Developmental origins of health and disease: concepts, caveats, and consequences for public health nutrition

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The purpose of this article is to define the concept of developmental origins of health and disease (DOHaD) as an emerging paradigm for relating evolutionary biology to contemporary health issues. As illustrated, several paradoxes emerge related to adaptations initiated in utero and in early life. Epigenetics is a concept that must be incorporated in order to understand plasticity adaptations, such as programming. The public health consequence of DOHaD challenges the one-size-fits-all norm and shows the need for prescreening prior to some interventions and for the eventuality of individualized, rather than collectively applied, preventive or remedial measures as the safest option.

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INTRODUCTION

Public Health Nutrition (PHN) has a number of dimensions. It is the subject of an international congress held in Barcelona in September of 2006, the title of a successful scholarly journal sponsored by the Nutrition Society,1 and the name of an academic graduate-degree major in universities in Europe and Australia. It embodies the study of nutrition at the population and community level to inform the practice of improving the diet and nutritional health of the populace.2 PHN has evolved from a series of antecedent nutritional disciplines. Early in the new millennium we find theory and technology advancing at an unprecedented velocity, with demographic and epidemiologic patterns changing rapidly as well.

The title of this treatise incorporates the word “paradigm”, which is defined as “the generally accepted perspective of a discipline at a given time”.3 From the middle of the 20th century, malnutrition has meant undernutrition when it came to the connotation for problematic nutrition. One of the evolving epidemiological patterns of our changing time is the emergence of overweight and obesity along with their associated metabolic disorders and chronic diseases.4

A new message, which has thus far escaped the nutrition community as a whole, and the PHN community in particular, is that of the important dependence of long-term health on early-life nutrition. The paradigm is derived from the works of Prof. David Barker5 and has various denotations; here, the term “developmental origins of health and disease (DOHaD)” shall be used, and the concept, caveats, and consequences of DOHaD for the science and practice of the PHN community shall be highlighted.

UNLEARNING LONG-HELD ATTITUDES IN NUTRITIONAL SCIENCE

The 20th century was the golden age for nutrition, a period in which scientific discovery flourished. By the time PHN coalesced as a discipline unto itself, it included multiple threads interwoven from other aspects of nutrition. The present century brings advances in biomedical and food technologies, opening the way for crafted, prescriptive interventions. There is peril, however, in adopting the last century’s lessons in too literal a manner when the science is applied to populations and put into practice in PHN. The field of clinical nutrition arose in the context of

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secondary nutrient deficiencies associated with severe acute and chronic diseases; the degree and context of nutrient deficiency varies widely among free-living populations. Nutritional biochemistry unravels the chemical nature of specific nutrients and bioactive substances and their metabolic pathways; the original and natural sources of the chemical array of nutrition are the foods and beverages in the diet. Experimental nutrition employs littermates from inbred, genetically customized varieties of domesticated small animals; the experimental outcomes show little variation. Not surprisingly, such outcomes often lead to one-size-fits-all solutions. Among wild-type, outbred species, such as heterogeneous human populations, however, the true genetic and life-experience variance among individuals is broad. The poultry and livestock industries worked under economic pressure to achieve the greatest weight-gain over the shortest time using the least expensive fodder; “fattening on the cheap” might be a way to encapsulate their mission. Any uninformed cross-pollination from the tenets of the companion disciplines would tend to bring to the public health scenario the use of supplements and fortificants, in maximal uniform doses, in support of a premise that “larger is healthier.” Thus, PHN cannot afford to adopt as its own the philosophical legacies from the rest of the nutrition community.

**EVOLUTION AND ADAPTATION**

The aforementioned achievements of nutritional science have at times led to a sense of prescriptive omniscience, lacking the appropriate humility and balance. We allowed ourselves to be informed by the concepts and theories of evolutionary biology; evolution was the basis of human survival, both individual and collective, and it involved genetic and epigenetic adaptation. On the collective side, a species undergoes selection of genetic constitutions better adapted to the demands of its environment. The consequence of selection is the evolutionary imperative: Not all those born are destined to survive and reproduce. This natural selection is based on genetic mutations and the reshaping of the collective genotype (Table 1).

Two additional mechanisms come into play in adaptation for individual survival over the short term: accommodation and plasticity. Accommodation is a temporary and reversible alteration in tissue composition or metabolism, as exemplified in Table 1. Plasticity is an irreversible, lifelong structural or functional adaptation, with examples provided in Table 1. Genetic mutation, accommodation, and plasticity have all operated in concert over millennia to assure that there were sufficient numbers of humans to reproduce and conserve the *Homo sapiens* species.

