Review Article

The Microbiome in Early Life: Self-Completion and Microbiota Protection as Health Priorities

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This minireview considers the benefits of refocusing attention away from treating the patient as a mammalian human to managing the complete patient: a majority microbial superorganism. Under the "completed self" model for formation of the human-microbial superorganism, the single, most pivotal sign in distinguishing a life course of health versus that filled with disease is self-completion (i.e., seeding of the minority mammalian human by the majority microbial portion of the symbiont). From a disease prevention perspective, microbial seeding at birth and subsequent nurturing of the microbiota are significant steps to reduce the risk of both noncommunicable diseases (e.g., type 1 diabetes) and certain infectious diseases. Management of the microbiome during pregnancy, birth, and shortly thereafter appears to be the most significant critical window for healthy superorganism formation. However, the bolus for microbiota seeding at birth and the nurturing process are subject to environmental influences and disruption, such as exposure to toxic chemicals and drugs, infections, and other physical and psychological stressors. Additionally, childhood and adult corrective measures, such as fecal transplantation and administration of prebiotics and probiotics, while potentially useful, may have limitations that are yet to be fully defined. This minireview considers (1) basic features of management of the microbiome to facilitate self-completion, (2) protection of the microbiota from environmental hazards, and (3) the benefits of using a superorganism focus for health management beginning with pregnancy and extending throughout childhood and adult life. *Birth Defects Res (Part B)* 00:1–8, 2014. © 2014 Wiley Periodicals, Inc.

Key words: ***completed self; developmental management; health trajectory; immune maturation; microbiota; microbiome; noncommunicable diseases; recurrent infections; birth delivery mode; pregnancy management***

INTRODUCTION

Pediatricians, general practitioners, obstetricians, and/or gynecologists have vital roles as gatekeepers of the patient's overall health. With the trend of increasing specialization in medical education and training, concern has been raised about having a sufficient future supply of these gatekeepers of the patient (Hing and Schappert, 2012; David, 2013). But it is also a useful time to examine precisely what constitutes "the patient" whose gate is being kept. Our biomedical and ecologic understanding of "the patient" appears to have shifted.

For much of the past century, we have followed an us-versus-them paradigm in which the mammalian, human patient was being protected from, among other things, microbes. However, a future formula is more likely to be that of an us-plus-them, human-microbial superorganism patient being protected against anything that would produce superorganism dysregulation and/or microbial dysbiosis (Eberl, 2010; Sleator, 2010). Establishment and maturation of an initially diverse microbiome appear to be important for reducing later-life health risks. For example, there is evidence suggesting that dysbiosis of the gut microbiota is associated with elevated risk for a wide spectrum of diseases and conditions, including obesity (Nieuwdorp et al., 2014), cardiovascular disease (Tuohy et al., 2014), liver disease (Goel et al., 2014), kidney disease (Ramezani and Raj, 2014), type 1 diabetes (Endesfelder et al., 2014), type 2 diabetes (Tilg and Moschen, 2014), rheumatoid arthritis (Taneja, 2014), multiple sclerosis (Berer and Krishnamoorthy, 2014), colorectal cancer (Zhu et al., 2013), and asthma (Abrahamsson et al., 2014).

This is not the first publication to offer the perspective that our health management focus needs to shift toward the majority microbial component of humans, which exerts such a profound influence on children and adults beginning in early life. Murdoch and Detsky (2012) argued

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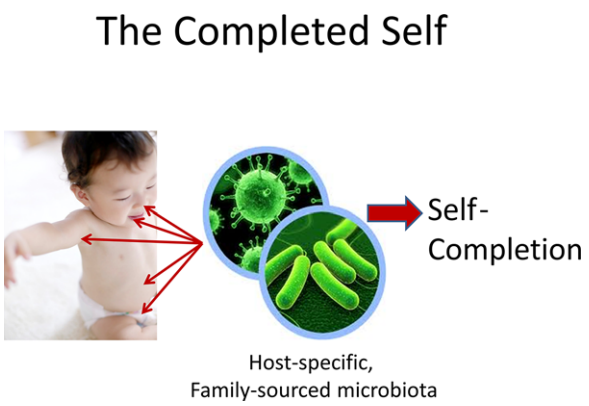

