Early Life Origins of Health and Disease

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Early Life Origins of Health and Disease

Edited by

E. Marelyn Wintour

Department of Physiology, Monash University, Clayton, Victoria, Australia

Julie A. Owens

Department of Obstetrics and Gynaecology, University of Adelaide, Adelaide, South Australia

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PREFACE

When we agreed to edit this book we established some guidelines for the authors who were asked to contribute. The authors were asked to include all relevant material currently available, but to be critical of the methodology used to obtain the various types of data. In addition to evaluating the methodology used in each quoted study, they were asked to suggest the optimal state of the art methodology which should be used for each type of investigation. Thus Denton et al (Ch. 9) considered the optimal way (conscious and undisturbed) and length of time for which blood pressure should be measured, for the results to be most meaningful. They also considered all the components of the cardiovascular system which required examination if the full impact of some programming stimulus were to be investigated fully. This is continued in the examination of other aspects of cardiovascular dysfunction (Poston et al, Ch. 10) The same criteria were applied to assessment of nephron number (Moritz and Cullen-McEwen, Ch.11) and optimal methodology (unbiased stereology) suggested. All authors paid attention to the type of statistics to be used and stressed where appropriate the importance of studying both sexes of offspring. Equal rigor was used in assessing metabolic changes induced by pre/perinatal conditions (Gatford et al, Ch.13). Simon Langley-Evans (Ch. 8) was asked to make sure that readers would appreciate that not all low-protein diets are equivalent. Ruth Morley (Ch. 3) was commissioned to make it clear that not all monozygotic twins share one placenta and to give a critical evaluation of what can or cannot be learned from a study of twins. In short, any investigator planning a study of the early life origins of health and disease, having read this book, should be able to devise the best possible experiment, using optimal methodology, to give the utmost reliable outcomes.

The book covers data relevant to humans (Chs. 1-5), and various animal models (Chs. 8-14). After the whole background to the concept is set by the current president and secretary of the international society devoted to this area (DOHaD), an expert in epidemiology (Fall, Ch. 2) gives a masterly summation of the past findings. In a timely reminder the peri-implantation embryo is considered as a vulnerable stage (Thompson et al, Ch. 5). In addition, the potential mechanisms by which such programming might occur are covered in the two chapters on epigenetics (Chs. 6, 7).

Finally there are four chapters which cover emerging areas of great potential interest (Chs. 15-18). In all these areas (vitamin D deficiency, hypoxia, alcohol

exposure, adult mental health) there are limited data which suggest that an influence exerted during development might have long-term consequences for adult offspring, but much more investigation is required.

This should be a most valuable resource book for all those currently engaged in the study of the influences of the prenatal environment on future health, as well as for those who are just contemplating beginning work in this area.

E. Marelyn Wintour and Julie A. Owens

PARTICIPANTS

James A. Armitage
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology and Development
King s College
London
UK
james.armitage@kcl.ac.uk

Leanne Bellinger
Centre for Reproduction and Early Life
School of Biosciences
University of Nottingham
Sutton Bonington, Loughborough
Leicestershire
UK
sbxlbl@gwmail.Nottingham.ac.uk

Laura Bennet
Fetal Physiology and Neuroscience Group
Department of Physiology
University of Auckland
Auckland
New Zealand
l.bennet@auckland.ac.nz

Bernhard H. Breier
Liggins Institute for Medical Research
Faculty of Medical and Health Sciences
University of Auckland
Auckland
New Zealand
b.breier@auckland.ac.nz

Luke C. Carey
Department of Obstetrics and Gynecology
Wake Forest University School of Medicine
Winston-Salem, North Carolina
USA
lcarey@wfubmc.edu

John B. Carlin
Department of Paediatrics
University of Melbourne
and
Murdoch Childrens Research Institute
Royal Children s Hospital
Parkville, Victoria
Australia
jbcarlin@unimelb.edu.au

Luise A. Cullen-McEwen
Department of Anatomy and Cell Biology
Monash University
Clayton, Victoria
Australia
luise.cullen-mcewen@monash.edu.au

Miles J. De Blasio
Department of Obstetrics and Gynaecology
Monash University
Victoria
Australia
miles.deblasio@adelaide.edu.au

