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Childhood Nutrition from Bench top to Outreach: Considerations to Advance the Science

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Supplement: Childhood Nutrition from Bench-top to Outreach: Considerations to Advance the Science

Environmental Forces that Shape Early Development: What We Know and Still Need to Know

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Abstract

Understanding health requires more than knowledge of the genome. Environmental factors regulate gene function through epigenetics. Collectively, environmental exposures have been called the "exposome." Caregivers are instrumental in shaping exposures in a child's initial years. Maternal dietary patterns, physical activity, degree of weight gain, and body composition while pregnant will influence not only fetal growth, but also the infant's metabolic response to nutrients and energy. Maternal over- or underweight, excess caloric intake, nutrient imbalances, glucose dysregulation, and presence of chronic inflammatory states have been shown to establish risk for many later chronic diseases. During the period from birth to age 3 y, when the infant's metabolic rate is high and synaptogenesis and myelination of the brain are occurring extremely rapidly, the infant is especially prone to damaging effects from nutrient imbalances. During this period, the infant changes from a purely milk-based diet to one including a wide variety of foods. The process, timing, quality, and ultimate dietary pattern acquired are a direct outcome of the caregiver-infant feeding relationship, with potentially lifelong consequences. More research on how meal time interactions shape food acceptance is needed to avoid eating patterns that augment existing disease risk. Traditional clinical trials in nutrition, meant to isolate single factors for study, are inadequate to study the highly interconnected realm of environment-gene interactions in early life. Novel technologies are being used to gather broad exposure data on disparate populations, employing pioneering statistical approaches and correlations applied specifically to the individual, based on their genetic make-up and unique environmental experiences. *Curr Dev Nutr* 2018;2:nzx002.

Introduction

Exposures during early life shape health behaviors, but these exposures can also be responsible for influence at a much deeper level. The contemporary view of nutrition in health is one that encompasses environment-gene interconnections. In this concept, each nutrient, through its wide variety of actions at the molecular level, contributes to the total system, keeping it poised to adapt to perturbations and return the body to a state of homeostasis. This casts nutrition in personal terms. It is not whether a dietary pattern or an individual nutrient, such as sodium or sugar, is broadly recommended for all humans, but rather whether it is optimal for helping an individual reach their health goals at this moment in their life. Based on mounting clinical evidence, more recent versions of the Dietary Guidelines for Americans have embraced the broad health benefits of a nutritious dietary pattern. The role of nutrition is to ensure that cellular networks are fully supplied with sufficient energy and nutrients to optimize their flexibility. Nutritional sufficiency, then, is defined by whether the collective physiologic response to the nutrient flow can meet an individual's ever-changing physical and psychologic demands. In order to capture an individual's



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genetic-environmental response to health risk, there is a need to overcome the challenges found in molecular nutrition research as well as a need to make assessments on a system-wide basis instead of individual cause-and-effect trials (1).

Around 50 y after the discovery of the structure of DNA, the human genome sequence was fully characterized. Yet, for all its promise, knowledge of the genetic code has afforded only a limited ability to predict the risk of a complex disease. Environmental factors that influence gene function have been shown to be a powerful force, but one that is even more challenging to study. Environmental exposures, ranging from the prenatal to the geriatric phase of life, can alter gene expression and, through it, human health (2). Understanding disease requires identification of the mechanisms through which environmental influences alter cellular responses contributing to pathology (3). Environmental influences occur in several overlapping domains: the broad external environment (community, climate, social, financial), more specific environmental hazards (sun exposure, environmental toxicants, alcohol, tobacco, nutrient deficiencies, lifestyle), and the internal physiologic environment (cardiometabolic activity, stress response, immune and inflammatory systems, hormonal communication, the commensal microbiota). Collectively, these environmental exposures have been termed “the Exposome,” representing the nongenetic counterpart to the genome (2–4). Describing the “exposome” is only the first step in characterizing the system. The fact that lifelong exposome-genome interactions accumulate means that we are faced with the principle of “unique disease” (3, 5). This principle states that any disease or disorder will manifest uniquely in everyone, because of their personal genetic makeup coupled with their history of exposures during critical periods. Although delineating the specific way in which each discrete disease will act in different individuals may seem like a daunting task, it is a line of research that is already well underway. Studies on the epigenome, transcriptome, proteome, metabolome, microbiome, and interactome hold promise for understanding the range of potential reactions that a disease can engender within a population. With these data, disease can be characterized in relation to the external macroenvironment alongside the cellular microenvironment.