Fig. 1. The installation of a full diversity of microbes to respiratory, gastrointestinal, dermal, and urogenital tissues in the newborn allows for superorganism formation, facilitating both immune maturation and properly regulated interactions with the environment. Self-completion has been proposed as the key signal to start a child on a healthy life course.

that it is high time to recognize our microbiota as central players in human health management. Raipal and Brown (2013) advocated that management of the human microbiome will be the therapeutic paradigm for the future. Likewise, Wallace and Redibo (2013) identified the human microbiome as a major target of clinical significance and potential pharmacologic therapy. Finally, Ma et al. (2014) recently suggested that whole genome, shotgun metagenomics may be a useful approach for perinatal clinical management of the microbiome.

To aid this newly emerging paradigm of what constitutes humans, Dietert and Dietert (2012) developed "The Completed Self" model (depicted in Fig. 1), which is a model designed to represent human beings in their healthiest state and most seamlessly and fully connected to their environment (Dietert and Dietert, 2012). This model, emphasizing the self-completion of humans, arose from a scientific journal's (Entropy) challenge to envision a single sign or measureable parameter that would best distinguish a life course of health from one filled with disease. While we can measure many biomarkers, it is an intriguing question to consider which single biological sign taken in isolation is the best predictor of childhood and adult health. The answer that was developed, which ironically originated from a dream, was that of the self-completion of the human-microbial superorganism in the newborn. Self-completion is defined as: the newborn's successful and timely seeding with an optimal microbial bolus best suited to organismally and ecologically complete the infant. This priming event initializes a dynamic process in which microbial nurturing and environmental conditions give rise to both a tailoring of the microbiota and a progressive sequence of dominant flora as the child ages. Figure 1 also depicts the seeding of the infant's oral gastrointestinal, nasal respiratory, dermal, and urogenital regions by what are ideally maternally derived microbes.

This minireview discusses nine topics: (1) the basis of viewing superorganism self-completion as a health-promoting priority, (2) developmental windows of significance for self-completion, (3) potential measures of self-completion success, (4) microbiota as our seamless connection to our environment, (5) viewing microbiota as an "integral organ," (6) functions of the microbiota, (7) how an increased emphasis placed on formation of the human microbiome provides new opportunities for pediatric-centered health management, (8) why microbiome management is likely to become part of the pediatrician's toolkit, and (9) why increased focus on superorganism formation and management is likely to produce useful outcomes across the entire life course.

TIMELY AND EFFECTIVE SELF-COMPLETION AS A HEALTH PRIORITY

One of the pivotal factors of managing the microbiome across a life course begins with the neonatal installation of a genetically tailored microbiota that is then added to and optimally nurtured during infancy. The developing fetus can be exposed to the components of maternal microbiome through perinatal contact taking many forms (Stencel-Gabriel et al., 2009; Funkhouser and Bordenstein, 2013). Ardissone et al. (2014) reported evidence of bacteria in fetal merconium and posited that this may reflect fetal exposure to bacteria via amniotic fluid. Aagaard et al. (2014) reported evidence of a low-abundance placental microbiome that was most closely aligned with that of human oral microbiota. However, a pivotal seeding event of the baby's microbiota occurs at birth (Prince et al., 2014). This process appears to involve the transfer of microbes that can be traced directly from the mother's cecum to the infant's gastrointestinal tract during vaginal delivery (VD; Makino et al., 2013). Transfer of microbes both during VD and skin–skin contact shortly thereafter are critical processes that significantly mold the infant's subsequent microbiome involving the gut, respiratory tract, skin, and urogenital tract (Biasucci et al., 2010; Dominguez-Bello et al., 2010). Mouth–mouth interactions (e.g., kissing) have also been discussed as an opportunity for oral microbial transfer (Montiel-Castro et al., 2013).