Kate M. Denton
Department of Physiology
Monash University
Victoria
Australia
kate.denton@med.monash.edu.au

Miodrag Dodic
Department of Physiology
Monash University
Victoria
Australia
miodrag.dodic@med.monash.edu.au

Terence Dwyer
Murdoch Childrens Research Institute
Royal Children s Hospital
Parkville, Victoria
Australia
terry.dwyer@mcri.edu.au

Caroline H.D. Fall
Reader in Epidemiology and Consultant in Child Health
MRC Environmental Epidemiology Unit
University of Southampton
Southampton
UK
chdf@mrc.soton.ac.uk

Kathryn L. Gatford
Department of Obstetrics and Gynaecology
Monash University
Victoria
Australia
kathy.gatford@adelaide.edu.au

Dino A. Giussani
Department of Physiology
University of Cambridge
Cambridge
UK
dag26@cam.ac.uk

Peter D. Gluckman
Liggins Institute
University of Auckland and National Research Centre
for Growth and Development
Auckland
New Zealand
pd.gluckman@auckland.ac.nz

Alistair J. Gunn
Fetal Physiology and Neuroscience Group
Department of Physiology
University of Auckland
Auckland
New Zealand
aj.gunn@auckland.ac.nz

Mark A. Hanson
Centre for Developmental Origins of Health and Disease
University of Southampton
Princess Anne Hospital
Southampton
UK
m.hanson@soton.ac.uk

David J. Henderson-Smart
NSW Centre for Perinatal Health Services Research
Queen Elizabeth II Research Institute
University of Sydney
Sydney, NSW
Australia
dhs@perinatal.usyd.edu.au

Dane M. Horton
Department of Physiology
University of Adelaide
Adelaide
South Australia
dane.horton@adelaide.edu.au

Michelle M. Kett
Department of Physiology
Monash University
Victoria
Australia
michelle.kett@med.monash.edu.au

Karen L. Kind
Department of Obstetrics
and Gynaecology
Monash University
Victoria
Australia
karen.kind@adelaide.edu.au

Stefan O. Krechowec
Liggins Institute for Medical Research
Faculty of Medical and Health
Sciences
University of Auckland
Auckland
New Zealand
s.krechowec@auckland.ac.nz

Michelle Lane
Department of Obstetrics
and Gynaecology
Research Centre for Reproductive
Health
University of Adelaide
Adelaide
South Australia
michelle.lane@adelaide.edu.au

Alison Langley-Evans
Centre for Reproduction and Early Life
School of Biosciences
University of Nottingham
Sutton Bonington, Loughborough
Leicestershire
UK
alison.langley-
evans@nottingham.ac.uk

Simon C. Langley-Evans
Centre for Reproduction and Early Life
School of Biosciences
University of Nottingham
Sutton Bonington, Loughborough
Leicestershire
UK
simon.langley-
evans@nottingham.ac.uk

Sarah McMullen
Centre for Reproduction and Early Life
School of Biosciences
University of Nottingham
Sutton Bonington, Loughborough
Leicestershire
UK
sarah.mcmullen@nottingham.ac.uk

Karen M. Moritz
Department of Anatomy
and Cell Biology
Monash University
Clayton, Victoria
Australia
karen.moritz@med.monash.edu.au

Ruth Morley
Department of Paediatrics
University of Melbourne
and
Murdoch Childrens Research Institute
Royal Children s Hospital
Parkville, Victoria
Australia
morleyr@unimelb.edu.au

Timothy J.M. Moss
School of Women s and Infants Health
University of Western Australia
Crawley
Australia
tmoss@cyllene.uwa.edu.au

Julie A. Owens
Department of Obstetrics
and Gynaecology
University of Adelaide
Adelaide
South Australia
julie.owens@adelaide.edu.au

Helena C. Parkington
Department of Physiology
Monash University
Clayton, Victoria
Australia
helena.parkington@med.monash.edu.au

Julia B. Pitcher
Department of Obstetrics
and Gynaecology
University of Adelaide
Women s and Children s Hospital
North Adelaide
South Australia
julia.pitcher@adelaide.edu.au

Lucilla Poston
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology and Development
King s College
London
UK
lucilla.poston@kcl.ac.uk

