

Introduction to special issue on: the David Barker commemorative meeting, September 2014; the future of the science he inspired

The papers in this special issue result from a symposium held at the University of Southampton, UK, in September 2014, to celebrate the life and work of Professor David Barker, FRS CBE, the ‘founding father’ of DOHaD, who died suddenly in August 2013. David Barker was not the first to propose that the early-life environment determines health throughout life, but he felt the implications of this so certainly and so strongly that he made it his life’s work to build the evidence and promote action to improve the health of mothers around the world. His legacy is a vigorous field of science in which developmental biologists, population scientists and clinicians in almost every field are working together to make an impact on international policies for better maternal health. The power and breadth of David’s work are reflected in the range of contributors to this special issue, who worked closely with him. All recounted moving personal memories of David and his influence on their lives and research, but above all they looked to the future of the science of DOHaD that he inspired.

In the first paper, Kent Thornburg reviews the evidence from animal and human studies linking maternal, fetal and placental phenotype with three causes of cardiac death: coronary artery occlusion, impaired cardiac contractility and arrhythmias. He describes the effects of impaired placentation on the haemodynamic forces acting on the developing heart, and how these, and circulating factors that stimulate or suppress proliferation, influence cardiomyocyte maturation and the coronary arterial tree. He finishes by saying that it is every DOHaD scientist’s responsibility to drive the social dialogue to improve maternal health, whether this be by fighting to end chronic poverty or fighting the ‘high calorie malnutrition’ of the western diet (‘food has been engineered to stimulate tasteful bliss but lacking nutrients’), which threatens to spread round the globe.

Tom Fleming’s review explains how very brief exposures to maternal undernutrition or infection can alter embryonic development in specific ways that cause disease in later life. In mice, maternal protein restriction limited only to the pre-implantation period changes the amino acid and glucose composition of the fluid in the uterine lumen; the embryo senses these signals and ‘makes decisions’ about the balance of cells between the trophoblast and the primitive endoderm. There is a multitude of downstream effects, including altered invasiveness of the trophoblast. In adult life, the resulting epigenetic, cellular metabolism and structural changes lead to obesity, hypertension and reduced arterial compliance.

David Barker’s initial cohort studies showed strong associations of low infant weight gain with high rates of adult heart

disease and diabetes, and highlighted infancy as a critical developmental period on a par with intra-uterine life. However, as Sian Robinson points out in her review, infant nutrition has received less attention than fetal nutrition from the DOHaD community. Studies have mainly compared breast feeding with bottle feeding, and there has been little research on weaning, the transition from milk to a mixed diet. Difficulties are that diet changes rapidly during infancy, and we do not know the most important ages, and there remains uncertainty as to what constitutes optimal infant growth for both short- and long-term health. Nevertheless, if we can develop a better understanding of nutrition at this age, infancy represents a prime opportunity for intervention. Sian calls for the development of instruments to characterize infant diet across different settings, and close collaboration between epidemiology and mechanistic research.

Moving into childhood, Michelle Lampl presents a thought-provoking paper on DOHaD and growth from an ‘auxological perspective’. She says that some fundamentals of David Barker’s thinking sometimes get lost. For example, the importance of time- and place-specific interactions between the maternal environment and the developing child, and growth as a mechanistic link to later disease risk. She highlighted David’s ability to recognize the importance of observations that others had brushed over. For example, the fact that neonatal mortality at the turn of the 20th century was low in London, even though it was a filthy and dangerous environment for infants, and his speculation that this was because their mothers, well nourished because they had only recently migrated in from the countryside, had healthy bodies. She concludes that fetal programming is not only a reflection of pathology, but a universal biological phenomenon, changing as every maternal circumstance changes. Her paper also gives some eloquent insights into the shortcomings of birth weight as a measure of fetal growth, the inherent insensitivity of ‘clinical’ cut-offs such as smallness for gestational age, the distinction between ‘catch up’ and ‘compensatory’ growth, and the potential pitfalls of universal fetal growth standards.

Epigenetics has caught the DOHaD imagination in recent years, offering as it does a mechanism, whereby a memory of the early-life environment is permanently retained. Keith Godfrey’s review is a clear and jargon-free description of the variety of epigenetic marks, and the evidence that (a) they are influenced by nutrition in early life and (b) cause disease. He reviews recent evidence that paternal as well as maternal diet can affect the offspring’s epigenome, how epigenetic changes

can cause trans- and multi-generational effects, the potential for epigenetic markers to become biomarkers of future disease, and the potential for interventions to reverse adverse epigenetic changes.

Two papers in the special issue are written from the point of view of clinical obstetrics. In a unique perspective, Rebecca Painter describes how DOHaD concepts influence her day-to-day practice. As she puts it: 'David Barker walks with me every day on my ward round'. Along the way, she reviews what is known about the long-term sequelae of common obstetric problems such as prematurity, gestational diabetes, hyperemesis and assisted reproduction and/or their therapeutic interventions. Kermack *et al.* present a wide-ranging review of the 'responsibilities that DOHaD places on the obstetrician'. Their main focus is the developmental origins of ovarian function and ageing, but they also review the role of placenta in programming, and that of n-3 fatty acids in early development. They conclude with a discussion about the importance of pre-conceptional care and the barriers to this becoming the norm in the near future.

David Barker took a special interest in low- and middle-income countries (LMICs) and was strongly supportive of DOHaD research in Asia (especially India) and Africa. In David Phillip's contribution to this special issue, we get an insight into David Barker's attachment to LMICs, based on his experience as a young epidemiologist working in Uganda. It was here that he learned the importance of keen observation of how people lived in order to understand the diseases they suffer from, and developed the theory that Buruli Ulcer was transmitted by scratches from razor-sharp reeds growing along rivers. David Phillips describes common diseases in sub-Saharan Africa today as being part of a 'long tail of chronic poverty', and evidence that rheumatic heart disease and insulin-dependent diabetes in adults have their origins in early life.

As David Barker repeatedly advocated, a DOHaD approach to public health would focus on improving the health and nutrition of mothers. In her review, Mary Barker writes that in the drive to do the next randomized controlled trial or discover the key DOHaD interventions, it sometimes escapes our notice

that we need to learn how to change behaviour. She explains that lifestyle choices are moulded not only by knowledge and rational decision making, but also by habits imposed by a lifetime's social and physical environments. New understanding of what drives people to eat what they eat has led to new ways of supporting better behaviours. 'Healthy Conversation Skills', a technique developed by her group to empower women of low educational attainment to make healthy lifestyle choices is now being put into action among mothers in numerous countries and settings.

Mark Hanson presented a personal reflection on how controversial scientific ideas take hold and get translated, and how DOHaD got to where it is now. He describes how observations linking fetal development and adult health date back to Hippocrates, but failed to make an impact on science until David Barker started his concerted research. A major barrier to the acceptance of his ideas was a lack of plausible mechanisms. The links that he formed with fetal physiologists were crucial and led to incontrovertible evidence of programming in experimental animals. Mark's description of a meeting in Italy in 1989, at which fetal physiologist Geoffrey Dawes introduced David to the fetal physiology fraternity, and sceptical remarks made by (now) leading lights in the DOHaD field, is delightful. He then describes how the international DOHaD conferences and the formation of the DOHaD Society have established an effective 'community' of researchers across epidemiology, basic science and clinical research, and an advocacy platform that has now put DOHaD onto the international public health agenda.

A recording of all 17 presentations that were made at the David Barker commemorative meeting is available on DVD and can be obtained by contacting the authors.

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