In the study by Makino et al. (2013), infants from Cesarean delivery (CD) lacked the microbial strains derived from the mother's cecal microbiota. In fact, the exact source of the microbes and process through which CD infants receive microbial colonization has yet to be clearly defined. CD has been associated with a lower total microbial diversity, delayed colonization of the Bacteroidetes phylum, and altered immune maturation during the first 2 years of life (Jakobsson et al., 2014).

From the standpoint of the total genome comprising the human microbial superorganism, multigenerational microbial strain transfer through VD is a significant part of our overall genetic composition. In some ways, microbiota transfer across several generations might parallel that of chromosomal inheritance or the intergenerational transfer of mitochondria (Zhang et al., 2013). Deficits in the transfer of maternal gut microbiota to the newborn results in a genomically and biologically incomplete infant. It is not so different from the infant missing part of a mammalian chromosome via inheritance. Both are likely to have adverse health consequences. Given the health risks that have been associated with reduced gut microbial diversity and/or a skewed microbiome during infancy, as discussed later, self-completion in the newborn should be a priority across the perinatal period of development.

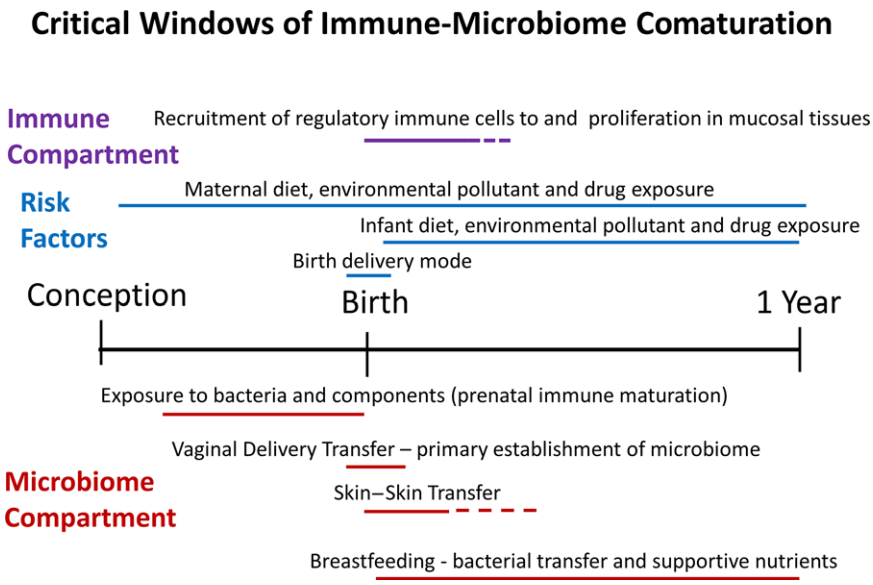

Fig. 2. The comaturation of the microbiome and the immune system depend upon several factors (depicted) that occur during precise prenatal and neonatal windows of early life development. The developmental trajectory and status of mucosal regulatory immune cells in tissues such as the gut appears to become established during a narrow window of postnatal development. Lack of self-completeness at this time may result in persistent immune dysfunction. Color coding is used to separate the immune (above the timeline) and microbiome (below the timeline) compartments as well as the risk factors.

CRITICAL DEVELOPMENTAL WINDOWS FOR SELF-COMPLETION

Developmental timing is critical when it comes to the seeding of and maturational changes for the microbiome. Information to date suggests that self-completion of the human-microbial superorganism appears to have a narrow developmental window for effective seeding surrounding birth. This is depicted in Figure 2. While later-life manipulation of microbiota can occur through the use of probiotics and fecal transplantation, evidence suggests that the immune dysregulation created by the missing gut microbes during key periods of immune maturation may remain (Olszak et al., 2012; An et al., 2014). Therefore, such treatments may have limitations and a priority is placed on timely self-completion.