Sarah Robertson
Department of Obstetrics
and Gynaecology
Research Centre for Reproductive
Health
University of Adelaide
Adelaide
South Australia
sarah.robertson@adelaide.edu.au

Jeffrey S. Robinson
Department of Obstetrics
and Gynaecology
University of Adelaide
Women s and Children s Hospital
North Adelaide
South Australia
jeffrey.robinson@adelaide.edu.au

Jeff Schwartz
Discipline of Physiology
School of Molecular and Biomedical
Science
University of Adelaide
Adelaide
South Australia
jeff.schwartz@adelaide.edu.au

Dean Sculley
Centre for Reproduction and Early Life
School of Biosciences
University of Nottingham
Sutton Bonington, Loughborough
Leicestershire
UK
dean.sculley@nottingham.ac.uk

Deborah M. Sloboda
School of Women s and Infants Health
University of Western Australia
Crawley
Australia
dsloboda@obsgyn.uwa.edu.au

Marianne Tare
Department of Physiology
Monash University
Clayton, Victoria
Australia
marianne.tare@med.monash.edu.au

Paul D. Taylor
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology and Development
King s College
London
UK
paul.taylor@auckland.ac.uk

Jeremy Thompson
Department of Obstetrics
and Gynaecology
Research Centre for Reproductive
Health
University of Adelaide
Adelaide
South Australia
jeremy.thompson@adelaide.edu.au

Mark H. Vickers
Liggins Institute for Medical Research
Faculty of Medical and Health Sciences
University of Auckland
Auckland
New Zealand
m.vickers@auckland.ac.nz

Nicola Vickaryous
School of Molecular and Microbial
Biosciences
University of Sydney
Sydney
Australia
n.vickaryous@mmb.usyd.edu.au

Robert A. Waterland
Departments of Pediatrics
and Molecular and Human Genetics
Baylor College of Medicine
USDA Children s Nutrition Research
Center
Houston, Texas
USA
waterland@bcm.tmc.edu

Emma Whitelaw
School of Molecular and Microbial
Biosciences
University of Sydney
Sydney
Australia
e.whitelaw@mmb.usyd.edu.au

E. Marelyn Wintour
Department of Physiology
Monash University
Clayton, Victoria
Australia
mwc@med.monash.edu.au

CONTENTS

The Human Context

CHAPTER 1

The Developmental Origins of Health and Disease:

The Breadth and Importance of the Concept

Peter D. Gluckman* and Mark A. Hanson

Fetal Origins of Adult Disease (FOAD)

The concept of a 'fetal origins of adult disease' (FOAD) or 'fetal programming' was developed by Barker and colleagues to describe the relationship between birth size and subsequent risks of cardiovascular disease and insulin resistance/Type 2 diabetes mellitus. As a concept, FOAD was initially received with criticism. Some held the view that the answers lay within genetics and the gene; for others that the original epidemiological interpretations were flawed.

It is now nearly two decades since these landmark observations and concepts first appeared. It is apparent that those original findings have had far-reaching implications regarding human health and lifestyle choices, not only explaining the rapid societal rise in diabetes and obesity, but also covering areas as diverse as osteoporosis, depression and sedentary behaviour. With the wisdom of hindsight, we can see that some of the reluctance to accept the FOAD concept arose precisely from the problem which FOAD addressed: namely that the underlying causes of the common chronic diseases of adulthood (heart disease, diabetes, stroke) could not be explained purely in terms of genetic inheritance or lifestyle factors, such as diet or exercise. That instead, gene-environment interactions would hold the clues.

The concept of FOAD has expanded since the initial observations. The term 'fetal origins of adult disease' has now been replaced with 'developmental origins of adult disease' (DOHaD) to take into account its influence over an expanded developmental time-frame. Moreover, it has launched a new way of thinking about the evolution of human health and disease, which we refer to as the 'predictive adaptive response' and will be discussed further.

Early Clues

The linkages between early developmental events and eventual adult susceptibilities had been noted before, and in some rather unexpected ways. Kawahata and Sakamoto[1] noted that of those soldiers stationed in the tropics during WWII, those born in hotter climates had more sweat glands and were least at risk for heat stroke than soldiers born in cooler climates. Moreover, Roland[2] reported on anecdotal evidence that WWII prisoners of war who were smaller in size—presumably of smaller birth size—were more likely to survive the conditions of their captivity, such as starvation, than larger prisoners.

