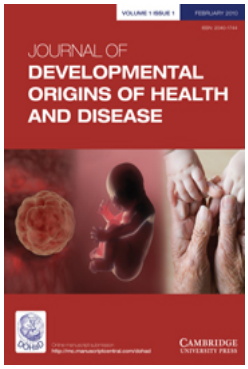

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REVIEW

A conceptual framework for the developmental origins of health and disease

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In the last decades, the developmental origins of health and disease (DOHaD) have emerged as a vigorous field combining experimental, clinical, epidemiological and public health research. Its goal is to understand how events in early life shape later morbidity risk, especially of non-communicable chronic diseases. As these diseases become the major cause of morbidity and mortality worldwide, research arising from DOHaD is likely to gain significance to public health and economic development. But action may be hindered by the lack of a firm mechanistic explanation and of a conceptual basis, especially regarding the evolutionary significance of the DOHaD phenomenon. In this article, we provide a succinct historical review of the research into the relationship between development and later disease, consider the evolutionary and developmental significance and discuss the underlying mechanisms of the DOHaD phenomenon. DOHaD should be viewed as a part of a broader biological mechanism of *plasticity* by which organisms, in response to cues such as nutrition or hormones, adapt their phenotype to environment. These responses may be divided into those for immediate benefit and those aimed at prediction of a future environment: disease occurs in the mismatch between predicted and realized future. The likely mechanisms that enable plasticity involve epigenetic processes, affecting the expression of genes associated with regulatory pathways. There is now evidence that epigenetic marks may be inherited and so contribute to non-genomic heritable disease risk. We end by discussing the global significance of the DOHaD phenomenon and its potential applications for public health purposes.

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Introduction

The idea that disease risk can be passed across generations is not new. Much effort has been devoted to understanding the mechanisms underlying such heritability, yet it success has been limited as the extent of heritability for many complex traits is not clearly known and may have been exaggerated in traditional family based studies (twin and adoption). Genome-wide association studies (GWAS), after several years of intense research, have produced strong associations with certain diseases but nonetheless account for only a small fraction of their occurrence.[1–3] Although polymorphisms associated with particular disease traits or risk factors such as obesity have been discovered, the attributable risk in the general population on a purely fixed genetic basis for such common conditions is very small.[4] To solve the problem of 'missing heritability' several other avenues have been proposed.[5] The first concerns the finding of rare genetic variants with strong effects, not identified in GWAS. This approach is now increasingly possible thanks to the sharp decrease in sequencing cost.[6] The second avenue relates to the effects resulting from copy-number variations (CNVs), which are often not identified in GWAS. Gene-gene interactions (epistasis) offer a further opportunity. Finally, interactions between genes and environment provide a large and promising source of heritability. Within this field, epigenetics, in its narrow sense a study of molecular mechanisms that establish and maintain mitotically stable patterns of gene expression yet do not alter DNA sequence, is a burgeoning field.[7] As we shall show later, it holds a strong promise for elucidating the emergent body of knowledge now known as the developmental origins of health and disease (DOHaD).

The understanding of DOHaD is further enriched by setting it in a broader, biological and evolutionary context. In the second half of the twentieth century, a new set of intellectual and empirical approaches, often abbreviated to evo-devo[8] and eco-devo,[9] appeared, exploring how development and environment interact with evolved mechanisms to drive phenotypic development and evolution. Developmental systems theory was an influential example of the reaction of evolutionary theorists and philosophers to the prevalent genetic determinism with its manifest flaws.[10] It is in this historical context and within this conceptual framework, drawing on fields from epigenetics to evolutionary biology, that we need to understand the phenomenon of DOHaD.

The need for such an understanding is evident at several levels. Firstly, the DOHaD field has been repeatedly charged

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with being merely a collection of phenomenological associations.[11,12] A theoretical and mechanistic explanation of how and why early life events can affect disease vulnerability in later life is, thus, critical. Furthermore, a framework is necessary not only to encompass the proximate causes of the relationships between early life events and later life pathophysiology but also for the ultimate mechanisms, that is their evolutionary significance.

Without such understanding, the overall relevance of the observed phenomena cannot be understood and the question of whether several distinct processes have been lumped into one, under the general term DOHaD, cannot be answered. Such conceptual and mechanistic considerations are essential if the DOHaD field is to receive greater consideration in designing public health preventative approaches. This review, therefore, opens with a brief historical overview, then focuses on conceptual and mechanistic basis of the DOHaD phenomenon and briefly comments on the public health implications.

Development, evolution and biological thought

Development has had a chequered history in medical and biological thought. In the 1800s, embryology was a key biological discipline that, together with comparative anatomy, promised to elucidate both ontogeny as well as phylogeny at a single stroke.[13] Following Jean-Baptiste Lamarck, who argued that organic evolution proceeded by somatic modifications which resulted from the development of particular habits, Etienne Geoffroy St-Hilaire founded the field of teratology which aimed to elucidate evolutionary mechanisms. He saw artificially produced embryonic malformations, 'monsters', as the result of the arrest of development that could provide insight into evolutionary pathways.[14,15] But by the 1880s the increasing lack of consensus among scientists regarding the relative weight of embryological *v.* comparative evidence in understanding the animal form engendered a disciplinary crisis. Embryologists shifted their attention from evolutionary to narrower developmental questions they hoped to address with mechanistic experiments, while the emerging field of genetics replaced embryology as the core of evolutionary studies, and indeed of biology more widely. Genes became seen as the only source of heritable variation and other approaches were increasingly deemed controversial or even unscientific. For instance, using the model of midwife toads, which in normal conditions mate on land, the Viennese biologist Paul Kammerer tested the proposal that acquired characteristics may be inherited by changing environmental conditions.[16] He artificially exposed the toads to dry, heated environment in F_0 generation and showed that the resulting change in reproductive behaviour – mating in water – persisted down to F_6, even when environmental conditions reverted to the original ones. Yet he was accused of fraud and his subsequent suicide in 1926 was understood as an admission of guilt. Only recently his work has been seriously re-examined and the possibility of an epigenetic explanation reconsidered.[17]