The dichotomy between genes and environment is now recognized to be an ever-changing complex interplay of nature via nurture. The developing fetus, neonate, and infant are especially susceptible to environmental influences, and it is here that the gene \times environment interaction is in full display. The physical and emotional environments that surround and engage the mother directly mold her child's lifelong potential. The preconception period within the human life course is the first to manifest environment-gene interactions, and these affect the molecular on-off switches that control DNA expression. Nongenetic factors that control gene expression in a stable manner are termed “epigenetic.” Epigenetic mechanisms are fundamental to expressing phenotypically different states from a single genetic blueprint, as typified by lineage commitment and differentiation from pluripotent stem cells. Epigenetic mechanisms also serve as an interface between environmental and exogenous stimuli and cellular responses, and eventually the phenotypes they confer. Epigenetic forces may involve alterations in the DNA methylation patterns at cytosine, post-transcriptional modifications of histones, around which the DNA is wrapped and via regulation of noncoding RNA. These chemical changes alter the type, timing, and extent of protein production by genes. Maternal diet and health

condition, as well as the quality and balance of the child's diet during the first years after birth, contribute not only to the child's physical habitus and well-being, but also fuels a unique neurocognitive expansion on which their future academic, social, and behavioral success will be based (6). Given these important outcomes, research has sought specific ways to ensure optimal environments and experiences for the developing child. In this article, we will examine examples of what is known and unknown in terms of the biological and environmental nutritional forces that shape the fetus, neonate, infant, and child in the early years (Table 1) (7, 8). Illustrations of the way that early experiences affect lifelong health risk will be presented in 4 areas: in utero and developmental programming of metabolism, neurodevelopment and cognition, postnatal behaviors around food choice, and a “Future Vision of the Exposome.”

Effects of Maternal Nutrition and Weight on Fetal Development

The co-occurrence of obesity, hunger, and malnutrition around the world complicates public health policy. Worldwide, the overweight population now exceeds the underweight population (9). Cardiometabolic diseases, such as heart disease, dyslipidemia, type 2 diabetes, metabolic syndrome, and fatty liver are diagnosed not only in adults and seniors, but also in children and adolescents. Unraveling the intersecting circumstances that result in obesity will require a better understanding of how an individual's environmental exposures create or mitigate risk. Increasingly, a systems perspective has been invoked that examines layered exposures to food quality, to agricultural practices, to community and social factors, and to personal and family lifestyle (10). The identification of “epigenetic” forces—environmentally triggered DNA modulations that adapt gene expression to the environment—has expanded the role of genes in the development of obesity and its complications to include a more complex perspective (11).

The first awareness of the role of maternal nutritional status on adult health began with studies on the effects of malnutrition during pregnancy. In the late 20th century, the developmental origins of the health and disease hypothesis were advanced based on the finding that undernutrition during critical periods in utero permanently altered the development of the fetus, including structure, function, weight, and metabolism (12–14). Since those initial studies, a wide variety of environmental factors occurring during pregnancy have been identified, ranging from toxins and chemicals to diseases and depressive symptoms, all of which raised the risk for health and mental health disorders in adulthood.

