Developmental plasticity and human health

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Many plants and animals are capable of developing in a variety of ways, forming characteristics that are well adapted to the environments in which they are likely to live. In adverse circumstances, for example, small size and slow metabolism can facilitate survival, whereas larger size and more rapid metabolism have advantages for reproductive success when resources are more abundant. Often these characteristics are induced in early life or are even set by cues to which their parents or grandparents were exposed. Individuals developmentally adapted to one environment may, however, be at risk when exposed to another when they are older. The biological evidence may be relevant to the understanding of human development and susceptibility to disease. As the nutritional state of many human mothers has improved around the world, the characteristics of their offspring—such as body size and metabolism—have also changed. Responsiveness to their mothers' condition before birth may generally prepare individuals so that they are best suited to the environment forecast by cues available in early life. Paradoxically, however, rapid improvements in nutrition and other environmental conditions may have damaging effects on the health of those people whose parents and grandparents lived in impoverished conditions. A fuller understanding of patterns of human plasticity in response to early nutrition and other environmental factors will have implications for the administration of public health.

Adaptive responses

Striking evidence from a number of disciplines has focused attention on the interplay between the developing organism and the circumstances in which it finds itself[1,2,3]. Fields of research as diverse as evolutionary ecology, behavioural development, life-history theory, molecular biology and medical epidemiology have converged on the key finding that a given genotype can give rise to different phenotypes, depending on environmental conditions[4]. Many organisms can express specific adaptive responses to their environments. Such responses can include immediate, short-term changes in physiology and behaviour. However, responses to the environment may be expressed in the offspring rather than in the parent.

The freshwater crustacean *Daphnia* yields a classic example: offspring whose mother has been exposed to the chemical traces of a predator are born with a defensive 'helmet' that protects them against the predator. This structure can, however, be a liability in a predator-free environment, where its construction cost reduces competitive success relative to non-helmeted individuals[5]. Such phenotypic mismatches between the offspring's phenotype and its current environment can be costly in terms of both survival and reproductive success. The desert locust (*Schistocerca gregaria*) provides another well-known example of developmental plasticity. Under low density conditions, the locust is cryptic, shy, nocturnal and sedentary. Under crowded conditions, the individuals become increasingly conspicuous, gregarious and diurnal over several generations and then migrate in enormous swarms[6]. Both of these examples demonstrate how the impact of the environment experienced by one generation can shape the development and behaviour of the next.

Not all of the effects of the environment are adaptive. Variation within a species may be affected by temperature, acidity, nutrient and water availability, population density, the presence of pathogens or predators, and exposure to toxins. Different phenotypes may reflect inevitable physical or chemical constraints. For example, reduced metabolic rates caused by low temperature will influence growth rate and body size. Environmental events may disrupt developmental processes, leading to abnormalities. If conditions for development are not optimal, the individual may still be able to cope, but at a cost to its future reproductive success[7]. The mature phenotype is different from one expressed under optimal conditions and is not as well adapted to adult life as it could have been. Such cases are clearly distinguishable from those where the expressed phenotype is better adapted to local conditions than alternatives[8,9]. Many organisms have evolved to express specific adaptive responses to their environments. Such responses can include short-term changes in physiology and behaviour, as well as long-term adjustments to conditions predicted by the state of the environment when the organism is in its early stages of growth. In mice (*Mus musculus*), food restriction can slow ageing by enhancing cellular maintenance and repair processes, while reducing or shutting down fertility[10,11].

The varied developmental pathways triggered by environmental events may be induced during sensitive, often brief, periods in development. Outside these sensitive periods an environmental influence that sets the characteristics of an individual may have little or no effect[12]. The reasons for plasticity being restricted to a particular period of life may be the difficulties of reversing developmental processes or the costs in terms of survival or reproductive success of changing the characteristics of the adult organism[13].