The idea that the heritable basis may be changed by the environment acting either directly or indirectly, termed as 'soft inheritance' by Ernst Mayr and associated with Lamarck and Geoffroy St-Hilaire, was further marred by its association with the ideologically charged and scientifically flawed version of Neo-Lamarckism pioneered by Trofim Lysenko and adopted by the Soviet establishment.[18] However teratology gained new importance from the 1930s onwards with investigations into how nutritional factors, X-rays, viruses and then pharmaceutical agents might disrupt development. Yet this discipline has, however, remained focused almost exclusively on disrupted development that is clearly outside the normal range.

Only late in the twentieth century, development began to make a comeback to the forefront of life sciences. At first its return reflected the dominance of genetics, as the emergent discipline of (molecular) developmental biology approached development as a set programme of precisely timed gene expression. The supremacy of genetics was furthermore evident in an increasingly wide search for the genetic basis for disorders presumed to have a heritable basis.

The emergence of the DOHaD concept

Some of the first suggestions, based on epidemiological, clinical and experimental observations, that early life events might have long-term effects on the risks of disease came from European and American researchers working in a novel environment of technological innovation and rapid social change. In the 1930s it was suggested that childhood conditions influenced later mortality.[19] But it was only in the early 1970s that a series of papers by the East German endocrinologist Günter Dörner and his group proposed that the conditions before and soon after birth were related to later risks of arteriosclerosis and obesity, and that gestational diabetes presented a risk for subsequent diabetes mellitus.[20–23] Dörner's work was used in East German public health measures to support longer maternity leave and breastfeeding;[24] indeed discussion on the long-term benefits of breast *v.* bottle feeding, later given great impetus by Lucas[25], has remained an important part of DOHaD research. Conceptually, Dörner also contributed by introducing the term 'programming' (*die Programmierung*) in the sense that it is now, rightly or wrongly, used and he argued for the notion of 'functional teratogenesis' to describe the observed phenomena.[24,26] Along the same lines and at the same time, the diabetologist Norbert Freinkel developed the hypothesis of 'fuel-mediated teratogenesis' to explain how the metabolic state of the mother could influence her offspring as well as intergenerational transmission of risk of diabetes. In his 1980 Banting lecture, he stated that 'developing fetal structures may be exquisitely attuned to fine alterations in maternal fuel economy… It is suggested that concepts of teratogenesis should be expanded to include alterations occurring subsequent to organogenesis during the differentiation and proliferation of fetal cells. Such changes could cause long-range effects upon behavioral,

anthropometric and metabolic functions.'[27] In a series of important studies (e.g. De Prins and Van Assche[28]), Frans Van Assche and his group showed that offspring of rats experimentally growth-restricted by uteroplacental arterial ligation had both insulin resistance and abnormalities of the pancreatic islets. They also showed that experimentally induced diabetes mellitus in the dam could pass risk of metabolic dysfunction to her offspring.[29]

Independently, scientists working with epidemiological and historical demographical data came to similar general conclusions. In 1977, Anders Forsdahl pointed out that there were relationships between the conditions at the beginning of life and the risks of cardiovascular disease in later life.[30] In 1985, Michael Wadsworth reported in a study of the 36-year-old members of the UK national birth cohort that birth weight was related to blood pressure, but did not comment on its significance.[31] In the same year a Finnish study linked poverty in childhood with increased risk of ischemic heart disease, myocardial infarction and coronary death.[32] In 1986, David Barker reported a correlation between the geographical distribution of infant mortality and of later cardiovascular disease in the UK.[33] In 1988, a Swedish group reported that low birth weight was a significant factor in the later risk of hypertension.[34] A contemporary study of Arizona Pima Indians showed that intrauterine environment was an important determinant of the development of diabetes.[35] These observations were soon followed by the much more extensive and multiple studies of Barker's group, which continue to this day, and then by many others.[36] While cardiovascular and metabolic diseases have remained the dominant focus of DOHaD, epidemiological and clinical studies have reported relationships between birth weight and a range of other conditions, such as osteoporosis, mental health disorders including depression and schizophrenia, risks of certain cancers, obstructive lung disease and asthma, as well as cognitive ability.[37–42]

Animal studies have been an important part of DOHaD research from its early days, supporting epidemiological observations and testing hypotheses that for obvious ethical reasons could not be examined in humans; many are reviewed in this article. Caution has to be applied in extrapolating from animal experiments to observations in humans: while the key principles of fetal nutrition and its supply line are closely related in all mammalian species, there are important differences in maternal metabolism, placental structure, relative composition of fetal diets, growth rate, body composition of the offspring, as well as other aspects. The sensitivity and response to nutritional interventions may thus differ.[43] While researchers are aware of the limitations of each animal model,[44] they nevertheless indicate helpful avenues for research.

