner *et al.*,[3] who were the first to use the term 'programming' (*progammierung*) to describe such effects. Much of Dörner's work related to effects on neuroendocrine and reproductive function, but he also conducted studies linking development to the early origins of diabetes and cardiovascular disease.

A pioneering, and relatively unrecognized, study of Higgins *et al.*[4] linked pregnancy complications such as pre-eclampsia with elevated blood pressure of the offspring. Higgins *et al.* noted that this effect became more exaggerated as the offspring became older and, importantly, the association persisted after correction for the mother's blood pressure. In a prescient conclusion, the authors suggested that the prenatal environment, rather than genetic effects, was likely to be involved in their observations, and suggested that future research should involve the prospective studies of women and their children. Many of us in the audience today are engaged in just such studies.

In 1985, Wadsworth *et al.*[5] reported an inverse association between birth weight, parental social status and systolic blood pressure in young men and women. The studies were accompanied in 1986 by the pioneering work of David Barker and Clive Osmond,[6] showing that infant mortality, childhood nutrition and ischaemic heart disease in England and Wales were associated. Parallel studies by Gennser *et al.*[7] showed that low birth weight was indeed linked to risk for elevated blood pressure in adulthood, and Barker *et al.*[8,9] went on to link growth *in utero* and weight in infancy to death from ischaemic heart disease. These latter observations on children were confirmed in the study by Peter Whincup *et al.*[10]

The developmental physiologists are converted

By the late 1980s, the epidemiological observations of David Barker and colleagues were becoming much discussed in biomedical circles and, although the previous papers that led up to his work were little known, it was clear that his observations fitted into a history of research into the long-term consequences of environmental effects on human development. However,

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broader acceptance in the biomedical community was hampered by the lack of knowledge of plausible underlying mechanisms. This problem was detected by Professor Geoffrey Dawes, CBE, FRS, who directed the Nuffield Institute for Medical Research in Oxford and was the leading fetal physiologist in the United Kingdom. When I moved from Oxford to the University of Reading, I began to work in developmental physiology, and thus, of course, collaborated with Geoffrey's group in Oxford as well as many of his international collaborators. Then, early in 1989, I was invited by Geoffrey to attend a meeting on fetal autonomy and adaptation to be held in Lerici near La Spezia in Italy in early October of that year. I knew nothing of this beautiful Italian port except that the poet Shelley had swum from there and drowned in 1822. I arrived expecting a large international meeting – it was indeed international, but there were only about 20 of us attending; we stayed in a beautiful villa overlooking the sea. Most of the others were fetal physiologists I knew, and we greatly enjoyed ourselves over long Italian lunches and dinners, presenting our ideas on fetal autonomy and discussing future research. There was one attendee at the meeting who was not known to us – David Barker – and it was only towards the end of our 3 days in Lerici that we began to get a sense of the real purpose of the meeting. Geoffrey, with funding from local industry and the obstetric community in Le Spezia, had funded this small international workshop to give us the opportunity to discuss David Barker's observations with him and to explore the opportunities for further research. Suffice it to say that we went away convinced that Barker had hit upon something very important and that it would behove us to test his ideas experimentally. Investigations into the possible underlying mechanisms commenced in many laboratories around the world as a result.

The Lerici meeting was published by John Wiley in 1990, and the volume is significant because it contains synopses of the discussion,[11] which followed the presentation of the individual papers. These make interesting reading. To quote:

- 'Patrick wondered whether the results might have been distorted by smoking…' (p. 33).
- 'Redman asked whether the association between hypertension in adults and placental weight was genetically determined…' (p. 34).
- 'Hanson wondered whether the differences which Barker had described would disappear if the data were re-analysed for social class …' (p. 35).
- 'Thornburg thought it far fetched that a short-term adaptation of a fetus in trouble would have such long-term effect on the likelihood of ischaemic heart disease in adult life' (p. 36).
- '…and Visser was still concerned about the effects of smoking'.
- 'Nevertheless, Barker stuck to his hypothesis, which of course must be validated by further measurements' (p. 36).