There is an important coordination between microbial seeding at birth and early nutrition. VD allows the mother's microflora from the cecum and vaginal flora to become established in the newborn's gut. There is evidence that the exact same strains of bacteria from the mother take up residence in the baby's gut and will comature during infancy along with the baby's mucosal immune system. Breastfeeding is designed to supply the infant with specific maternal immune-derived factors, additional microbes, and the nourishment exquisitely tailored for a well-populated gut microflora. Additionally, breast milk can facilitate the progression of maturational changes in the microbiome (Walthall et al., 2005; Yu et al., 2013). But an improperly seeded infant gut may be unable to take full advantage of breast milk driven microbiome maturation. Problems with microbe seeding surrounding birth present opportunities for pathogenic microbes to gain a greater tissue presence. The defective immune maturation that results from a lack of the maternally supplied microbes and their gut microbial signals elevates the chances that the host response to pathogenic bacteria will be dysregulated with an increased likelihood of prolonged tissue inflammation and eventual pathology.

SELF-INCOMPLETENESS AS A BIOMARKER FOR SPECIFIC HEALTH RISKS

Myriad biomarkers and clinical measures obtained during pregnancy and early infancy have been useful in predicting later-life health risks and/or disease prognosis across the child's life course. Among examples are phenylketonuria as a biomarker for a rare metabolic defect with neurologic implications (González et al., 2011), measures of low birth weight associated with risk of cardiovascular disease (Barker, 2000), prolonged gestation and Hodgkin's lymphoma (Barker et al., 2013), homocystein and hydrogen sulfide levels associated with risk of pulmonary hypertension in pediatric cardiovascular disease (Sun et al., 2014), microRNA-206 with Duchenne muscular dystrophy (Hu et al., 2014), urine fibrinogen peptide with clinical measures and necrotizing enterocolitis (Sylvester et al., 2013), periodontal disease with risk of gut microbiota alterations and metabolic disease (Arimatsu et al, 2014), and selected adipokines and pediatric systemic lupus erythematosus (Al et al., 2009). Most of these biomarkers are useful for a limited spectrum of subsequent health risks. Obviously, biomarkers capable of reflecting increased risk of multiple, highly prevalent diseases would have great utility both for prevention strategies as well as early clinical interventions.

Recently, microbiome-associated biomarkers have gained recognition as potential indicators of elevated risk of multiple noncommunicable and infectious diseases.

Table 1
Examples of Infant Microbiome Signals Associated with Specific Pediatric Health Risks

(1)	Low microbial diversity of the infant's gut microbiota preceding later childhood asthma (Abrahamsson et al., 2013)
(2)	The production of excessive propionic acid by certain bacterial species (e.g., Clostridia, Bacteriodetes, Desulfovibrio) being associated with autism spectrum disorders (MacFabe, 2012, 2013)
(3)	Microbiota signatures being associated with obesity and its likelihood of modulation by nutrition (Korpela et al., 2014)
(4)	A subprofile of the duodenal microbiota appearing to separate celiac disease and healthy control children (Cheng et al., 2013)
(5)	Alterations in the bacterial interaction networks between children who would develop autoantibodies associated with type 1 diabetes versus those who would not (Endesfelder et al., 2014)
(6)	Specific short-chain fatty acid production by gut microbiota that is associated with epigenetic regulation of type 2 diabetes (Remely et al., 2014)

These biomarkers reflect both the diversity and numbers of different microbial species and strains that are housed in the infant's mucosal tissues, particularly the gut. As a symbiotic part of a healthy human, they help to direct our immunologic view of what constitutes self in contrast with the external environment. They also direct much of our metabolism. Table 1 shows examples of potentially useful signals within the infant's microbiota that are associated with specific health risks. The range of these associations suggests that monitoring of pediatric microbiome status may become a useful and widespread preventive tool.