The theoretical basis of DOHaD

From the earliest days of the field, researchers have suggested theoretical models that explained the DOHaD phenomenon. The accumulation of clinical and experimental data raised new questions, in the first place: 'Why does early life experience become manifest in the modern world as an increased risk of metabolic and other disease?', and then later: 'Why have such prenatal processes been selected during evolution and why do they result in disease in adults?' Most current DOHaD research focuses on what evolutionary biology generally terms as 'proximate' causes, that is physiological mechanisms involved in an observed effect.[45] While such research is essential, a conceptual framework must also encompass 'ultimate' causes, which describe the phenomenon in terms of its evolutionary origin and in particular the fitness benefit which allowed the DOHaD phenomenon to be selected and then to be maintained within a lineage and the processes by which it develops. This section is devoted to the discussion of the latter.

Evolutionary processes revolve around selection for maintaining the reproductive fitness, not the health or lifespan. The human life span is now much longer than 26 years, the estimated mean life expectancy at birth in the Palaeolithic when *Homo sapiens* evolved,[46] although there has always been a significant proportion of the population who lived substantially longer.

In the early 1960s James Neel first suggested that the major changes in lifestyle – including diet, nutrition and exercise expenditure – of the modern world contributed to disease risk because humans exceeded a genetically limited capacity to adapt.[47] He argued that some populations had been selected for 'thrifty genes' to survive periods of famine; such populations were now at risk in a world of abundant nutrition. While the 'thrifty genotype' concept has major limitations and has thus been much criticized,[48] the search for thrifty genes remains a dominant part of the gene-dominated research into the determinants of heart disease and diabetes.

In 1992, David Barker and Nicholas Hales offered a developmental alternative to the thrifty genotype hypothesis, which built on the evolutionary concept of trade-offs.[49] According to their original model, the fetus in difficult circumstances trades-off growth to survive *in utero* but might then suffer later adverse consequences. Developmental trade-offs are common in many species: for example, the spadefoot toad will trade-off growth during development by undergoing early metamorphosis in drought conditions, increasing the chance of reproductive success at the expense of greater risk of predation associated with smaller size.[50] The 'thrifty phenotype' hypothesis of Barker and Hales proposed that the nutritionally deprived fetus limited its growth by developing insulin resistance in order to survive to birth. Whilst this may have conveyed a fitness advantage in a postnatally nutritionally poor environment, it resulted in an increased later disease risk if the nutritional environment became enriched. This model provided an insightful initial non-genetic explanation of the DOHaD concept. Yet the proximate explanation inherent in this model may be inadequate, as subsequent data have suggested that growth-restricted infants do not develop insulin resistance until later after birth and in some animal models of DOHaD insulin resistance is preceded by a period

of greater insulin sensitivity.[51] Furthermore, like many initial conceptual approaches in other domains, the Barker-Hales model had limitations: it placed fetal growth on the causal pathway; it assumed that the change in development was always induced by signals of deprivation; and it assumed a need for a severe insult or stress to the fetus. All of these assumptions have now been shown to be invalid. In particular the focus on low birth weight has been the subject of much criticism and caused much confusion. This has probably slowed research progress, with some researchers arguing that confounding variables had not been adequately taken into account.[12,52] The emphasis on low birth weight has led to a bias towards teratogenic classes of model and experiment. This in turn led sceptics to assume that DOHaD processes contributed little to the risk of developing common non-communicable diseases (NCDs), as the proportion of low birth weight in most populations is relatively small. That the effects occur across the entire normal range of birth size, and are not a function of low birth weight *per se,* was commonly ignored. Finally, the model artificially separated fetal and postnatal cues, and neglected the importance of peri- and even preconceptional periods, now thought to be critical.

A new evolutionary model that took into account these limitations became necessary. Bateson and ourselves addressed the question of ultimate cause by suggesting, independently[53,54] and then collectively,[55] that the embryo, fetus or infant draws information from its environment and adjusts its developmental trajectory accordingly but that, in doing so, it could suffer from longer term consequences. In other words, DOHaD was a manifestation of the normal processes of developmental plasticity. Plasticity provides a developing organism with the capacity to respond to environmental change, which may occur in a regular or an irregular way and on a time scale that may be from one to several generations. This is a time scale that is thus intermediate between selection processes and homeostasis. The evolutionary advantage is obvious: if the environment is unstable, plasticity makes survival more likely by better matching the organism to its environment. We suggested that severe insults which disrupted the developmental programme and caused gross abnormalities should be treated separately from lesser ones, and that the term 'teratogenesis' should be restricted to the former, in contrast to Dörner's and Freinkel's earlier proposals.[56]

We saw heuristic value in identifying two classes of potentially adaptive responses: those where the fetus had to make phenotypic responses for immediate benefit and those where the fetus altered its phenotypic development for potential later fitness advantage. We termed the latter 'predictive adaptive responses'. It is important to note that these definitions reflect ends of a continuum: indeed, it would be expected that immediate responses might also be accompanied by predictive responses although the reverse need not be the case. The latter scenario might, however, reflect the sensitivity with which the phenotype can be characterised. Both classes of responses to cues within the normal range of fetal exposures are part of the processes of developmental plasticity.