Among the most keenly studied and reproducible outcomes have been the mechanisms that link maternal body composition to the child's risk for future obesity (15–17). In utero exposure to maternal obesity and high-fat diets in rodent models has illuminated the extent to which preconception maternal body habitus, excess gestational weight gain, and dietary imbalances can lead to a “hyper-responsive infant”; that is, an infant prone to accumulate excess body fat, fatty liver, and metabolic derangement when exposed to postnatal high-calorie or high-fat feeding (18, 19). This risk is associated with alterations in a multitude of metabolic processes, including impaired glucose homeostasis and insulin sensitivity (20, 21), lower skeletal muscle mass (22), altered

TABLE 1 Summary of “what we still need to know”

Effects of maternal nutrition and weight on fetal development
Specific molecular factors involved in fetal programming
The influence of maternal dietary pattern on the offspring health
Diet quality and individual micro- and/or macronutrients during critical windows in pregnancy on offspring health outcomes
The impact of obesity in the preconception phase vs. from excess gestational weight gain on glucose-insulin axis perturbations
The effect the inflammatory response has in programming cardiometabolic risks
Early nutrition, brain structure, and cognitive development
The impact of diet quality on cognitive development in infants and toddlers
The identification of epigenetic mechanisms by which acute changes in dietary behavior affect cognitive function in children and teens
The identification of key factors that may protect the developing child and turn early cognitive “potential” into lifelong social, emotional, and academic skills
Early life environmental exposures and eating behavior
Longitudinal studies on the acquisition of dietary habits in the first years of life are needed to establish tailored interventions
Data documenting successful strategies to help inform about when and how less nutritious eating patterns become entrenched
Deeper understanding of child development and developmental norms in response to food behavior (neophobia, food jags, increasing selectivity with age, strong preferences for the same foods at each meal, and shifting food preferences)
Microbiome for childhood health
Characterization of the exposome
The role of the microbiome on metabolic and physiologic processes that comprise the maternal-infant feeding relationship
A vision of the future
Methods to translate personal longitudinal health data into practical personal dietary advice

appetite and food preferences (23), and epigenetic changes in DNA methylation patterns that favor adipogenesis (24). In experimental models, accumulation of ectopic lipids in the liver (25, 26), increased lipogenesis in white adipose tissue (24), and a greater tendency for stem cells to differentiate into adipocytes (24) have all been noted. Similarly, alterations in pathways regulating lipid oxidation and basal energy expenditure (such as PPAR- α , adenosine monophosphate protein kinase and insulin signaling) in metabolically important tissues such as liver, muscle, and adipose tissue create a milieu that favors storage over oxidation (27–29).

Human studies, similarly, have shown that babies born to obese mothers, even in the absence of glycemic disturbance, have greater adiposity and a higher risk of insulin resistance (30, 31). With >60% of women in the United States overweight at the time of conception (32) and with steadily rising rates of weight gain and gestational diabetes during pregnancy, poor nutrition puts both the fetus and the mother at risk. In the face of excess energy, the composition of the fetus changes quickly, with it developing a higher fat mass, insulin resistance, and excess growth (33). Meta-analysis has confirmed the association between maternal BMI and the risk for high gestation-weight babies (34), which, in turn, is associated with higher cesarean delivery rates and complications during delivery. As early as 2–4 y of age, obesity risk is doubled, and this continues into adolescence and young adulthood, as shown in several studies (30, 35, 36). Likewise, cardiometabolic risk markers for dyslipidemia, glucose-insulin dysregulation, and diminished hunger-satiety control are also closely associated with maternal obesity and gestational diabetes.

In the Beginnings Study, a USDA-funded prospective observational study tracking the growth and development of children from 2 mo to 6 y of age, 325 infants born to normal weight, overweight, or obese mothers were followed longitudinally (37). By school age, significantly higher BMI z-scores and percentage of body fat were seen in children of

obese mothers. Differences became apparent after age 2–3 y, with boys showing a more striking response than girls. Another study showed the relation between maternal adiposity and child obesity in children born to morbidly obese women before and after they had undergone bariatric surgery. Those infants before the intervention had a significantly higher risk for later obesity than did their siblings born after the surgery-induced maternal weight loss (38, 39).