### Table 1 Primer on “adaptation” in evolutionary biology.

<table>
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<th>Adaptive process</th>
<th>Examples</th>
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| **Accommodation:** Accommodation is a process of somatic change of an acquired and reversible nature that allows the organism to be more comfortable, functional, and successful through a change of environmental or ambient conditions. There is a regression to the basal state when the initial conditions return. | 1. Sun-tanning and increasing melanin pigment production in response to increased summertime solar exposure.  
2. Increased red cell production and more concentrated cell volume on emigrating from sea-level to high altitude. |
| **Plasticity:** Plasticity is a process of somatic change of an acquired, but irreversible, nature that allows the organism to be more comfortable, functional, and successful through an extreme of environmental or ambient conditions. These changes are permanent throughout the life of the individual, but not hereditable to offspring. | 1. The development of increased thoracic volume (“barrel chest”) for those born at altitude to provide for greater gas exchange and oxygen capture in a low-oxygen environment.  
2. Similar increase in pulmonary volume and efficiency among island oyster-harvesting (pearl diver) populations.  
| **Genetic adaptation:** This is the classic Darwinian concept of differential participation in reproduction due to improved survival to reproductive age, increased access to the opposite sex, and/or increased fertility or fecundity for those with a specific genetic constitution that favors it. Hence, the beneficial genetic polymorphism increases in frequency in the population | 1. Dominance of the lactase persistence allelic polymorphism in pastoral groups to foster intestinal tolerance to a high-lactose diet based on milk and cheese.  
2. Dominance of the “caucasoid” (melanin-reduced) skin pigmentation to increase vitamin D production at temperate latitudes of lower solar ultraviolet penetration.  
3. Dominance of the “negroid” (melanin-enhanced) skin pigmentation to increase the protection of skin from damage at tropical latitudes of higher solar ultraviolet exposures. |
PLASTICITY TO PROGRAMMING AND EPIGENETICS MECHANISMS

Of the adaptive mechanisms discussed, plasticity seems to be the most under-recognized in nutritional science and the most compelling for PHN. It is interlinked with the emerging phenomenon of early-life (intrauterine, infantile) programming.

Programming

In 1991, Professor Alan Lucas defined programming as “either the induction, detection, or impaired development of a permanent somatic structure or the ‘setting’ of a physiological system by an early stimulus or insult operating at a ‘sensitive’ period.” The concept is central to the DOHaD tenets. Professor Peter Gluckman et al. explain the changes in life-long growth and metabolism of nutrients that originate in fetal life as “adaptive plasticity”. They present a “match-mismatch” thesis, which postulates the “sensing” of the maternal environment by the fetus. The fetus’s metabolism is then adaptively programmed to respond to what is expected for postnatal life. If ambient conditions are harsh, the fetus adapts by conserving nutrients maximally; if the environment is favorable, the fetus adapts by disposing of nutrients expediously. To the extent that the predicted conditions prove to be correct as postnatal reality, there is a fetal adaptation/true environment match, i.e., the conditioning is favorable to individual survival. Should there be a mismatch, however, a state of nutrient conservation meeting the “sensing” of the maternal environment by the fetus. The fetus’s metabolism is then adaptively programmed to respond to what is expected for postnatal life. If ambient conditions are harsh, the fetus adapts by conserving nutrients maximally; if the environment is favorable, the fetus adapts by disposing of nutrients expeditiously. To the extent that the predicted conditions prove to be correct as postnatal reality, there is a fetal adaptation/true environment match, i.e., the conditioning is favorable to individual survival. Should there be a mismatch, however, a state of nutrient conservation meeting the “sensing” of the maternal environment by the fetus. The fetus’s metabolism is then adaptively programmed to respond to what is expected for postnatal life. If ambient conditions are harsh, the fetus adapts by conserving nutrients maximally; if the environment is favorable, the fetus adapts by disposing of nutrients expeditiously. To the extent that the predicted conditions prove to be correct as postnatal reality, there is a fetal adaptation/true environment match, i.e., the conditioning is favorable to individual survival. Should there be a mismatch, however, a state of nutrient conservation meeting the “sensing” of the maternal environment by the fetus. The fetus’s metabolism is then adaptively programmed to respond to what is expected for postnatal life.

Antecedents to the current match-mismatch postulates can be found in a debate that raged in the 1980s. One school of thought proposed that maximizing height was not an obligatory goal, and that smaller size as an adaptive response could be healthier. This was rebuffed from within the nutritional community with the assertion that creating the conditions for maximizing genetic growth potential was an imperative. Today, a quarter of a century later, converging evidence suggests that periods of rapid growth adjustments generally have adverse consequences for metabolic health later in life.