Predictive or anticipatory adaptive responses can be made to nutritional or hormonal signals from the mother (*in utero* or during lactation), and they allow the fetus or neonate to anticipate its future and adjusts its trajectory of phenotypic development accordingly.[57] Predictive adaptive responses may occur together or in isolation from immediately adaptive responses depending on the situation, nature and magnitude of the cue. It is important to point out that these are integrated responses affecting multiple components of the phenotype: endocrine and reproductive function, development of adipocytes and myocytes, central nervous system function, endothelial function and intermediary metabolism.[58] These are analogous to polyphenisms in other species (see below) where developmental cues can induce quite distinct phenotypes which affect multiple systems. The only difference is that, whereas polyphenisms refer to apparently very distinct phenotypes, in the phenomena we are considering the phenotypic variation appears to be continuous. But, in fact, in many cases of insect polyphenisms intermediate forms are observed. As we will discuss later, there may be effects in mammals that might be considered polyphenic.

Potentially anticipatory responses are common in many taxa. For example, in polyphenic species, such as the African locust or the plant-hopper, the phenotype induction by early life environmental signals occurs at a time when there can be no immediate advantage.[59] The 'decision' by the locust larva to develop the migratory phenotype, characterized by an omnivorous diet, fat-based metabolism and large wings, is made at a time when it cannot fly and is induced by chemical signals from its parent(s) about population density. As developmental constraints generally limit plasticity in most organs to early life, the fetus, embryo, neonate or larva must take what cues it can and make the best developmental 'choices'. In this way, developmental plasticity fills the gap between evolutionary selection, which operates on a time base of many generations, and homeostasis, which operates on a time base of minutes to days. Indeed, a better description of predictive responses might be to posit that the trajectory of development is altered by the developmental cue with potentially adaptive consequences to the phenotype at different stages in the life course: infant obesity may represent, for example, a predicted need for adipose reserves to buffer the brain against nutritional insults at or after weaning as suggested by Kuzawa,[48] accelerated puberty is an appropriate fitness response to high extrinsic mortality (see below) and reduced muscle, mass and insulin resistance developing in adulthood is indeed an appropriate thrifty response as posited by Barker and Hales.[49]

Plasticity has a high energetic cost and hence in general is limited to an early phase of development because re-engineering the body after the phenotype has been fully developed is costly. Experimental and clinical evidence suggests that the plastic phase in humans extends from conception through the weaning period, which in pre-modern times extended at least for the first 2–3 postnatal years. Because the

windows of plasticity are not the same for different effector components, the timing of experimental insults can be expected to produce differing outcomes. For example, prolonging prenatal undernutrition into the infant period in the rat may modify some aspects of the resulting metabolic phenotype[60] but not obviate the change in tempo of puberty, whereas a different timing of the nutritional challenge affects both.[61]

While many physicians find the concepts of anticipation in developmental biology difficult to grasp, much of biological development is anticipatory (see below). Even bacteria have been reported to show adaptive prediction.[62] A simple human example is the thickened heel pads on the feet of infants at birth – in this case the prediction is reliable and has been assimilated into genomic determinants – there is no evolutionary explanation for these which does not involve an anticipatory component. While this is an example of a developmental process, which is fixed in the genome, it is still a predictive response.

For predictions to be accurate, the environment should remain the same from conception to the adulthood. But environments can change within a life course. However, Jablonka *et al.* have pointed out that the fidelity of the prediction need not be high for it to confer a selective advantage and indeed, as pointed out above, much of the advantage may be in childhood and in the young adult period.[63,64] Jablonka has shown the fitness enhancing advantage of such predictive responses when environments shift on a time-base equivalent from 0.5 to 2 generation times for the species. While these mechanisms evolved in invertebrates and persist in vertebrates, the challenge for the mammalian fetus is that its ability to read the future environment is compounded by the imperfect transduction of environmental information from its mother. The mother may consume a diet or have a workload or social situation unrepresentative of the contemporary environment in general; she may suffer from pathological conditions such as hypertension, gestational diabetes or placental insufficiency. Yet, although mammals may have lower fidelity in their predictive adaptive responses, we would argue that the process evolved and has been sustained because it nonetheless confers sufficient adaptive advantage.[65]

Kuzawa has pointed out there is evolutionary value in having a degree of 'inertia' in the cueing of such anticipatory responses: for a fetus trying to anticipate its likely future environment, cues from the mother which represent aspects of the environment integrated over her lifetime may be a better indicator than short-term environmental signals operating only during development.[66] Thus, maternal body composition at conception appears to be an important cue to the developing embryo.[67,68] The nature of the signalling is unclear, but likely to be reflected in the composition of tubal or uterine fluids. Some nutrient-dependent signalling has a longer time base: for example, the presence of insulin-like growth factor (IGF) binding proteins means that some components of IGF-1 and 2 mediated responses respond to slow, rather than acute, changes in maternal nutrition.[69] Similarly, placental metabolism of hormones such as glucocorticoids provides a buffering mechanism against minor fluctuations in maternal plasma hormone levels.