I was invited to move to the University College London in 1990, and in discussion with Professor Sir John Pattison, who had recently taken up the post of Dean, I was able to persuade the college to set up a sheep laboratory and to provide support for my group to undertake a series of experiments. Here was the opportunity I needed to test what became known as the 'Barker hypothesis'. I reasoned that if David Barker was correct that fetal development was fundamental to later health, then even a mild degree of undernutrition in an animal model in early gestation, which would not be sufficient to produce a reduction in birth weight of the offspring, should, nonetheless, produce significant effects on cardiovascular and neuroendocrine function. My colleagues at the time thought that I was mad to waste such valuable support on such a speculative programme. However, the experiments were conducted, taking many years as some of the offspring were followed-up to adulthood, and my hunch was proved correct. Even a 15–30% reduction in the balanced nutrition of the pregnant ewe in the 1st month of gestation, which caused her to lose only a few kilograms of body weight for a short period, was sufficient to produce alterations in fetal blood pressure (lowering it) followed by postnatal effects (an increase in blood pressure, enhanced hypothalamic–pituitary–adrenal axis function, etc.). I was converted to Barker's way of thinking.

The 1990s saw an enormous expansion in animal models of fetal programming (as it became, unfortunately in my view, known), and this area was firmly established by the turn of the century; however, in retrospect, many of us believe that David Barker's observations triggered a renaissance in fetal integrative physiology at a time when the gene-centric view of the developmental programme and the likely origins of chronic disease, as being a combination of genetic predisposition and unhealthy adult lifestyle, were becoming predominant. These ideas are discussed by others in today's symposium.

Fetal Origins of Adult Disease (FOAD) becomes DOHaD

The first international meeting of the researchers concerned with the FOAD was held in Mumbai in India in February 2001. This was a landmark meeting for those attending, not only because it introduced many of us to India and the obvious consequences of undernutrition to development and the longer-term consequences for the developing world but also because it established a sense of community among those who had been working independently in epidemiology, clinical research and basic science in many countries around the world. As I had now moved to the University of Southampton, I 'volunteered' to organize the Second World Congress on FOAD, scheduled for June 2003. We decided to hold the meeting in Brighton in the United Kingdom. FOAD had gone from strength to strength in the intervening 2 years, and on the opening platform we welcomed HRH the Princess Royal, the Nobel Laureate Amartya Sen, Professor Lord Robert Winston and Professor Colin Blackmore (who had recently taken on the role of Chief Executive of the MRC). By the time of the congress, it was clear to many of us in this research area that FOAD was an inappropriate term for the field. Apart from some

unfortunate interpretations of the acronym, it was clear that the effects of early life were manifest not only during the fetal period but also in development more widely, starting in the early embryo and extending through childhood. The addition of development to the title allowed child development and other considerations to be brought into the fold. Then it was clear that the fundamental biological mechanisms, which had been demonstrated so extensively in animals, could have a range of evolutionary and other implications that had to be seen as part of normal developmental strategies – these might lead to adaptive responses promoting health as well as maladaptive responses leading to potential disease. Therefore, FOAD changed to DOHaD, and an international society for this field was established at the Brighton meeting. I clearly remember when we were designing the set for the meeting, sketching the DOHaD Society logo at home one rainy Sunday afternoon and wondering about the future of the field. I need not have worried: if one Googles Developmental Origins of Health and Disease now, there are 1.09 million hits (over 200,000 on Google Scholar). In the current year (2014), there have been nearly 44,000 citations or references on Google and 10,500 on Google Scholar. The DOHaD Society now has over 550 members from 57 countries and has established affiliate societies or chapters in China, Japan, Australia/New Zealand, France and the Spanish-speaking countries.