What are the mechanisms underlying fetal programming of obesity? Maternal obesity, diet, and the resulting metabolic milieu, including the lipids and nutrients delivered to the developing fetus, can alter gene expression. During critical windows of development, external events directly shape every cell, tissue, and organ under development. In total, these adjustments reset the fetal—and later child and adult—metabolic response. Gene expression responds to environmental cues very quickly. Shifting the maternal diet toward one that is high in fat intake upregulates fetal inflammatory markers as early as the oocyte and embryo stages in animal models (40). The placenta, which senses nutrient flow, adjusts to the needs of the fetus (41). The placenta has also shown a capacity not only to monitor nutrients, but also to produce inflammatory compounds and lipotoxic mediators in response to the type and quantity of circulating nutrients, which further modifies the uterine environment (42–44). It is possible that a proinflammatory environment and pathways sensitive to excess nutrition in the peri- and postconception environments serve to regulate systems that promote adiposity in the offspring. The specific molecular factors involved are yet to be fully elucidated.

The specific dietary choices of the mother may influence epigenetic mechanisms. Most of the available evidence comes from rodent and nonhuman primate studies on the effects of a few dietary components, including folic acid, fructose, long-chain PUFAs, and protein content. However, the mechanisms that underpin cardiometabolic risk are being targeted in several human studies, as well. The Healthy Start Study

has shown a strong association between maternal insulin resistance and late-term circulating glucose concentrations with the development of the neonatal fat mass, independent of maternal preconception BMI (45, 46). The ongoing USDA-funded Glowing Study has been designed to follow 320 human maternal-infant pairs from early pregnancy through to age 2 y, specifically examining the interconnected nature of maternal weight, body composition, dietary intake, and energy expenditure on adiposity, weight gain trajectory, and fat oxidation in the child.

Despite steady progress in understanding pivotal links between maternal and offspring health, several knowledge gaps need to be addressed in this area. These include a better understanding of the influence of maternal dietary patterns, diet quality, and individual micronutrients and/or macronutrients during critical windows in pregnancy on offspring health outcomes. How does obesity in the preconception phase differ from excess gestational weight gain in terms of impact on glucose-insulin axis perturbations? Is fat distribution a key factor? After birth, are there postnatal factors that could be manipulated to lower risk, such as the effect of the microbiome on metabolic and physiologic processes, or the social-emotional-behavioral conditions that comprise the maternal-infant feeding relationship? What is the combined effect of diet quality, nutrient components, physical activity, and fitness? To what extent is the inflammatory response central to programming cardiometabolic risks?

Early Nutrition, Brain Structure, and Cognitive Development

In utero and early life factors also program and impact systems beyond adiposity, including the brain and neurocognitive development. Mental health and wider health risks resulting from gene-epigene interactions accumulate over time. As in pregnancy, postnatal early life exposures and experiences are the foundations on which a child's future social, emotional, cognitive, and motor skills rest (47). Like other major organs of the body, the brain and neurodevelopment are strongly affected by maternal nutrition during pregnancy (48, 49). Neural tube formation, neurogenesis, neuron migration, programmed cell death, the expansion of the nervous system, and the structural coordination between regions of the brain occur sequentially over the 40 wk of gestation (50, 51). By parturition, the neonate has developed >85 billion neurons, which, with the exception of 2 areas (the hippocampus and the cerebellum), amount to the infant's total for life (52–54). Brain imaging studies have shown that maternal obesity is associated with decreases in the white matter content of the central nervous system in several different regions of the neonatal brain (55). Besides obesity, nutrient deficiencies from an unbalanced maternal diet, a persistent high-risk metabolic and inflammatory state, and many other deleterious exposures that occur during sensitive periods can negatively influence fetal brain structure and function. For instance, not only diet quality (56, 57), regular physical activity (58), and body composition (59) affect the fetal brain; so, too, do psychological stresses (60), social interactions (61), daily routines (62, 63), sleep (64, 65), chemical toxins (66), emotional and sensory stimulation (61, 67), financial status (68), family structure (69), and the child's experiences with acute and chronic diseases (70–72).