We have here placed the emphasis on predictive adaptive responses, but there is no sharp distinction between these and the immediate responses mentioned earlier. Similar mechanisms are likely to be involved, albeit to a different degree. Indeed, one would expect that, whenever there is an immediate adaptive response, there will also be induction of responses for later potential advantage. However, in the case of less extreme cues the developmental trajectory may be altered subtly and have no obvious immediate phenotypic effects.

This general model allows for both a high and low nutrition environment as well as for other cues such as stress to affect later outcomes. It allows for effects within the unexceptional and expected range of fetal exposures and so it permits explanation of why the phenomenon has been retained through evolution.

There has been some debate whether immediate adaptive responses are made for maternal or for fetal benefit. Jonathan Wells has argued that maternal survival is the driver of this response: that is, the fetus does not make responses for its advantage but that responses are driven by the maternal needs.[70] This might well be the case in polytocous, frequently reproducing species which manipulate reproductive performance much more than slow monotocous reproducers. But the weight of evidence in humans would suggest that these immediate adaptive responses primarily act for fetal/offspring advantage: by definition, they will thus improve maternal fitness.

There are several lines of evidence against applying Wells' proposition in humans. The first comes from the effects of severe environmental challenges, when maternal preservation, if biologically important to our species, should be most obvious. Unlike some other species, humans do not completely cease reproduction during famine conditions or employ embryonic diapause to match the progression of pregnancy and birth to nutritional environments. Even in extreme nutritional environments fetal development is remarkably normal, as demonstrated by the relatively subtle effects on the birth weights of the offspring of Dutch Winter Famine pregnancies.[71] Further, there are considerable data to show that the maternal condition at the beginning of pregnancy is a major determinant of pregnancy outcomes.[67,72,73] This accords with Kuzawa's proposition that the fetus is able to mount an response to environmental conditions integrated over a longer time-base, in order to forecast the future environment.[66] In humans, lactation is remarkably well sustained in famine conditions too, suggesting that the available energetic supplies are invested to produce viable offspring, who will then have a chance to reproduce themselves. It seems probable that fetal growth retardation in humans generally has an adaptive value for the offspring: as shown by data in both humans and rats, those born smaller have earlier onset of puberty.[61,74] This is perhaps the equivalent of the accelerated tempo of maturation seen in the

spadefoot toad under adverse environmental conditions, suggesting that if the forecast includes the expectation that life may be shorter, accelerated reproductive maturation ensures a chance for gene flow to the next generation. But perhaps the most compelling argument against Wells' concept comes from the (DOHaD) phenomenon in which long-term effects can be shown independently of any obvious fetal responses. For example, vascular structure and function in children is related to maternal diet before and during pregnancy independent of birth weight.[75] There is no evidence in such effects that the fetus was compromised for maternal benefit.

There are generally limits on the environmental conditions, which the fetus can detect and thus predict, partially because there are limits on the nutrient or endocrine signals, which reach it and partially because of our evolutionary history. Species have not evolved with the ability to respond to environments that exceed the experience of their lineage – when they experience such environments, pathological outcomes are likely.[76] In humans, the phenomenon of 'maternal constraint' effectively overrides purely genetic influences on fetal growth. The size of the fetus is limited to match maternal size so that vaginal delivery is possible.[77] Maternal constraint is a continuous process and a manifestation of developmental plasticity. It is present in other mammals, but its role in humans allowed *Homo sapiens* to develop a large brain, delivery being timed to a point when head size was likely to be limiting, with rapid postnatal growth thereafter. But, in addition, it may have conferred a fitness advantage, because it would always limit development to match a poorer postnatal environment than exists, giving a fail-safe phenotype. The selective advantage of such an asymmetrical response has been modelled.[78]

The modern world is very different for much of the world's population from that in which *Homo* spp. evolved, especially in relation to lifestyle, longevity, risk of infectious disease and nutrition.[47,79] Moreover these aspects of the environment can change very rapidly. They have done so within a generation in the developed world, with major changes in the sources of food, with migration, and with socio-economic improvement in the developing world. The likelihood of a mismatch developing between the environment anticipated during development and the actual environment encountered later is thus greater. Human phenotypes are increasingly likely to be mismatched to the contemporary world.

The scope of the general model

Dörner and Freinkel initiated a concept that we now recognize as DOHaD, but a broader recognition emerged with the enormous contribution of Barker, which led to a focus on poor fetal conditions reflecting maternal undernutrition and/or stress and/or disease. While the latter area has dominated in the last two decades of research, there is now a growing interest in the effects of nutrient excess. There are data showing that fetuses exposed to higher cholesterol levels have a higher capacity to cope with a cholesterol load postnatally,[80] perhaps because of predictive changes in their metabolism. Larger human fetuses are also less likely to get metabolic disease for a given body weight that those who are smaller.[81]

Yet since the early work of Dörner and Freinkel, it has become clear that the dramatically increased access to food in recent decades and the linked rise in maternal obesity and diabetes can have consequences for the offspring by creating a second developmental pathway to obesity.[82]

It should be remembered that obese mothers may give birth either to smaller children, as a result of their own pathological conditions, or to children of normal to large birth size who later become obese. The latter outcome may be mediated in a manner similar to gestational diabetes,[83] by inducing fetal hyperinsulinemia and consequent high fat cell number, possibly by exposing the fetus to increased oxidative stress associated with high fatty acid transfer[77,84] or it may involve quite distinct mechanisms. In such studies, the relative effects of pre- *v.* postnatal nutrition cannot easily be separated: both postnatal growth and mode of infant feeding are undoubtedly important factors.[25] Studies of the developmental contribution to later obesity are furthermore complicated by confounders such as parental genomic and psychosocial input. While it was shown that high maternal pre-pregnancy body mass index (BMI) increases the relative risk of offspring obesity,[85] a recent study, which tried to account for genomic influences by using paternal BMI and common genetic variants predisposing to type 2 diabetes mellitus via BMI, showed a relatively weak effect of maternal pregnancy BMI.[86] This effect was thus unlikely to make a major contribution to the offspring obesity but could produce a slow and steady increase in obesity over multiple generations.