Epigenetics

One of the underlying mechanisms for the postulated early-life programming is that of epigenetics. This can be defined as “the study of heritable changes in gene function that occur without a change in the sequences of nuclear DNA”. Although not all of the ways that epigenetics can be affected are known, the two mechanisms that seem to be most prominent are alterations in 1) the background chromatin proteins, which act as the scaffold for the DNA during transcription, and 2) the degree of methylation of the nucleotide bases of the DNA. Both of these routes to epigenetic modification of genetic signaling are associated with nutrients, and hence with diet and nutritional status. For the chromatin modifications, the acetylation, phosphorylation, glycosylation, and methylation of histones produce the conformational changes. These are all linked to metabolic substrates. For the methylation of DNA, the intake and status with respect to dietary methyl sources such as folate, vitamin B12, riboflavin, choline, betaine, and methionine are determinant. One example is the agouti mouse, whose coat color and susceptibility to metabolic disorders can be meticulously controlled by the offering of dietary methyl donors. Within its consideration of individual adaptation, PHN continuously incorporates the evolving understanding of the role that epigenetics exerts on human metabolism.

FROM “ONE-SIZE-FITS-ALL” TO “LET THE ADAPTATION BEGIN”

The dominant modus operandi of public policy has traditionally been collective efforts for the common benefit. This can be seen in very successful formats in immunization programs, iodization of salt, and fluoridation of water. These are all examples of generalized, one-size-fits-all programs. A paradox can be defined as “an apparently sound argument, leading to a contradiction.” As additional opportunities for nutrient intervention have been explored, an increasing number of paradoxical findings are challenging the generality of one-size-fits-all solutions to newer PHN initiatives.

For example, a recent study in South Asia on supplementation with multiple micronutrients during pregnancy produced the paradoxical outcome of higher birth weights along with a greater mortality risk in infancy for those born larger. Katz et al. comment: “The biologic pathways affecting intrauterine growth may vary by micronutrients such that some may confer a benefit among the most vulnerable infants, whereas others may have a more constant effect across the entire distribution. Future analytic approaches to estimating the benefits of maternal supplementation with regard to birth weight should examine whether there is a constant or a variable treatment effect across the distribution of birth weight.”

Routine, universal, daily supplementation with 12.5 mg of iron and 50 μg of folic acid for preschool children in regions where anemia rates exceed 40% in this
age group has been officially advocated by the World Health Organization. A study to test its safety and efficacy on the Pemba Island of Zanzibar, where malaria is holoendemic, produced mixed results. Benefit was shown in those with anemia of iron-deficient origin and low Plasmodium loads. Adverse effects, specifically increased hospitalization and death, were seen, however, in those with active malaria and adequate iron stores.

Folic acid represents another case in point. The recommended intake of dietary folate has been doubled in the last decade for all adults, with the goal of preventing neural tube defects (NTD). NTD risk can be reduced by increased maternal folic acid intake. In many nations, fortification of flour and breakfast cereals with folic acid (pteroylglutamic acid) has been mandated. However, folic acid is not a natural dietary form, and evidence is accumulating that oral intake from fortification and nutrient supplements can accelerate the progression of incipient colorectal tumors.

Health policy can and should aspire to the most equitable and efficient delivery of preventive services. For ethical reasons surrounding the Hippocratic dictate of “first do no harm”, however, vigilance and concern for the paradoxical situations in which benefit for some results in harm for others within the same intervention cannot be avoided. This consequence is clearly anticipated, and partially explained, in the concepts of DOHaD. Differential environmental damage as well as different programmed, adaptive strategies set the stage for a non-homogeneous population. To the extent that adaptation is linked to a survival strategy for the individual, it should be respected and nurtured, rather than countermanded and overridden by prophylactic interventions. A stark conclusion for the PHN community to swallow on the programmatic side is to accept a need for screening and for individualization of interventions that were once destined to be routine, collective, and universal. On the investigative side, we are called upon to identify more instances of adaptive response in human biology, to understand their mechanisms, and to judge their implications for appropriate nutrient and dietary exposures.

CONCLUSION

In sum, for professionals moving into PHN from a background and training in one of the other subdisciplines of nutritional science, it is important to make the transition in such a way that the best information is applied to the public without any narrowly disciplinary worldview behind it. PHN does a disservice to the public when only the confining paradigms that grew up around the foreground disciplines of clinical, experimental, biochemical, and animal nutrition are considered. PHN will best move forward in step with the degree to which it incorporates evolutionary biology and new paradigms, such as DOHaD, into its disciplinary culture.

Declaration of interest. The author has no interests to declare.

REFERENCES