*Corresponding Author: Peter D. Gluckman—Liggins Institute, University of Auckland and National Research Centre for Growth and Development; 2-6 Park Avenue, Grafton, Private Bag 92019, Auckland, New Zealand. Email: pd.gluckman@auckland.ac.nz

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In the 1970s, Forsdahl reported on the relationship between poor childhood living conditions in Norway and later adult heart disease.[3,4] But it wasn't until the landmark studies of Barker and colleagues[5-7] that these linkages received renewed attention. Their observations have since been supported by other large cohort studies in the USA,[8-10] Jamaica[11] and India.[12]

As a marker of early life conditions, birth size had never really been considered causal in the pathway to disease risk, an element often misunderstood by critics and supporters alike. Namely, birth size as a parameter has limitations—it is a reflection of maturation (i.e., gestational age) and growth, and both are influenced by environmental and genetic factors. Also, not all adverse events that occur in utero result in reduced birth size.[13] Nevertheless, birth size and, in particular, birth weight, remain the most accessible parameters to consider when assessing the impact of early developmental factors.

The Importance of Timing

The FOAD concept focused attention on environmental factors operating during *fetal* life. However, both experimental and clinical data suggest that adult disease risk may well be influenced by events that occur prior to conception until well after birth, and that there is an interaction between the prenatal and postnatal environments. For instance, it has been shown that those most at risk for insulin resistance and cardiovascular disease have evidence of an impaired fetal environment and put on weight rapidly in childhood,[14,15] though there are other data that suggest simply the altered pattern of infant and/or childhood growth alone is enough.[16,17] More recently, data regarding the premature infant[18] further confirm the linkages between pre and postnatal life. Not much is known about the optimal level of nutrition for these infants or the required dietary components, but it has been a long-held view that nutrient-enriched formula is beneficial in promoting growth and brain development. Alan Lucas and colleagues have shown that in adolescents born premature and fed nutrient-enriched formula, their likelihood for insulin resistance and heart disease in later life is increased than if fed a lower-nutrient diet.[19,20] Hence, metabolic regulation and nutritional compartmentalization at one stage in life can be influenced by events earlier in life.

There is also increasing focus on the consequences of the peri-conceptual status of the mother (her diet, body composition, level of physical activity, for example) for the health outcome of her offspring. In the Dutch winter famine of 1944-45, those who were conceived during the famine were not necessarily of smaller birth weight, but as adults became prone to insulin resistance and obesity.[21] Similar observations have been reported in sheep, in which periconceptual undernutrition has been shown to reset the HPA axis,[22] and in rodents where the conditions in which the preimplantation embryo develops later influence fetal growth and postnatal cardiovascular phenotype.[23] In humans, similar considerations are likely to apply as IVF is associated with a greater incidence of anomalies,[24] and in embryo donation the birthweight of the resulting offspring relates more closely to the birthweight of the recipient than the donor.[25] For these reasons, the earlier terminology 'fetal origins' has been replaced by 'developmental origins'. Moreover, it is clear that greater awareness of the importance of this time of life will not only have an impact in reducing the incidence of disease, but will provide an important platform for new measures aimed at promoting a healthy lifestyle. FOAD has therefore been replaced by DOHaD (Developmental Origins of Health and Disease) and an international society was formed in 2003 to promote this endeavour (www.dohadsoc.org).

DOHaD—Underlying Mechanisms

This book is very much concerned with mechanisms, so only general comments are appropriate here. Despite the plethora of epidemiological and experimental animal observations, it is clear that only a limited number of mechanisms can drive a long-term change in phenotype. One likely mechanism may be epigenetic regulation.

