

David James Purslove Barker: clinician, scientist and father of the ‘Fetal Origins Hypothesis’

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Professor David Barker was responsible for a sea-change in the way we understand a wide range of chronic diseases, from cardiovascular disease to cancer. He challenged the accepted view that such conditions were a result of genetic susceptibility in combination with an unhealthy lifestyle, arguing that they had their origins during growth and development either *in utero* or during early infancy. Because of its emphasis on destructive models of disease, he felt strongly that public health medicine was failing, and believed that a new approach to public health was needed based on practical efforts to improve the health and nutrition of mothers and babies. Although this became widely known as the ‘Barker Hypothesis’, he resisted this term, preferring to refer to the ‘Fetal Origins Hypothesis’. Promoting these ideas, often accompanied with sharp comments directed at his adversaries, unsurprisingly put him into conflict with many in the medical establishment. As a result, he was denied much of the recognition that he deserved.

The early years: medical training, social medicine and Uganda

David Barker’s scientific career was sparked by an exceptional biology teacher at Oundle School. He trained in medicine at Guy’s Medical School, and in 1963 a year after qualifying, became a research fellow in the Department of Social Medicine at Birmingham University where his PhD thesis related growth *in utero* and obstetric complications to childhood intelligence. In 1969, with a grant from the MRC, he took his first wife and family to Uganda, to research *Mycobacterium ulcerans* infection (Buruli Ulcer). Little was known about this disabling infection, but David questioned the received wisdom that this was a mosquito-borne infection, demonstrating that it was a result of wounds caused by the razor-sharp reeds growing near the river Nile rather than mosquito bites that caused the disease transmission.

University of Southampton: geographical prevalence studies of chronic non-cardiovascular disease

David was appointed Professor of Clinical Epidemiology at the University of Southampton in 1979. He was also a consultant

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physician at the Royal South Hants Hospital, stressing the importance of strong clinical links in a research career. During the early years in Southampton, he carried out a series of studies on the geography of several non-cardiovascular chronic diseases of obscure aetiology, based on routinely collected health service data in a group of English towns. Each new research fellow was assigned one of these diseases and for many of us this provided the springboard for future careers. Paget’s disease of the bone was an early interest and David carried out an innovative prevalence study based on X-ray films of the abdomen and pelvis stored in radiological departments. This study demonstrated large geographic variations in the prevalence of the disease with a notable focus on the county of Lancashire. Another technique he used with great success was the use of case registers to study diseases, which were otherwise inaccessible to epidemiological investigation. A register of cases of Perthe’s disease of the hip showed that this disease of obscure aetiology was strongly linked to socio-economic deprivation and characterized by abnormal skeletal growth. Using biochemistry laboratories to study the prevalence of hyperthyroidism led to a series of studies demonstrating the role of iodine nutrition, past and present, in the aetiology of toxic nodular goitre. Other notable work at this time included studies on gallstones, renal stones, motor neurone disease, Alzheimer’s and appendicitis. The latter in which David suggested that trends in the prevalence of appendicitis followed the changing pattern of infectious disease in childhood was arguably one of the earliest descriptions of the role of the ‘hygiene hypothesis’ in human disease. He was an inspired teacher who supervised many research fellows who went on to have successful careers in epidemiology. With Geoffrey Rose, he started an annual course in Southampton (epidemiology for clinicians), which still runs today, and wrote books and articles that introduced a generation of researchers to epidemiology.

The MRC Environmental Epidemiological Unit: the birth of the ‘Fetal Origins Hypothesis’

David succeeded Donald Acheson as the director of the MRC Environmental Epidemiology Unit in 1984 and shortly after this made his key observation that neonatal and post-neonatal mortality in the 1910s and 1920s were similar to maps of death from heart disease 60–70 years later. This led to the idea that an

adverse environment in the womb or during early infancy might be linked to the risk of cardiovascular disease in later life. He initiated a UK-wide search for birth records of people born 60 or 70 years ago, and discovered the Hertfordshire health visitor records and obstetric records from hospitals in Preston and Sheffield. By linking data from these records to death certificates, and later to direct measurements among survivors, he showed that cardiovascular disease, hypertension and type 2 diabetes were much more prevalent in those who had been born with a low birthweight. A large body of epidemiological and clinical physiological research in support of the hypothesis was created.

He established important collaborations with physiologists in Adelaide, Auckland and Toronto, who were studying foetal development in animals. Linking human epidemiological or clinical research to animal studies carried out by these groups provided strong evidence to support the idea that early life undernutrition had lifelong adverse effects on all body systems. Annual meetings bringing together the hitherto separate worlds of foetal physiology and epidemiology led to the formation of the International Society for Developmental Origins of Health and Disease (DOHaD) and international conferences.