MICROBIOTA AS THE CONNECTION TO OUR ENVIRONMENT

Because our microbiota are harbored at all the portals of environmental exposure (e.g., oral gastrointestinal, nasal respiratory, skin, urogenital), they represent a front line that literally communicates with and sometimes filters the chemicals, drugs, and physical factors (e.g., radiation) when encountered from sources external to our body. One of their roles is to soften or blur the boundary of what is biochemically us compared with what is not us. This seamless connection to the environment appears to be the desired state of optimized health. Real, innocuous environmental exposure is less likely to produce tissue-directed responses resulting in allergic, autoimmune, or inflammatory diseases. It should be noted that the timing of specific microbial appearance in the gut is also important. For example, *Clostridium difficile* is among the first bacteria detected in the newborn's gut; the same bacterium is pathogenic later in life (Rousseau et al., 2011).

In fact, Figure 3 illustrates that it is the microbiota that are most likely to receive the first exposure for dietary components, drugs, organic chemicals, and heavy metals. In some cases they protect the mammalian component of the child from more serious exposures. In other cases, they metabolize and help to dispense the chemical by-products that affect risk of the tissues and overall health of the child. Environmentally induced dysbiosis of the microbiota can have far reaching health consequences (Greenwood et al., 2014; Power et al., 2014). Hence, a first question worth asking with any drug treatment or environmental exposure is: how will this affect the child's microbiota?

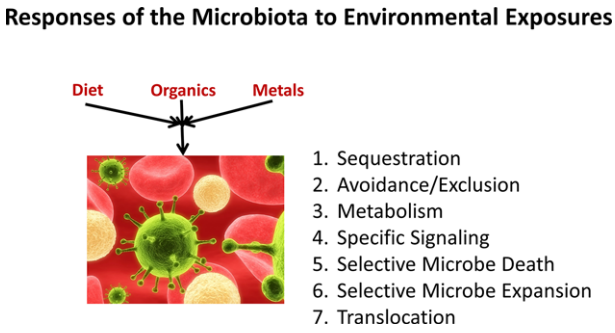

Fig. 3. The infant's microbiota is a front-line of environmental exposure to both environmental pollutants and drugs. The commensal microbes can respond to the exposure in different ways (depicted) depending upon the specific microbiota composition of the individual. For this reason, chemical and drug metabolism can vary significantly among individuals with different microbiota.

VIEWING THE MICROBIOTA AS AN INTEGRAL ORGAN

A particularly useful view of the human microbiome is that of an additional organ (Beebe et al., 2014). In fact, more pointedly it represents an integral organ. While investigators have used this perspective of the additional organ relative to metabolism, the integral organ view has utility from a host-immunologic perspective. Evidence from mother–infant pairs suggests that strain-specific bacterial transfer occurs between the mother's gastrointestinal microbiota and that of the newborn as a result of VD but not CD. There is a familial and, in fact, matriarchal transfer of microbiota that is not so different in heritable lineage from that of mammalian chromosomal transfer. For this reason, the microbiota in a healthy, fully formed infant are more likely to be closer in strain and clonal specific relationships to the microbiota harbored by a matriarchal great-grandmother than to that found outside the matriarchal relations (e.g., spouse/significant other, neighbors, hospitals, communities).

This heritable lineage concept may have implications for attempts to manage the microbiota after initial seeding at birth. Mothers who themselves have skewed microbiota (from environmental exposures, altered immune function, exposure to certain drugs, or even ancestral/epigenetic events) are likely to transfer to the infant a microbiota profile that is elevated in health risks compared with that in the general population.

Because probiotic administration and fecal transplantation are possible, they may play a role in future microbiome management. A first step is the identification of the most useful microbiome (for reduced health risks) that also matches symbiotically with the individual infant. A discussion of combinations of microbes that may help comprise the backbone of a healthy microbiome is already underway (Allen-Vercoe, 2013).

MICROBIOTA FUNCTION

Our gut microbes participate in a significant portion of human superorganism metabolism. Gut microbes affect metabolism both directly and indirectly through their chemical interaction with host cells and the subsequent production of peptides influencing glucose metabolism, energy homeostasis, gut barrier function, and metabolic inflammation (Cani et al., 2013; Li and Jia, 2013).