While epigenetic regulation is more generally understood in terms of parental imprinting of certain genes, it is also the basis of many other changes in gene expression. Recently, clear

evidence has emerged, both with respect to parentally imprinted and nonimprinted genes, of environmentally-induced epigenetic change. In ruminant embryos subject to prolonged culture in vitro and then reimplanted, there are long-term changes in the expression of imprinted components of the IGF-2 system.[26] In the agouti mouse, the degree of imprinting can be influenced by the folate/B12 status of mother at the time of conception.[27] In the rat subject to experimental reduction of uterine blood flow, altered methylation of the p53 gene has been described in the kidney.[28] And in rat pups, Meaney and colleagues have shown that an altered neonatal behavioural environment results in altered methylation patterns in the promotor region of the glucocorticoid receptor gene.[29] If the latter could be generalized, it would suggest that there are a number of yet to be discovered mechanisms by which epigenetic change at very specific sites in the genome have evolved. Their specificity means these have not have been selected by evolution randomly, but rather because they have adaptive value. Mitochondrial DNA has been suggested as a particular target for epigenetic change[30] and this would explain the nongenomic inheritance of the phenomenon via the maternal lineage (as mitochondrial DNA is only of maternal origin); it also provides a potent way in which cellular metabolism and the response to nutritional stress can be programmed, complementing the well-known effects on growth.

At the next level, the DOHaD phenomenon involves changes in the growth and function of tissues and organs in relation to overall body size. These changes may be induced during development to reduce energy consumption by these tissues and organs during development itself, and also in expectation of a deprived postnatal environment (see Fig. 1). Much interest in the field concerns such effects on the developing kidney,[31] pancreas[32] and heart.[33] These organs are particularly interesting for several reasons. First, changes induced in them in early life, such as reduced numbers of nephrons, pancreatic beta cells or cardiomyocytes, may limit the individual's ability to respond adequately to a physiological challenge in later life, especially in the face of declining function of these organs with age, and may explain the link between developmental factors and diseases occurring after middle age, rather than in adolescence. Furthermore, cell number within these organs is set prenatally in the human, so that prenatal environment can exert permanent effects on their development.

The DOHaD phenomenon also involves changes in vascularity and, indeed, in vascular endothelial cell function,[34] with vascularity reduced in several tissues of the rat pup exposed to a low protein diet in utero.[35,36] Skeletal muscle mass may also be reduced.[37] It may be that these observations are adaptive responses to survive a poor intrauterine environment. However, it can also be viewed as a 'thrifty' adaptive response to a poor environment postnatally, staying small and trading off growth for reproduction and survival of the genotype. Because skeletal muscle is a major determinant of peripheral insulin sensitivity, these adaptive responses can also play a part in the aetiology of Type 2 diabetes and the metabolic syndrome. Endothelial function is now increasingly realized to be linked to organ and tissue growth, including that of adipocytes, and endothelial dysfunction is linked to Type 2 diabetes, hypertension and atherogenesis. A range of animal studies support the concept that this dysfunction can be induced before glucose intolerance, elevated blood pressure or obesity set in.

Lastly, there is considerable evidence both from human and from experimental animal studies that the early environment can induce permanent changes in homeostatic regulatory function. In humans born small for gestational age, there is often an altered feedback of the HPA axis, leading towards a tendency of hypercortisolemia;[38] similar changes are noted in experimental animal models, as in Meaney's behavioural model,[29] or following exposure to maternal undernutrition[39] or glucocorticoids in utero.[40] Overall, these changes are underpinned by alterations in the glucocorticoid receptors of the central nervous system via processes that are not necessarily distinct from the epigenetic processes referred to above. Other changes to homeostatic regulatory function include altered regulation of insulin release and action,[41] altered hepatic handling of glucose,[42] and altered muscular sensitivity, both to insulin and to insulin like growth factors.[43]