As in *Daphnia*, parents of other species can make adjustments that tailor the phenotypic development of their offspring to match

prevailing environmental circumstances. Female birds, for example, are able to alter many aspects of egg composition, including nutrients, hormones, antioxidants, immunoglobulins, and even embryo sex, in response to food availability, levels of sibling competition and the quality of their mates[14]. Such maternal effects can result in the influence of a particular environmental factor on phenotypic development persisting across a number of generations, even if the factor itself has altered[14,15]. In a number of vertebrates, environmental factors experienced by females during early development affect the growth and breeding success of their offspring. Mammalian mothers that themselves experience poor nutrition as a fetus often produce relatively light offspring during their breeding lifespan. For example, the daughters of food-restricted hamsters (*Mesocricetus auratus*), themselves reared with food freely available, produce smaller litters and relatively fewer sons than the daughters of control females that were not food-restricted[16].

If the effects of past conditions produce mismatches with current, changed conditions, developmental plasticity may have an adverse effect on survival and reproductive success. Extensive theory has been developed to explain why developmental plasticity should be advantageous to particular plants and animals and not to others. Relevant factors include the variability of the environment, the presence of reliable environmental cues to produce an adaptive response and the rate of environmental change relative to the length of the life cycle of the species in question[8,17,18,19].

Triggers for human development

These broad considerations from many fields of biology are relevant to understanding of some critical variation in humans[13,20]. The human baby responds to undernutrition, placental dysfunction and other adverse influences by changing the trajectory of his or her development and slowing growth. Although the fetus was thought to be well-buffered against fluctuations in its mother's condition, a growing body of evidence suggests that the morphology and physiology of the human baby is affected by the nutritional state of the mother[21,22]. It is possible, therefore, that human development may involve induction of particular patterns of development by cues that prepare the developing individual for the type of environment in which he or she is likely to live. Individuals may be affected adversely if the environmental prediction provided by the mother and the conditions of early infancy prove to be incorrect[13]. Indeed, people whose birth weights were towards the lower end of the normal range and who subsequently grow up in affluent environments are at increased risk of developing coronary heart disease, type 2 diabetes and hypertension[21,23,24]. Those born as heavier babies and brought up in affluent environments enjoy a much reduced risk. The long-term influences may arise from cues acting from before conception to infancy[25]. The ill effects of being small, which in the short term include high death rates and childhood illness, are usually treated as yet another inevitable consequence of adversity. However, a functional and evolutionary approach derived from the rest of biology suggests that the pregnant woman in poor nutritional condition may unwittingly signal to her unborn baby that it is about to enter a harsh world. If so, this 'weather forecast' from the mother's body may result in her baby being born with characteristics, such as a small body and a modified metabolism, that help it to cope with a shortage of food. When sufficiently high levels of nutrition are available after the development of a small phenotype has been initiated, marginal benefits of rapid growth may offset the costs[26], but they may also trigger the health problems arising in later life.

Although adaptive responses may explain some variation in human development, it would be implausible to argue that all responses to the environment should be explained in these terms. Undernutrition, stress or hypoxia may impair normal development. Babies with low birth weight have a reduced functional capacity and fewer cells[27]. The latter may be part of a general reduction in cell numbers or a selective trade-off in the development of tissues that are less important to the baby, such as the kidney[28]. Reduced numbers of nephrons at birth is a life-long deficit, as all nephrons are formed during a sensitive period of development in late gestation. The resulting increased functional demand on each individual nephron, for example by increased blood flow through each nephron, may lead to acceleration of the nephron death that accompanies normal ageing, with a consequent rise in blood pressure[29,30].

The diversity in past and present ecological conditions of humans is also likely to introduce complexity into the relationship between developmental prediction and later health outcome. For example, some populations may have adapted genetically to conditions of nutritional stress, especially seasonal food shortages, over a long time span, while others will have been buffered from such local evolutionary effects. The sharp increase in glucose intolerance leading to type 2 diabetes might arise from genetic differences between populations[31,32]. The possibility of a thrifty genotype well adapted to harsh conditions is not incompatible with the plastic induction of thrifty phenotypes from a pool of uniform genotypes. However, the hypothesis that differences in susceptibility to diabetes are explained by genetic differences would not readily account for the evidence from the Dutch famine of 1944–45 that glucose intolerance is induced by maternal malnutrition during the final three months of pregnancy[33].