There are sensitive periods between birth and 3 y of age during which the brain's structure and function greatly expands, becoming more co-

ordinated and refined (57, 73). From birth, the brain doubles in size by year 1 and triples in size by year 3, nearly to complete adult size, as a result of increasing myelination and synaptic connections, spurred on by the infant's sensory-motor experiences (74, 75). Play, nonverbal expression, acquisition of verbal language, and routine problem-solving stimulate the formation of synaptic linkages. These form the basis for all future cognitive, social, and behavioral performance. Synaptic connections are formed at 700 connections/s during this crucial period. Arborization reaches a lifetime maximum around age 3 y, after which weak or unused synapses are “pruned back,” leaving only 50% by young adulthood (75). For the child in a stimulating, nurturing, and healthful environment, this results in a well-structured, highly responsive brain built on early exploration and expanded through the child's experiences. However, for those children who are not raised in such a stimulating and supportive environment, those who lack the kind of constant verbal and emotional exchange that anchors basic language and literacy skills, or those who face persistent or severe adverse events in early life, the brain displays a very different, attenuated capacity that can potentially leave the child at a cognitive disadvantage for life (73, 76).

Scientists have used 2 primary methods for studying brain structure and function noninvasively. Brain imaging (MRI) procedures are used to quantify brain structural integrity and connectivity, and functional MRI is used for observing brain activation during the performance of specific tasks (77). Imaging procedures require the absence of movement to obtain acceptable data, making such procedures difficult to use successfully in active infants and young children. Consequently, electroencephalogram measures, which are more tolerant to movement, have been the primary source of information describing brain-behavior relations in early life. During the infancy-early childhood period there is rapid development of processes involving attention, arousal, sensory-motor skills, emotion, working memory, social orientation, and language acquisition. Optimal operation, maintenance, and repair of the growing brain require a steady stream of nutrients and energy.

Nutrition continues to be a central environmental factor throughout childhood. Infants and children have a metabolic rate >2.5 times higher than in the adult (78, 79). Their metabolic demands make them sensitive to variations in energy or nutrient flow during even short periods of fasting. Recognition of this vulnerability has emphasized the importance of breakfast, since this meal follows the longest naturally occurring fast that occurs daily. Academic performance among school-age children is better in those who regularly eat breakfast (80, 81), but there have been few studies using measures of brain activity—and none using imaging procedures—to describe the neural correlates associated with eating or skipping breakfast in young children. Electroencephalogram studies have shown changes in brain activity, indicating increased attention and memory processes, resulting in faster decision making and more efficient mental math in children fed compared with those who skipped breakfast (82, 83). Decision making and mental arithmetic rely on processes known as “executive functions.” These functions, which are largely controlled by the frontal lobe (84–86), involve processes contributing to self-regulation and mental flexibility, such as attention, emotional control, and memory (87).

Sensitivity of executive functions to even transient variations in morning nutrition suggest that the cognitive deficits resulting from meal skipping or chronic poor diet are likely to be far worse for the obese child (88). Imaging studies have shown that both gray and white matter

are diminished among obese children (89), and that frontal brain activation is reduced when the obese child is given tasks involving memory, attention, and verbal and motor skills that challenge the prefrontal cortex (90, 91). The obese population also shows impaired outcomes on a variety of tests measuring executive function (92). Physical exercise, similar to breakfast consumption, has been shown to be capable of improving these executive skills (93–95), even in obese children (90, 91). Such studies illustrate how one's prior "programmed" risks associated with obesity may interact with more proximate environmental exposures to alter the immediate cardiometabolic state and affect cognitive function.

More research on the environment-gene relations that result from nutritional status and body composition is needed. The individual and collective components of diet, along with the benefits of regular physical activity, may present ways to alleviate the detrimental effects of weight, adiposity, or other programmed risk. Studies on diet quality and cognitive development in infants and toddlers are just beginning. Identification of the epigenetic mechanisms by which acute changes in dietary behavior affect cognitive function in children and teens is needed. An integrated approach that combines studies of brain structure, function, environmental exposures, and personal variables will be necessary to identify which key factors may protect the developing child and turn early cognitive potential into lifelong social, emotional, and academic skills.