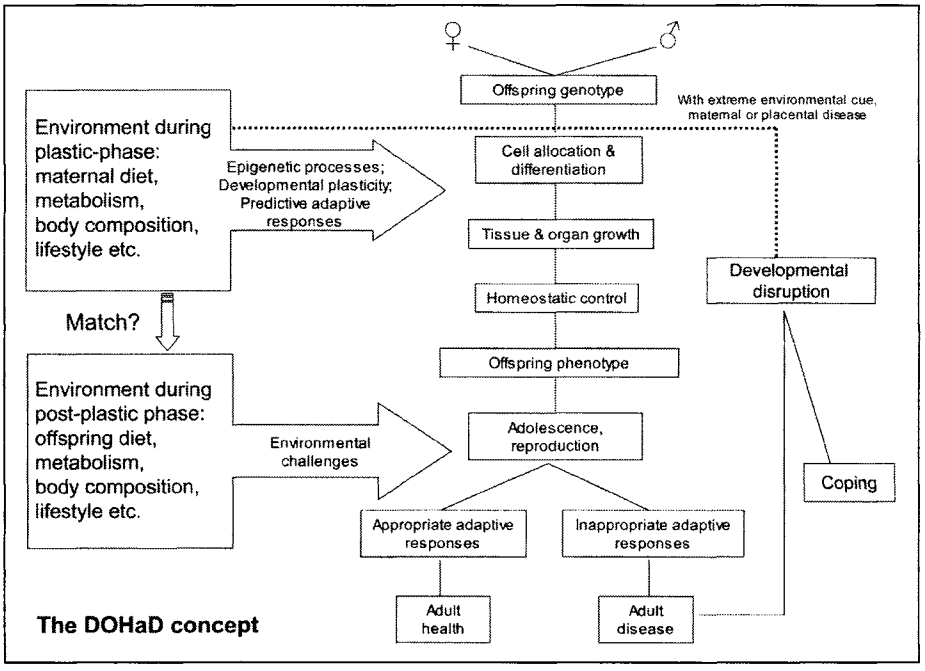

Figure 1. Diagram of the DOHaD concept. The offspring's genome inherited from both parents is subjected to a range of environmental influences in early life, which determine its phenotype. These include epigenetic processes and utilize the normal processes of developmental plasticity. Some of these effects may have predictive advantage in the postnatal environment. The processes involved can be categorized as changes in cell allocation and differentiation, tissue and organ growth and homeostatic control, and to an extent these occur sequentially as shown. If the environmental effects are severe (e.g., famine, excess, maternal or placental disease), they may induce clear disruption of development (equivalent to teratogenesis, dotted line) of reduction in developmental trajectory such that the offspring only 'copes' and is at risk both pre and postnatally. Even within the normal physiological range of adaptive responses, the risk of health vs. disease in the post-reproductive period depends on the extent of matching between the prenatal and the postnatal environments, or between the predicted and the actual environment in the post-plastic phase.

A Conceptual Framework

Some of the earliest concepts of the 'programming' of human disease have focused on the processes of mutation, genetic drift and selection, which may have created genotypes that were thrifty—the so called "thrifty genotype" hypothesis.[44] The thrifty genotype would have created a level of insulin resistance which allowed a population to cope in times of nutritional stress, but in times of plenty would have led to insulin resistance. As insulin is important to fetal growth, a genotypic change in insulin secretion or action would lead to smaller fetuses. The glucokinase mutation has been suggested as one such thrifty mutation.[45] Nevertheless, there is much that the thrifty genotype model cannot explain, such as the broader range of consequences of early life events (i.e., osteoporosis), the fact that the induction of these responses need not involve altered fetal growth, or the rapid appearance of increased risk of disease in a population subject to a brief environmental challenge (i.e., Dutch winter famine).

We think that some of these questions can be answered by a developing concept we refer to as 'predictive adaptive responses' (PARs). PARS are responses made by the developing, plastic organism, not for immediate advantage but as an adaptive strategy aimed at thriving in the environment predicted to be experienced as an adult. In other words, if the environmental

stimuli are suggestive of a deprived future environment, the fetus adjusts its physiology accordingly. The biology of PARs has been the subject of several recent reviews.[46-48]

Examples of PARs in nature include the setting of the HPA axis in response to glucocorticoid exposure during development. There may be no immediate advantage to having a hyper-responsive HPA axis, but clearly if the developing organism interprets a surge in glucocorticoids as a sign of a stressful environment, there may be survival advantage in having a hyper-responsive HPA postnatally. Another clear-cut example is that of coat thickness in the meadow vole.[49] This phenomenon (reviewed in ref. 50) shows that coat thickness in the vole at birth is determined by the thermal environment anticipated some weeks later. PARs provide an evolutionary compatible explanation of why the DOHaD phenomenon has evolved and is maintained.

