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Towards a New Developmental Synthesis: Adaptive Developmental Plasticity and Human Disease

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Viewpoint

Towards a new developmental synthesis: adaptive developmental plasticity and human disease

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The Lancet has rightly given attention to the goals of reducing the burden of maternal and childhood undernutrition,¹ focussing primarily on short-term outcomes such as infant survival and stunting.² However the longer-term effects on adult health of a poor start to life³ suggest a further perspective. Developmental effects have been traditionally viewed in the context of teratogens, prematurity and growth retardation. However, developmental plasticity operates across the entire environmental range, from undernutrition to the excessive nutritional environments associated with gestational diabetes or maternal obesity,^{4,5} leading to multigenerational cycles of disease.⁶ The design of intervention strategies needs to take account of these complexities.

Realising the potential for health improvement across the life-course requires integrating knowledge from several disciplines. Sponsored by the Rockefeller Foundation, an interdisciplinary meeting, representing clinicians and public health specialists from both higher and lower income countries, developmental and evolutionary biologists, geneticists, anthropologists and economists was held in December 2006. Our starting point was the question: how might adopting a developmental perspective on the human life-course inform efforts to reduce the burden of non-communicable disease, particularly for populations in rapid nutritional transition? This paper summarises the conclusions from the ensuing dialogue.

Individual variation in risk of chronic disease

Humans now live in evolutionarily novel environments, and mismatch between our evolved physiological capabilities and contemporary exposures may lead to ill-health.^{7,8} This is particularly relevant to food preferences and consumption and to energy expenditure, which have changed greatly over several decades in affluent societies and more recently in lower income countries undergoing socioeconomic improvement. Substantial variations in disease risk exist between individuals, even in the same environment,⁹ as well as between populations.¹⁰ This may have a genetic component,^{11,12} but experimental work in the 1970s, followed by retrospective epidemiological cohort studies, has revealed additional non-genetic developmental contributions to risk of later disease. Whilst caution must be exercised in extrapolating from historical cohorts to current conditions, a wide variety of experimental, clinical and prospective epidemiological studies show that changes in maternal or infant nutrition can produce heritable effects on risk of chronic disease.¹³

Timescales of responses to environmental change

Organisms respond to challenges over a range of timescales (Figure 1). At one extreme, rapid and reversible homeostatic mechanisms counter an immediate challenge. Then, stressors or exposures during critical developmental periods can affect growth, tissue differentiation and physiological set-points, influencing responses to environmental challenges for life. Such adaptive plasticity, mediated in part by epigenetic processes,^{14,15} gives advantage in environments which change over several generations. The fidelity of cues inducing adaptive plasticity might be enhanced by integrating the experience of recent generations, and new evidence suggests that epigenetic mechanisms may contribute to such non-genomic transgenerational inheritance.^{16,17} On a longer timescale, the genomes of populations can change over many generations as the result of selection or drift, and increasingly there are examples of responses to environmental change being integrated into the human genome.^{18,19} Clinical medicine and public health have focused largely on causation and intervention at the short-term end of this spectrum. It is now important to consider the consequences of developmental plasticity acting over the intermediate timescale.²⁰

Developmental processes and longer-term outcomes

Developmental plasticity evolved because it is adaptive, promoting Darwinian fitness by enhancing survival and reproductive success.²¹ Plasticity uses environmental cues, which in mammals are transduced and buffered by the mother, to optimise the life-course strategy for maximal fitness, both making the best of present conditions and being well prepared for the future environment.²² The hormones and nutrients crossing the placenta can be affected by the mother's body composition, metabolism and longer-term lifestyle as well as by her immediate diet and stress levels. Thus, environmental cues affecting development provide historical information which offspring use to predict the future.²³

However, there are limitations to this anticipatory strategy, especially for long-lived species such as humans, with the result that challenges during development can induce responses which have short-term benefits for the mother or the fetus but then longer-term costs in terms of *reduced* fitness.^{24,25} When environmental conditions change markedly between conception and adulthood, as has happened in most present human populations, the potential for a substantial mismatch is especially great and this contributes to disease risk. Shift in environmental conditions between generations may also exceed the evolved capacity for

intergenerational transmission of information. Because in developed societies we now live on average twice as long as did our Palaeolithic ancestors, the detrimental effects of inaccurate predictions are more likely to be apparent.