Early Life Environmental Exposures and Eating Behavior

Diet quality in early childhood is also an important epigenetic force, given the intense increases in height and weight, ongoing organic development, and the extreme expansion of the brain during this time. Just as the maternal diet and obesity can affect the offspring's weight and brain development, so, too, can it start to shape food preferences and dietary habits, influencing the child's health and development well into the future. Establishing nutrient-rich dietary habits has proved challenging considering the complexity of human behavior, which often is resistant to change despite proven benefits. Research has shown the importance of initial experiences with food on later food preferences and dietary habits (96, 97). Typically, nonmilk foods offered during the second 6 mo of life represent the child's most intensive period of exposure to the many tastes, textures, and colors of foods and beverages. But it is not the first exposure. Studies show that both the fetus and the neonate can experience flavors through swallowed amniotic fluid and through breastmilk, both of which reflect components of the mother's diet, which are hypothesized to influence the infant food acceptance and preference (96, 98). However, given that most adults in the United States fail to achieve the recommended intake of fruit and vegetables, particularly low-income pregnant and lactating women, the potential for maternal diets to positively influence infant diet quality is not maximized (99, 100). Parental diet quality becomes an even more crucial factor in the second year of a child's life, when the transition from breastmilk- or formula-based feeding to family foods occurs.

Food preferences established in the first 3 y of life tend to persist (97, 101). Although children are more open to new food experiences during the first years, the daily parent-child negotiation around meals and snacks often prevents the opportunity to promote varied dietary

preferences. After instilling an acceptance of fruit and vegetable intake using infant food during the first year, intake of both falls quickly in the second year, not only in total consumption, but also in variety (102). Nearly one-third of toddlers and preschoolers eat no vegetables regularly (103). Irrespective of race, ethnicity, or socioeconomic status, intake in the United States consistently fails to achieve the recommendations of the Dietary Guidelines for Americans for vegetables and fruits (104). Snacks often introduce high-calorie, low-nutrient products that become strongly preferred by children already primed to like sweet, salty, and fatty items—a preference that has been honed throughout human evolution (104, 105). Conversely, bitter and sour, the attributes of vegetables, are more likely to be resisted (98, 106). These less-nutritious dietary patterns that do not meet dietary recommendations, especially for the food groups that are encouraged (fruits, vegetables, whole wheat, and dairy), put our population at an increased risk for consuming suboptimal amounts of essential nutrients, which in turn increases the risk for developing diet-related health concerns.

What is the pathway to broad food acceptance that establishes a lifelong high-quality dietary pattern? There are several factors in play, some individual to the child, such as neophobia (i.e., the extent to which children display resistance to trying new foods) (107), temperament (108), and intensity of response to bitter (109), and others related to the environment, such as education, income, food insecurity, and family norms (110). Children prefer what they know; that is, they tend to accept what is familiar and routine (111). Taste can be "trained" through familiarity or mere exposure (112–116). This seemingly simple principle requires that caregivers show patience and persistence in their efforts to shape food preferences and in their willingness to continue to offer and model consumption of previously rejected foods. The number of exposures to induce acceptance varies in the literature, with reports ranging from 8 to >15 times (117). Recent studies have shown a greater likelihood of establishing food acceptance through repeated exposure in children <24 mo old than in older children, emphasizing early life as a pivotal period (118). Pairing preferred flavors with new flavors can encourage acceptance, but the evidence for the effectiveness of this strategy is inconsistent (115, 116, 119, 120). Current resources have not been successful at guiding parental understanding of appropriate portion sizes, ways to meet recommended servings per day, or use of nutrient-rich options from each of the 5 food groups to improve children's intake at meals and in snacks. Repeated exposure takes patience, something that may arise from the parent's level of understanding of the developmental norms matching the child's age and a trust in the child's ability to eat sufficiently to meet the energy needs for appropriate growth.