Both the ultimate and proximate mechanisms of the effects of maternal obesity are still unclear and this remains an important research question within the DOHaD field. However, recent experimental studies show high fat diets both induce not only obesity in the offspring but also accelerated puberty with sustained ovarian function.[87] We have posited that this may reflect an optimisation strategy whereby the fetus predicts a nutritionally rich environment and can increase its fitness facultatively by extending is postnatal reproduction.[87]

There is no reason why these developmental considerations should be limited to embryonic and fetal life. The infant remains dependent on its mother for nutritional and other cues, and, while there are ultimately temporal limits on plasticity because of energetic costs, the infant can respond to environmental cues in ways similar to the fetus. Allowance must be made for pathway limitations, however, because as development proceeds there are increasing constraints on the degree of plasticity possible. There is an extensive literature on the long-term effects of inadequate or excessive infant nutrition, for example from certain types of formula feeding.[88]

The model can equally be applied to the compelling body of experimental literature relating maternal or infant stress,

glucocorticoid exposure or maternal nursing behaviour to later effects on the offspring.[89] In each case, the adaptive advantage of an appropriate prediction is obvious, and the potential for a maladaptive response, if the later environment does not match the prediction, exists. Other experimental evidence has suggested that exposure to prenatal salt loading[90] or of infants to changed temperatures can induce phenotypic effects.[91] The predictive model can well incorporate such observations.

Interestingly, the phenotypes that emerge from models that manipulate nutrition or stress are remarkably similar.[92] By and large, the prediction of a poor environment leads to obesity as well as altered insulin sensitivity, cardiovascular function, hypothalamic-pituitary-adrenal axis and mood. Over the course of evolution, predation and nutritional stress were probably closely linked, so it is possible that common signalling systems are involved. For example, maternal undernutrition reduces the placental activity of 11 beta-hydroxysteroid dehydrogenase type 2, thus exposing the fetus to higher levels of active glucocorticoids.[93] Most experimental studies, however, have used single exposures to high doses of synthetic glucocorticoids, which cross the placenta. There are, however, a few studies that have investigated chronic stress in the rodent and, while the data suggest phenotypically similar outcomes, the phenotypes are, not surprisingly, more subtle. The data on chronic stress in humans is much more confusing and this reflects the difficulties of extrapolation in this domain from animal models to humans, for example, because a wide range of social and cultural influences can be involved, and 'stress' is harder to define or measure in humans.

The proximate mechanisms

In medicine, phenomenology without consideration of underlying mechanisms is not well received. From the first epidemiological observations in the DOHaD field, the major criticism was that of biological implausibility. How could something acting at the beginning of life have effects, which were delayed until middle and old age? From a medical point of view, without knowledge of an underlying mechanism, developing a plausible way to intervene between early life and later disease risk remains elusive. However, once underlying mechanisms are understood, then biomarkers could be developed to predict risk early in life. This would permit interventions to be better targeted and it would also allow health professionals to get away from the use of proxy measures of development such as birth weight: a baby weighing 3.3 kg may have had an optimal, impaired or excessive trajectory of development. The trajectory it experienced affects how one might assess preventative or intervention strategies.

A growing amount of experimental data suggests that epigenetic processes explain a considerable amount of the DOHaD phenomenon. Work on tissue differentiation arising from the stem cell field clearly shows that epigenetic mechanisms, including DNA methylation and changes in histone structure, are central to cellular differentiation and developmental plasticity.[94] Additionally, epigenetic processes can affect the expression of genes associated with regulatory pathways through life. The specific mechanisms by which cells and tissues sense environmental conditions, inducing epigenetic change, are as yet unknown. Research on rats[95–97] and primates[98] has shown epigenetic changes in genes associated with metabolism and endocrine function in response to maternal nutritional state. Not only the type but also the timing of the challenge seems to play a role too. Feeding a methyl-deficient diet around conception to mature sheep altered the methylation status of 4% of CpG islands in the offspring and resulted in a range of clinical symptoms in their adulthood: increased fatness, lower muscular mass, an altered immune response, insulin resistance and elevated blood pressure. The effect was mostly found in males.[99] Another study showed that late gestational and, especially, periconceptional exposure to famine in humans results in a partially sex-specific alteration of the methylation profiles of loci implicated in growth, metabolic and cardiovascular disease.[100] While DNA methylation is probably the best studied epigenetic mechanism, the importance of non-coding RNAs is rapidly becoming more evident and it seems likely that they are central to developmental and epigenetic processes.[101]