Fitness versus health

Developmental plasticity evolved to maximize an organism's Darwinian fitness, not necessarily its health, and life-course strategies operate to ensure survival to reproduce rather than longevity. Anthropological and clinical data support this concept. Women throughout hunter-gatherer societies show an inverse relationship between age at menarche and anticipated life span,²⁶ and in high-income countries, lower birthweight individuals have earlier menarche, an effect exaggerated by prepubertal weight gain.²⁷ Although being a small (but healthy) individual may not be a 'disease' outcome, it incurs costs, in lower reproductive fitness, earnings or social status²⁸, costs which may be – biologically if not ethically – viewed as trade-offs for gains in survival through better match of metabolic requirements to energy availability.

Manipulation of developmental cues might be used to shift the adaptive capacity of the organism to cope in a later environment. This is possible experimentally (for example, metabolic disease induced by prenatal undernutrition can be prevented by postnatal hormonal manipulation²⁹), but it would be premature to recommend prenatal diets with a view to promoting human offspring health. The impact of multiple micronutrients on fetal growth³⁰ and birth outcomes³¹ suggests that factors other than energy and protein intake in pregnancy may be important. Postnatal plasticity may explain the long-term differences in outcome – metabolic and cognitive – for infants fed by breast versus formula.^{32,33}

Implications for human health and wellbeing

An improved understanding of adaptive developmental plasticity has three important implications for public health. First, interventions to improve adult health may need to start early in life and to take a cross-generational perspective, challenging though this is to policymakers and funders. Interventions starting in adult life need to take account of developmental history – for example, attempts to change health behaviours in adults may be less effective in populations which have, through adaptive responses to past environments of food insecurity, developed tendencies to excessive fat storage. Secondly, it must be

recognized that interventions in early life aimed at essential short-term gain, such as infant survival, may also have longer term effects on individuals throughout their life course, and that such effects may not always be beneficial. Programmes aimed at increasing birth weight may increase the risk of later diabetes, amplified by accelerated fat gain in childhood, a possible consequence of universal supplementation programmes.³⁴ Thirdly, recent drives to develop one uniform standard for human growth³⁵ assume that optimal health across the life course will be achieved through comparable growth in a variety of settings, irrespective of factors such as maternal diet, body composition or physical activity. The best outcome measure for postnatal growth remains uncertain – Black et al³⁶ in the recent *Lancet* series proposed stunting (height-for-age) as a better indicator of undernutrition than underweight (weight-for-age) but in turn this assumes that the only outcome associated with inappropriate undernutrition is that of impaired growth. The design of interventions to promote growth demands consideration of the variance of risk of later disease across the whole distribution of growth and size, not only that associated with shifting the population mean in what appears to be a healthy direction in the short term.³⁷

Approaches to interventions for improving maternal and child health have focused largely on issues of survival, in consonance with the Millennium Development Goals for reducing maternal and child mortality substantially by the year 2015.³⁸ Focusing on early survival, and on current differentials due to poverty³⁹ and social inequalities,⁴⁰ may not capture outcomes that have longer term implications for adult health, life expectancy, quality of life, and accumulation of human capital. Further, recommendations for nutritional interventions are frequently based on improving birth weight, focusing on gains in stature or micronutrient status in the short term.⁴¹ Where longer-term follow-up data are available they confirm the existence of a window of opportunity for intervention in early childhood, under 24 months of age, and only limited benefit, or even harm, of feeding strategies thereafter.^{3,42}

Health is often not included in calculations of human capital other than in terms of health expenditure, although a healthier population is an economically more productive population. Estimates of the true accumulation of human capital embodied in an individual should include more than the conventional economic measure of educational attainment: ideally it should incorporate the impact of events from conception or earlier, perhaps even extending to measures of intergenerational accrual of biological benefit.

Robust measures of economic benefit are required to persuade policymakers of the wisdom of investing in a life-course approach to health, and we arrived at two specific recommendations.

First, the use of linear discount rates in assessing benefit disadvantages early life interventions⁴³ and has limitations when considering intergenerational equity.⁴⁴ Secondly, while utility-based measures of disease burden such as DALYs allow comparison of intervention programmes,² they fail to capture intergenerational benefit or the monetary value of the ensuing savings in healthcare or increases in labour productivity. More sophisticated composite measures of outcome are required to demonstrate the true cost-benefit ratio of early life interventions.