The international dimension: mother–offspring cohort studies in Finland, the Netherlands, India and Jamaica

In 1994, David was eagerly looking for collaboration with groups that had access to extensive infant and childhood growth data. With Finnish colleagues, he obtained a grant from the British Heart Foundation – the first major award they had made outside the British Commonwealth – to start the Helsinki Birth Cohort Study (HBCS) of men and women born in the city during 1924–1944. Early results showed the importance of postnatal growth and especially the importance of a mismatch between birth size and later body size in predicting cardiovascular disease and type 2 diabetes. Within HBCS, it was also possible to study the importance of maternal body size and placental size in programming later health outcomes. Placental size proved to be strongly associated with several health outcomes. As genetic studies became more possible, David even wrote an article about the importance of the interaction between birth size and genes. In a very David-like way he said, ‘I never thought that I would like a paper on genes. But this is a great paper!’. He loved to visit Finland, where he was a popular speaker, and where his mentoring of young students was much appreciated. His ideas and suggestions were often surprising, but so often right. He was a great inspiration to the whole HBCS team, with whom he wrote more than 130 articles.

Another of David’s long-standing and fruitful collaborations was with researchers at the University of Amsterdam, with whom he studied men and women who had been *in utero*, been born immediately before or been conceived just after the Dutch Hunger Winter of 1944/1945. In early life these people had experienced a well-defined 5-month period of severe nutritional restriction. Did it have long-term consequences and, if so, did they

vary according to the timing of the famine exposure? For example, the earliest article showed that those exposed to famine in mid and late gestation had decreased glucose tolerance as adults.

David was a strong supporter of DOHaD research in developing countries, many of which are struggling with the dual burden of persisting widespread maternal and child undernutrition, alongside rapid transition and urbanization, causing rising obesity. He was a regular visitor to DOHaD projects in India, and helped found Sneha-India, the first national society for DOHaD research, which hosted the 1st World DOHaD Congress in 2001. After retiring from the directorship of the MRC Unit, David remained in touch with the international projects and intervention trials, while also indulging his interest in foetal physiology by becoming the visiting professor at Oregon Health Sciences University, Portland, a centre for placental research, and Emory University, Atlanta, studying the biology of human growth.

The MRC Lifecourse Epidemiology Unit: future research strategy for the DOHaD

The MRC Lifecourse Epidemiology Unit was established following David’s retirement and continues research into the developmental origins of adult disease, with a strong focus on the improvement of human health. The Unit provides a legacy for David’s epidemiological research and focuses on aetiological studies, which aim to delineate the mechanisms that underpin a development contribution to chronic metabolic and musculoskeletal disease, as well as the design of effective interventions during pre-conceptual life, pregnancy and childhood, which might translate into enhanced long-term adult health, life expectancy, quality of life and accumulation of human capital. The design of such studies requires an understanding of the behavioural and environmental influences on health that can be modified, and interventions need to target those in whom there is greatest need. Finally, a wide range of study designs are available for the assessment of population-based intervention ranging from traditional randomized controlled trials of micronutrient deficiencies such as vitamin D during pregnancy, through to complex intervention strategies aiming to optimize dietary pattern during pre-conceptual years and pregnancy. Examples of these approaches are incorporated within the current portfolio of the MRC Unit, including a randomized controlled trial of vitamin D supplementation during pregnancy; a randomized controlled trial of a pre-conceptual, multiple micronutrient intervention in Mumbai; and a complex intervention aiming to improve pre-conceptual and pregnancy and dietary pattern, within the United Kingdom.

Achieving change: intervention studies

David recognized the importance of progressing from observational studies to interventional research to strengthen the evidence for the concept of DOHaD and measure the benefits to human health of improving maternal nutrition, and as a

platform for understanding the mechanisms that underlie programming. He played a major role in setting up the Southampton Initiative for Health, which is testing the effect of training Sure Start workers in healthy conversation skills, with the aim of improving the diets of women and mothers. He was convinced of the importance of pre-conceptional interventions, and his thinking was integral to the design of two nutritional trials in India, one a food-based micronutrient intervention in Mumbai, and the other a trial of vitamin B12 in Pune.

Of all David's characteristics, the most striking were his warmth and humour. David created an academic environment

where science could prosper but, which at the same time, was alive with banter and fun. He published over 500 research papers and 10 books, was a Fellow of the Royal College of Physicians, the Royal College of Obstetricians and Gynaecologists, and the Royal College of Paediatrics and Child Health. Among many other honours, he was made a Fellow of the Royal Society and of the Academy of Medical Sciences in 1998 and awarded a CBE for his services to preventative medicine in 2005. He made his second documentary with the BBC Horizon team, *The Nine Months That Made You*, explaining foetal programming for a general audience, in 2011.