DOHaD and public health

Throughout the first decade of the millennium, the implications of the DOHaD concept to non-communicable diseases (NCDs) were becoming manifest. Attention was drawn in many books and reviews which members of the Society produced to the importance of taking an early-life approach to the prevention of the rising burden of NCDs in many countries. Despite this, the DOHaD concept was little recognized at an international level. Perhaps, this was not surprising as the NCDs themselves were not referred to in the Millennium Development Goals launched in 2000. Peter Gluckman and I, with other senior members of the DOHaD Society, made it our mission to undertake advocacy for the inclusion of the DOHaD concept in international health policy and to emphasize its applications to 21st century public health. This was not easy, but we were gratified when at the meeting of the United Nations General Assembly High-Level Meeting on the Prevention and Control of Non-Communicable Diseases held in September 2011 (at precisely the same time as the Portland Congress of the DOHaD Society) reference to the concept was included in the now famous clause 26, *viz*, '{We} note also with concern that maternal and child health is inextricably linked with NCDs and their risk factors, specifically as prenatal malnutrition and low birth weight create a predisposition to obesity, high blood pressure, heart disease and diabetes later in life; and that pregnancy conditions, such as maternal obesity and gestational diabetes, are associated with similar risks in both the mother and her offspring'.

The DOHaD concept relates very much to the life-course approach to the prevention of chronic disease, and this became enshrined in a range of influential documents, particularly the WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013–2020, in which one of the overarching principles states 'Life-course approach: A life-course approach is key to prevention and control of noncommunicable diseases. It starts with maternal health, including preconception, antenatal and postnatal care and maternal nutrition, and continues through proper infant feeding practices, including promotion of a healthy working life, health ageing and care for people with noncommunicable diseases in later life'. Most recently, Dr Margaret Chan, the Director-General of the World Health Organisation, has convened a commission on ending childhood obesity, and it is significant that Sir Peter Gluckman was asked to co-chair this and I was asked to co-chair the Working Group on Science and Evidence, reporting to the Director-General.

At the meeting of the Society in Singapore in November 2013, we were challenged by Dr Richard Horton, the Editor of the *Lancet*, to link DOHaD to other civil society organizations engaged in similar advocacy activities. This led me to work with the NCD Alliance, NCD Child and the Partnership for Maternal, Newborn and Child Health to produce a policy document – Sustaining human development: leveraging early life opportunities to prevent and control NCDS – which was published in May 2014.

The future

As Dr Lake and Dr Chan[12] note in their recent commentary, the debate about nature *v*. nurture is over, and it is time to put the latest science into practice to promote healthy child development. The observations of David Barker and his colleagues in Southampton and wider afield formed the nucleus around which several components of ongoing scientific research, which were all in solution but not linked together, joined and crystallized into a discrete structure. The beautiful crystal that was formed has several faces: it reminds me of something that Geoffrey Dawes said to me in a conversation many years ago. 'Imagine a crystallographer attempting to identify the nature of a crystal. He looks at it from one aspect and measures its shape, the lengths of its sides and the angles at which they intersect. But he is not content with that information to identify its structure. He turns it and makes observations from all the other faces before pronouncing upon it. It is just the same in science – we always need to take new approaches and new viewpoints if we are to address a problem effectively'. David Barker genuinely helped us to turn that crystal once it had formed. His work was not received without criticism and scepticism, some of it most acute in the United Kingdom, where his observations had first been made. There were many occasions when those of us working in the field felt that it should be better recognized at the level of government and policy formation, let alone by the funding bodies. David would have been heartened by the following quote from Dame Sally Davies in the Annual Report

of the Chief Medical Officer for England 2012 (published in 2013), entitled 'Our children deserve better: prevention pays': 'The evidence base for the life course approach is strong. What happens early in life (indeed in fetal life) affects health and wellbeing in later life'. There is no longer any doubt that DOHaD is now a thriving and vigorous field of research, and that its implications for future human health, along with the accompanying humanitarian, ethical and financial consequences, are widely recognized. At this memorial meeting for David Barker, we celebrate his contribution to science and medicine in making this happen, and we look forward to the future of the field and to the next congress of the International DOHaD Society to be held in November 2015 in Cape Town.

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