Parents who label their child a "picky eater" report halting presentation of rejected foods after only 3–5 tries, which may be insufficient to give the child enough experience to overcome their initial neophobic response (121, 122). They also tend to attribute their child's limited food acceptance to inheritance rather than to malleable behavior (123). Bribing or pressuring the child to eat, along with a permissive feeding style of catering to the child, fosters rejection, as does failure to create a supportive emotional milieu around mealtimes (124). Conversely, successful behavioral strategies include encouragement, task-centered praise, and monitoring of eating progress (125–128). Setting high expectations, establishing clear structure, the presence of family rules, and modeling by family members all have reinforcing benefits (129, 130).

The emotional environment surrounding the parent-child feeding relationship may be important in shaping feeding behavior, but remains largely unstudied (130, 131). Breastfeeding promotes a close physical-emotional attachment that transcends simply the supplying of food (132, 133). This feeding principle, termed “responsive feeding,” embodies a reciprocal relationship between the child and the caregiver in which the child’s cues are promptly met with contingent caregiver responses that support the child’s development of healthy eating behaviors (133, 134).

In the Totality of Early Environmental Exposures: The Body’s Other Biome

A recent corollary to the epigenetic manipulation of gene expression in animals and humans has been the expanding literature on the ways that our diet, diseases, and exposures act as inputs to alter the gut microbiome. Our microbiome serves as another epigenetic influence on a child’s genetic make-up. In the first years of life, the human gut is colonized by >1000 bacterial species, which encode as many as 5–10 million genes, compared with our own 20,000 genes. The microbiome illustrates a classic symbiotic relationship, one that closely intertwines the collective physiology of the bacterial population with our own. The presence of the microbiome greatly amplifies the complexity of a system-wide or exposome-wide approach to human health. The adaptive flexibility of the microbiome to rebound from environmental perturbations mirrors many of our own body’s adaptations. Consider the sum of the body’s response to a single invading enteric pathogen, which triggers reactions across the highly interconnected processes that control inflammation, immunity, nervous system function, and epithelial absorptive capacity in the gut. The resulting vomiting, diarrhea, loss of appetite, and dehydration dramatically diminish the amount of bacteria in the gut. Prolonged illness or complications might impede homeostasis, particularly if antibiotics are prescribed. Adaptations within the microbial system might be detrimental, chronically altering the gut milieu. Opportunistic overgrowth of other pathogens, such as *Clostridia difficile*, may further compromise the stability of the microbiome as well as the integrity of the gastrointestinal tract itself, causing a cascade of adaptations across physiologic and metabolic systems.

Can both systems, ours and the microbiome’s, be strengthened through diet to enhance our health, defined as our ability to resist stresses and maintain homeostasis? To approach this question, we need to use novel 21st-century technologies and innovations that can characterize and model the highly complicated relationships that involve humans within the many environments in which we live and grow. Complete characterizations of the human genome and the gut microbial genome have been undertaken successfully. Characterization of the exposome, although complex, is a pressing research endeavor (2).

The Search for Novel Methods to Study the Exposome-Genome Interaction

Scientists are designing projects to lay the groundwork. Among the most established are those examining environmental chemicals, occupational hazards, and their effect on health. Multiple agencies acting in concert are pooling large data sets and building platforms for

analysis in such projects as Exposure21, Health and Environment-wide Associations based on Large population Surveys (HEALS), and the Exposomics Consortium. A forward-looking report on exposure science was published by the National Academies of Sciences and funded by the National Institute for Environmental Health Services and the US Environmental Protection Agency, titled “Exposure Science in the 21st Century: A Vision and A Strategy” (8). The report called for multi-agency cooperation to gather pooled toxicity testing data, build platforms to handle massive data waves, develop novel statistical approaches, and design analysis paradigms that are publicly available to encourage information sharing. Many emerging research technologies have been cited as building blocks for such an undertaking, including microfluidics, nanotechnologies, mass spectrometry, capillary lab-on-a-chip technology for chemical analysis, LC/tandem MS to measure protein adducts (chemicals bonded to protein structures), high-tech sensor technology, global positioning systems, genomic techniques, and informatics. Many will provide the biomarkers needed to quantify chemical exposures. The report from the National Academy of Sciences also urged that the diverse information gleaned from these large-scale toxicology studies be applied not only to health care, but also to environmental regulation, urban and ecosystem planning, and disaster management.