People who had low birth weight are resistant to the effects of insulin in moving glucose out of the blood stream into the tissues. This resistance may be adaptive for a baby receiving inadequate amounts of glucose—a way of protecting the glucose supply to the brain. However, persisting into adult life, insulin resistance leads to increasing blood glucose and type 2 diabetes develops, especially in people who have become overweight. 'Thrifty' handling of sugar becomes maladaptive if undernutrition in the womb is followed by excess in later life[34]. Conversely, individuals with large bodies may be particularly at risk in harsh environments such as prison camps or during famines[13]. Especially striking is the evidence from a famine-exposed Ethiopian population, where the incidence of rickets was nine times greater in children who had been reported as having high birth weights than in age-matched control children[35]. No such differences were found in children with normal birth weights.

The general hypothesis is expressed in Fig. 1. The adult health and likelihood of survival of two groups of individuals with extreme phenotypes are given for a variety of nutritional environments. For individuals whose early environment has predicted a high level of

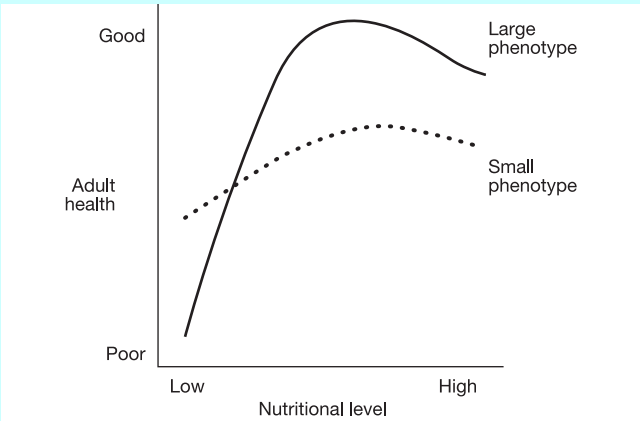

Figure 1 The hypothetical relationship between adult health and nutritional level during later development for two extreme human phenotypes that were initiated by cues received by the fetus.

nutrition in adult life and who consequently develop a large phenotype, the better the conditions, the better will be their health except perhaps at very high levels of nutrition[10]. For individuals whose conditions in fetal life predicted poor adult nutrition and who develop a small phenotype, the expected outcome is less clear. In very poor conditions they are expected to be healthier than those with large phenotypes. It seems plausible that their health would be benefited by some improvements in their nutritional environment in later life, but these improvements would diminish with further increases in the nutritional environment. Whether such individuals would be worse off in absolute terms than in a low nutritional environment, and the slope of the graph eventually becomes negative, is difficult to assess, but relative to the large phenotype individuals they are expected to be much less healthy.

Implications for public health

If the arguments developed here are correct, a critical public health issue is what help can be given to individuals whose characteristics were set early in life to an environment that subsequently changed. The environmental cues that trigger particular phenotypes in humans are mostly undiscovered. Nevertheless, some promising animal models have been developed, which may yield understanding of the underlying mechanisms[36,37]. Maternal exposure to glucocorticoids in pregnancy induces hypertension and/or evidence of insulin resistance, obesity and altered muscle mass as well as alterations in the hypothalamic–pituitary–adrenal axis in the adult progeny of several experimental species. When pregnant rats are given restricted diets, their offspring are smaller at birth; but when the offspring are subsequently given plenty of food they become more obese than the offspring of mothers given an unrestricted diet[38,39]; moreover, for mice that were malnourished *in utero*, the richer the post-natal diet, the shorter is the lifespan[40]. Using animals, long-term maternal effects can be assessed in experiments that tease apart the direct genetic effects and those of the environments experienced by parents and offspring. The observed links between maternal birth weight and offspring birth weight could be due to similarity in genes, to similarity in rearing conditions imposed on both generations, or to maternal effects: poor nutrition during her own early development may reduce the capacity of a female to assimilate nutrients, and so resulting in an impaired ability to provision her offspring. Cross-fostering coupled with environmental manipulations can disentangle such effects.

The general point made here is that humans, like a great many other organisms, are capable of developing in different ways; in stable conditions, their characteristics are often well adapted to the environmental conditions in which they find themselves. An understanding of the underlying biological mechanisms (and their possible adaptive origins) should accelerate the development of appropriate interventions that promote health during childhood without compromising it later in life. □

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