The fetus has a genetically determined repertoire of responses for responding to its immediate environment in order to ensure either its immediate or its future survival. If it needs to ensure its immediate survival it may select a developmental strategy which, for example, reduces growth even though this has postnatal costs which may become manifest as disease. Yet it appears increasingly that most normally grown fetuses set their development and their homeostatic control not so much for immediate advantage but rather in expectation of assisting postnatal survival to reproduction. If the fetal prediction of its future environment is correct, then the developmental path chosen in utero should lead to health in adult life. But if the fetal prediction is wrong for some reason then as an adult it will not have physiological settings appropriate for its environment and disease risk is enhanced. In other words, the risk of disease is determined by the degree of match between the environment the developing organism anticipates, on the basis of cues from its mother and placenta, and the environment it actually faces as an adult.

Such a model explains why so called life-style diseases appear in high frequency in populations undergoing rapid nutritional transition; why the relationship between birth size and the risk of adult disease is influenced by measures of the postnatal environment, such as rapid adiposity rebound; as well as why the phenomenon is not limited to those of small size, but occurs across the full range of birth sizes.

The Influence of DOHaD in Human Health

We are left with the challenge of identifying how important this phenomenon might be for human medicine. The only human estimate suggests that avoiding a developmental mismatch could reduce the incidence of heart disease and diabetes by over 50%—but caution must be applied to a single estimate.[51] However evolutionary, developmental and experimental considerations all suggest that environmental influences acting in early development can permanently alter the trajectory of development and determine the risk of later disease. Together with the human data, these approaches suggest that a mismatch between the environment as perceived during the phase of developmental plasticity and the actual environment the organism is exposed to later in life will increase the risk of disease.

Clinical practice will increasingly have to address issues of maternal health prior to and during pregnancy. The periconceptual period may be particularly critical. Sadly we still do not know the optimal nutritional recommendations for women at different stages in the reproductive cycle. Postnatal management may need to become increasingly individualized to match the postnatal environment more closely to the phenotype induced in early life. The research effort is likely to focus on a search for epigenetic processes and markers which could be prognostic, and on achieving a greater understanding of the processes of developmental plasticity and its potential reversibility.

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CHAPTER 2

Developmental Origins of Cardiovascular Disease, Type 2 Diabetes and Obesity in Humans

Caroline H.D. Fall*

Abstract

Fetal growth restriction and low weight gain in infancy are associated with an increased risk of adult cardiovascular disease, type 2 diabetes and the Metabolic Syndrome. The fetal origins of adult disease hypothesis proposes that these associations reflect permanent changes in metabolism, body composition and tissue structure caused by undernutrition during critical periods of early development. An alternative hypothesis is that both small size at birth and later disease have a common genetic aetiology. These two hypotheses are not mutually exclusive. In addition to low birthweight, fetal 'overnutrition' caused by maternal obesity and gestational diabetes leads to an increased risk of later obesity and type 2 diabetes. There is consistent evidence that accelerated BMI gain during childhood, and adult obesity, are additional risk factors for cardiovascular disease and diabetes. These effects are exaggerated in people of low birthweight. Poor fetal and infant growth combined with recent increases in childhood adiposity may underlie the high rates of disease in developing countries undergoing nutritional transition. Sub-optimal maternal nutritional status is a major cause of low birthweight globally but its impact on fetal growth in 'well-nourished' western populations has been inadequately studied. In experimental animals hypertension and insulin resistance can be programmed in the offspring by restricting maternal diet in pregnancy but there are currently insufficient data to determine whether maternal nutritional status and diet programme cardiovascular disease risk in humans.

Low Birthweight and Adult Cardiovascular Disease

The concept that events in early life have long-term effects on human health life is not new. In 1934, Kermack showed that death rates from all causes in the UK and Sweden fell between 1751 and 1930 with each successive year-of-birth cohort.[1] He rejected one possible explanation, that babies were born healthier in successive generations, and concluded that it was the result of social reforms and better childhood living conditions. In 1977, Forsdahl discovered a geographical correlation in Norway between coronary heart disease (CHD) mortality in 1964-67 and infant mortality rates 70 years earlier (1896-1925).[2] He suggested that growing up in poverty caused 'permanent damage' perhaps due to a 'nutritional deficit', which resulted in 'life-long vulnerability' to an affluent adult lifestyle. Studies in the UK a decade later shifted the

*Caroline H.D. Fall—MRC Environmental Epidemiology Unit, University of Southampton, Southampton SO16 6YD, U.K. Email: chdf@mrc.soton.ac.uk

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