Among the several nascent studies being launched on the exposome, early life exposures and their resulting health outcomes are being taken up in the Human Early-Life Exposome (HELIX) project, centered in Barcelona, but comprised of 6 birth cohort studies in Europe (135). The project will follow >32,000 mother-child pairs to examine chemical and physical environmental factors. A subset of 1200 dyads will have repeated biomarkers assessed, using smart phones to quantify mobility, physical activity, and personal exposures, coupled with -omics technologies to provide molecular profiles of each subject. Advanced statistical methods will correlate fetal and child growth, exercise, obesity, neurodevelopment, health, and respiratory outcomes (e.g., asthma) to begin to characterize exposure-response relations.

The intensity or persistence of certain stress events can impose permanent changes in the body, which can change the way that our body subsequently reacts to adversity. Significant environmental challenges have the capacity to alter not only gene expression, but also metabolic, neuronal, immunologic, and hormonal responses, which can alter the trajectory of an individual’s life. That is clear from the findings on the maternal-child relationship in gestation. Life-changing exposures are also well documented in studies on the effects of severe adverse events in early childhood, permanently altering the capabilities of the rapidly growing infant brain (136). Adult outcomes as disparate as emotional behavior, responsiveness to stress, resilience, academic success, and peer social interactions have been associated with adverse childhood events accumulated during the critical window of early life.

If the concept of health is represented by the flexibility, robustness, and durability of the body and mind, then a fundamental research question can now be stated: can we enhance a system’s adaptability to environmental exposures by challenging it (137)? That is, are there ways of “exercising” the body’s homeostatic networks to increase their resilience to perturbations of all kinds? Mounting evidence suggests that many different types of stimuli (antigen, pathogen, metabolite, chemical) can serve to stimulate and benefit existing physiologic processes (138, 139). It is conceivable that adjustments in the child’s socio-ecological connectedness, their diet quality, hygiene, and

physical activity might be manipulated to improve their system's "flexibility," with significant practical consequences for the growing fetus and child.

Complex Diseases in the Light of Gene × Exposome Interaction

The Human Genome Project was an investment of billions, but it in turn has reaped strong economic benefits. So, too, does the Exposome Project offer enormous economic and societal return on investment, but will require a similar financial and scientific commitment (7). Researchers are already compiling longitudinal and extensive data from individuals via the expanding electronic health records system, which has the capacity to outline the variations of "normal" during times of health and disease. Creating a screening tool derived from these data that compares one's personal biomarkers as well as those of the microbiome against that of the healthy population, for instance, offers an opportunity to identify deviations and potentially to adjust them. Consider assaying an individual's microbiome, comparing it with population norms, and, by undertaking specific adjustments to the dietary pattern, augmenting the symbiotic relationship with the human organism. A similar example might be a tool that quantifies the responsiveness of one's inflammatory system to a variety of stimuli. Such challenges might illuminate ways to modulate the inflammatory function for the prevention of disease or its rapid mitigation, allowing faster healing.

A Vision of Future Nutrition and Health

Rather than a one-size-fits-all dietary recommendation such as those of the past, a comprehensive health model, complete with challenges and biomarker-based assays, holds promise for creating individualized dietary recommendations that can help consumers develop an ideal dietary pattern to promote their personal health. New initiatives have begun to recruit consumers into "health data cooperatives," which are legal entities pooling system-wide health data from dozens of disparate sources, ranging from doctors and insurance files to government, school, and health service provider records (140). What makes this type of amalgamated data repository unique is that the individual citizen-consumers own their own data. These are the first seeds of truly personalized health care. When a child is born later in the 21st century, each parent may be handed a personal biological passport that, unlike the traditional infant book or electronic health supervision visit hand-out, not only gathers all the child's health information in one place, but also guides parental decisions, based on their child's gene-environment responsiveness and current health trajectory, proposing specific ways to use nutrition and other variables to "nourish" their child's optimal health for life.

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