In our studies in rats, we have not only shown that maternal undernutrition leads to permanent changes in expression of several genes associated with metabolic and endocrine regulation in the liver of adult offspring, but that these are underpinned by DNA methylation and histone structure changes in the promoters of these genes. In the low protein model, the phenotype and expression changes are prevented by supplementing the maternal diet with folate, which also reverses the epigenetic change.[95] When leptin is administered to the infant rat, it prevents the development of the metabolic phenotype.[102] This treatment is associated with normalisation of both the expression and methylation changes,[103] as if leptin signals to the infant offspring that they are well-nourished. Leptin in the infant rat can influence the development of the hypothalamus[104,105] and also has some peripheral actions[106] although the mechanistic basis of the neonatal leptin effect remains to be fully elucidated. The recent observations that a leptin antagonist has the opposite effects suggest that this may be a physiologically important process in determining the metabolic phenotype.[107]

The leptin experiment, supported by other observations,[108,109] raises the possibility that epigenetic processes are responsible for the mammalian equivalent of polyphenisms observed in insects. The effects of leptin on subsequent gene expression induced by the prior maternal nutritional exposure were not just quantitatively but directionally different.[103] This suggests that mammals have a range of morphs adapted to nutritional plane. Early life exposures might lead in some individuals to a phenotype better adapted to a higher plane of nutrition, while others may be adapted to a lower plane. It is important to note that such morphs must reflect integrated

phenotypes. A morph anticipating a lower nutritional environment might expect a shorter life and invest less for longevity and more for early reproduction.[58] This would explain a lower nephron and neuronal count in experimental animals subjected to antenatal steroids or maternal undernutrition. In this regard, childhood obesity in those with a poor start to life might reflect a strategy to accelerate weight gain, important for allowing a female to be energetically capable of supporting reproduction at an earlier age.

If the polyphenism concept has validity, then it might explain the varying relationships seen between body fat distribution and insulin resistance in different populations: for example, the 'thin-fat' Indian baby *v.* the Caucasian baby.[110,111] A further piece of empirical evidence is provided from studies of survivors of kwashiorkor and marasmus. After rehabilitation, these have very different capacities to mobilise protein and fat.[112] Within a population in Jamaica, children developing marasmus had lower birth weights than those suffering from kwashiorkor. The collected data are compatible with a model suggesting that marasmic children are better adapted to a lower nutrient environment than kwashiorkor children, adapted to a high nutrient environment.

Most recently, we have shown that the epigenetic profile at birth can predict phenotypic outcomes at 9 years of age and that this is independent of birth weight. Indeed we found that approximately 50% of the variance in body composition at 9 years of age could be explained by the methylation state of specific CpGs on candidate genes.[113] While it is still too early to draw definite conclusions as such associations need to be replicated, our studies suggest that a far greater proportion of individual vulnerability to disease may arise in development than has generally been considered, even by advocates of DOHaD. We have also shown that first-borns have different methylation and expression profiles than subsequent children, supporting the concept of maternal constraint discussed earlier. If these data are confirmed, epigenetic measures will provide a powerful tool for assessing the incidence of altered developmental trajectories in the population.

Finally, the question of heritability of the developmentally induced phenotype remains a pressing, if also controversial and difficult, question. How can environmental influences operating in one generation, especially during development, have biological echoes in subsequent generations? In a year that celebrates both the bicentenary of Charles Darwin's birth, 150 years of *On the origin of species* and the bicentenary of Jean-Baptiste Lamarck's *Philosophie Zoologique*, it is important to note that while the modern synthesis largely ignored the so-called 'soft' inheritance, an authoritative, recent review based on a substantial body of evidence showed that transgenerational epigenetic inheritance may be found across all taxa, and that it affects a range of traits, through several epigenetic mechanisms acting on diverse genetic loci.[114] Physiologists working on mammalian, mostly rat and mouse, models have demonstrated that epigenetic marks can be inherited at least by the F_2 generation.[115,116] In specialised models such as the Agouti mouse, where epigenetic processes are associated with retrotransposon silencing and the offspring develop obesity and other characteristics, the amplification of effect over several generations is prevented by dietary methyl donor supplementation.[117] There is also some evidence to suggest male line transmission which would demonstrate true trans-meiotic passage of epigenetic marks.[118] In line with this, it has been shown that the effects of endocrine disruptors (influencing gonadal development and sex determination when administered early in development), which include an increase in spermatogenic apoptosis and a reduction in sperm motility and number, are mediated by epigenetic processes that persist until at least F_4 and are passed via the male line.[119] The role of non-coding RNAs appears to be central and there is direct experimental evidence of their trans-meiotic transmission.[120] True transgenerational transmission should be demonstrable by effects induced in F_0 persisting to the F_3 generation, but such long-term studies are expensive and not frequently performed. It is clear that the part played by epigenetic processes in transgenerational transmission of disease risk requires much more research.

'Soft' inheritance can also operate indirectly, via re-creation in each generation of the conditions, which generate certain phenotypic effects in offspring. For instance, small mothers might generate small offspring through reduced uterine size in each generation, and through behaviour such as smoking or food preference which has a familial component.[121] The extent to which non-genomic inheritance participates in evolutionary innovation, and the kind of mechanisms that maintain the stability of epigenetic inheritance – leading to genetic assimilation – remain, for the time being, important unresolved issues in evo-devo biology. As they are beyond the scope of this study, the interested reader is referred to other reviews.[114,122]

The global landscape of DOHaD

The demographic pattern of metabolic and cardiovascular disease is rapidly changing: these conditions now affect 1 in 6 adults over the age of 20 years worldwide. Of great concern is the rising risk among young people.[123] By 2015, an estimated 20 million people a year will die from cardiovascular disease, which accounts for over 40% of all deaths.[124] Furthermore, an estimated 300 million people around the world are obese, that is they have a BMI greater than 30 kg/m^2, while 155 million school-age children are overweight or obese. Similar trends are being seen in other NCDs, in osteoporosis, atopic diseases, some forms of cancer and cognitive function.