The increasing prevalence of metabolic disease worldwide, with its enormous current and projected costs, challenges a wide range of disciplines to provide an explanation of the underlying human biology and to define the optimal ways to intervene (Table 1). Merely focusing on genetic predisposition or improving adult lifestyle is inadequate. Disease risk from mismatch is exacerbated by a relatively small change in nutritional conditions in societies starting from a low baseline level, and the resulting increased susceptibility to obesity and gestational diabetes passes risk on to the next generation. Because early growth and development is a time in human life when substantial biological stock is transferred to future generations,^{3,45} ignoring the processes by which this occurs risks erosion of future human capital in both health and economic terms. As developmental plasticity results in variation in human phenotype and life-course strategy, adopting a ‘one size fits all’ approach to intervention will fail in efficacy for a percentage of the population, and may put some individuals at greater risk of later poor health.

Author contribution statement

All authors participated in the workshop in Bellagio, Italy, in December 2006 entitled “Towards a Developmental Synthesis: Developmental Plasticity, Ecological Developmental Biology and Human Health”, contributed to subsequent discussions, and have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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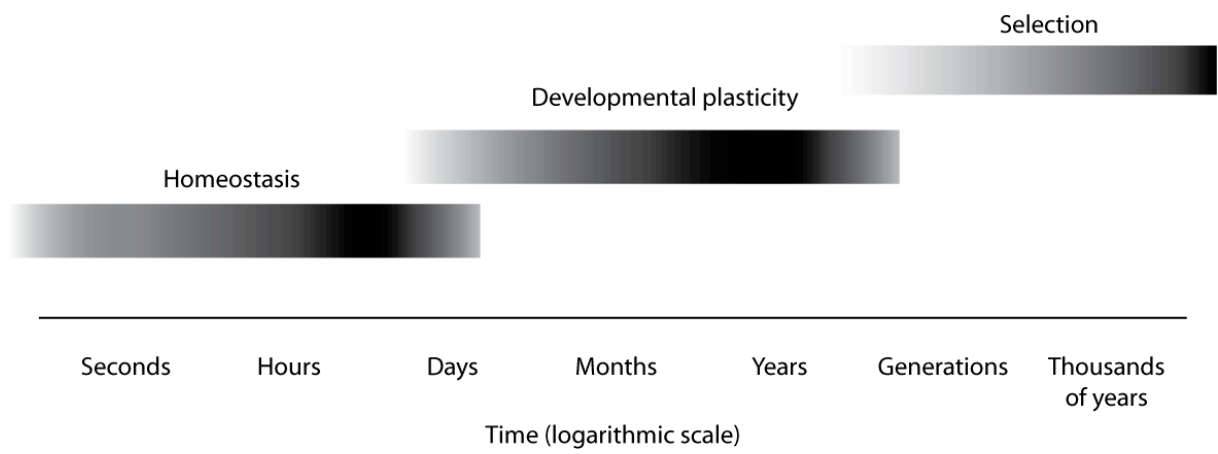


Figure 1. Modes of human adaptability

Table 1. Adaptive plasticity and human health: research agenda

Basic research

- What are the mechanisms by which early life events have long-term effects, and can the pathway be altered or reversed?
- What is optimal fetal development – how can it be defined in relation to later risk?
- What are the indicators of optimal pregnancy outcome – e.g. birth size, duration of pregnancy – and what levels of risk do they constitute?
- To what extent could markers of specific nutrient status prior to or during pregnancy inform about the likely outcomes of the pregnancy?
- To what extent could postnatal epigenetic markers inform about the likely life course of the offspring?
- What are the postnatal windows of plasticity and therefore intervention?
- What is the extent and mechanism of intergenerational transmission of disease risk?

Operational research

- What is the significance of developmental processes in generating the burden of disease in different populations?
- What approaches are possible to intervene in individuals and in populations during different stages of the life course (preconception, pregnancy, lactation, childhood, adult, parent)?
- How can developmental interventions be made context-specific, balancing prevention of undernutrition against the later-life consequences of rapid postnatal weight gain?
- What level of developmental risk of later chronic disease is acceptable?
- How can the various levels of intervention (societal to individual) be designed appropriately within the cultural context?
- What are the societal costs of less than optimal development, measured with more appropriate models than simple discounting?
- What are the short-term and long-term economic benefits of optimizing early-life development?
- What is the cost-benefit ratio of early intervention?
- Which interventions are most likely to be cost effective?

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