It is of considerable geopolitical importance to note that the epidemic of chronic disease will by 2020 disproportionately occur in countries such as China and India. For both populations, the risk of metabolic and cardiovascular disease occurs at, by Western standards, relatively low waist-hip ratios[110,125] and Indians have relative visceral

adiposity even at birth.[111] We suspect that the high rate of metabolic disease in these two countries has a developmental component, although genetic contributions may also exist. Birth weights are low, mothers are generally of small stature, and the nutritional transition has been rapid. In these populations, we are also seeing the evidence of intergenerational passage of risk.[126] Thus in the first generation mothers are stunted, their offspring are small and at risk of developing obesity through the mismatch pathway. In time, these girls themselves may develop gestational diabetes, switching the pathway in the third generation to a hyperinsulinemic route to obesity.[127] In parts of Asia, the incidence of gestational diabetes is now 10% or greater.[128,129] At one time and within one population, four intergenerational cycles may be observed: the cycle of stunted, deprived, disempowered women giving birth to stunted children; then the transition through the mismatch pathway to metabolic disease after a degree of socio-economic development; this is followed by two new emergent cycles of women suffering from gestational diabetes giving birth to children who grow up with a higher risk of diabetes and obese mothers giving birth to children who similarly become obese. With projections for the prevalence of chronic disease in Asia painting a black picture,[124] which could have geopolitical ramifications, developmental science is important on a global scale.

This review has not considered many other aspects of the developmental pathways to health and disease; for example, it is clear that a particularly poor start to life is associated with a greater risk of stunting, of cognitive impairment and shorter life. The latter is not limited to increased infant mortality. For example, in The Gambia, the season of birth influences birth weight and longevity, but the differential effect is not manifest until the young adult years.[130] The earlier discussion of trade-offs and predictive adaptive responses explains such an observation. It serves to highlight our view that, while the focus of human evo-devo research has been on metabolic disease, as epigenetic tools develop and provide a new approach to epidemiological research, we will find that developmental processes play a much larger part in determining the human condition than is generally accepted.

The implications of this framework

The classification of some diseases as being of developmental origin introduces a new model of disease causation into medicine. In the nineteenth century, modern medicine emerged around the pathological–anatomical model, in which the cause of disease was perceived as a localised lesion. This model fitted well the views of disease derived from bacteriology (and infectious diseases more generally) and genetics. Indeed, the control of infectious diseases and the elucidation of the genetic causes of some diseases have been success stories of modern medicine. Yet this model has not managed to explain the causation of NCD. Fixed genetic variation is now known to account for only a small part of the attributable risk of NCDs such as coronary heart disease, hypertension or type 2 diabetes.[1,2] It is now clear that the risk of NCD involves interactions between inheritance, both genomic and otherwise, development and environment.

The concept that perinatal medicine might be the appropriate place to intervene to prevent adult disease inevitably invokes a reaction. When one adds that children do not vote or pay taxes and that the interval between an intervention and any beneficial outcome may take decades, then the political inertia is not surprising. Even the cost-benefit argument for such interventions is not easy to make, because the appropriate economic modelling has not been done. Economic models traditionally discount benefits far into the future and the pressing demands for cutting healthcare expenditure in increasingly ageing populations are hard to counter. But there are signs of change.[131] An initial economic model has been published[132] and there is now a major international project addressing this perspective.[133]

Governments are now beginning to understand the importance of development to human health and patterns of disease. The social inequalities in health commence during development. The recent report of the UK Government Office for Science Foresight Group[134] concluded that it is important to 'promote/implement a programme of early interventions at birth or in infancy' and that 'intervention in early life generated the highest average impact across all scenarios. It was in these scenarios where it was possible to implement and sustain a life course approach to prevention but also where society was prepared to measure success over longer time frames'. The message is slowly being understood that, for diseases with a developmental origin, the screening and the intervention need to take place during development itself. If not, the intervention may come too late for the affected individuals, and indeed for the next generation. A recent consensus report pointed out that development is a critical context to take into account and that a global standard for development is not realistic, rather each child's development needs to be assessed within the context of his or her own maternal and population environment: a 'one size fits all' programme will not reduce disease risk in many individuals, and may even exacerbate it in others.[131]

In 2009, the optimal way to promote a healthy life from conception to adulthood in different contexts is still not known. Yet the life course approach is an important and novel concept.[131] If epigenetic biomarkers at or soon after birth do prove to be good indicators of the developmental trajectory and of subsequent risk of disease, then we will be able to use them to identify optimal strategies for supporting health before and during pregnancy. This approach will lead to a better identification of vulnerable individuals and groups on one hand, and an improved assessment of information for planning economically modelled interventions. It will also provide the tools and arguments that will show persuasively that the best time in the life course to intervene for long-term advantage is at the very start.

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Statement of Interest

None.

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