In fact, investigators recently termed the human microbiome as the "apothecaries within" (Beebe et al., 2014). Klünemann et al. (2014) argued that the gut microbiota is a major site for drug and environmental chemical metabolism. Kang et al. (2013) recently reviewed the role of the microbiota in drug metabolism and pointed out that while there is limited information on this, the expectation is that drug metabolism and bioavailability can change dramatically based on microbiota status.

Some information exists from animal models. In Wistar rats, administration of the probiotic bacterial strain *Escherichia coli* Nissle 1917 compared against a nonprobiotic *Escherichia coli* strain, resulted in a 43% increase in absorbance of a metabolite (AUC0–30) of the antiarrhythmic drug, amiodarone hydrochloride. Increased drug metabolism and/or absorption may be involved in this increased bioavailability (Matuskova et al., 2014). For example, evidence in rats suggests that protection against toxicity medicated by the cancer therapy drug CPT-11 is determined by the comparative abundance of butyrate-producing bacteria (Lin et al., 2014). In the mouse, cyclophosphamide has been reported to alter gut microbiota composition and cause the translocation of gram-positive bacterial species to secondary lymphoid organs. The resulting immunologic effect is the generation Th17 and Th1 tumor fighting immune cells. The drug lacks efficacy in the absence of gut microbiota (e.g., in germ-free mice).

POTENTIAL MATERNAL MICROBIOME MANAGEMENT

Because the infant microbiome is shaped largely by that of the mother via birth and breastfeeding, there is interest in the possibility of managing the maternal microbiome as a starting point to reduce health risks in offspring. Mothers who have a skewed distribution of their own microbiota may transfer that limited diversity to the offspring. For example, maternal diabetes status has been reported to affect the diversity of bacteria found in meconium (Hu et al., 2013).

There is evidence that pregnancy itself affects a woman's microbiome. For example, Romero et al. (2014) reported that four *Lactobaccilu*s phylotypes (*L. vaginalis, L. jensenii, L. crispatus and L. gasseri*) were elevated in pregnant women compared with nonpregnant women, while another 22 were reduced. While microbiome remodeling during pregnancy is likely to occur, a period of stability during the latter stages of pregnancy and during lactation has been reported (Jost et al., 2014).

In a mouse study, Hansen et al. (2014) showed that feeding mice a gluten-free diet during pregnancy and lactation resulted in a coordinated shift in the microbiota of both mothers and offspring (e.g., increases in Akkermansia and Proteobacteriain) that was associated with altered immune maturation (increases in FoxP3+ T regulatory cells and anti-inflammatory M2 macrophages) and reduced inflammation and risk of diabetes in the offspring. This suggests that management of the mother's microbiota during pregnancy and lactation could be highly useful to reduce health risks for the child. Additionally, supportive evidence comes from an analysis of the breast milk from healthy mothers compared with that from mothers with celiac disease. The latter group had breast milk with significantly reduced serum IgA and immunoprotective cytokines (e.g., TGF-β1) along with reduced numbers of both *Bifidobacterium* spp. *and Bacteroides fragilis* bacteria compared with that of the healthy mothers.

MICROBIAL DYSBIOSIS, IMMUNE DYSREGULATION, AND PEDIATRIC DISEASE

Early life disruption of the gut microbiome has been associated with disrupted immune maturation, resulting in skewed T regulatory control and a predisposition for misregulated inflammation. The combined microbial dysbiosis and subsequent immune dysfunction promotes both the opportunity for more pathogenic microbes to gain a foothold and for improper immune responses, including inappropriate, misdirected, and/or unresolving inflammation (Belkaid and Hand, 2014; Galley and Bailey, 2014).

Kamada and Núñez (2013) recently described at least four separate signaling pathways in which the gut microbiota affects immune maturation. For example, segmented filamentous bacteria activate lamina propria dendritic cells (LP DCs) and Macs to induce Th17 and Th1 cells that in turn can help regulate the microbial community. Polysaccharide A + *B. fragilis* and other microbes promote development and activation of T regs (FoxP3+ regulatory T cells). Butyrate appears to play a role. Through toll-like receptor (TLR) stimulation, microbiota can promote the differentiation of IgA-secreting plasma cells. Finally, the microbiota is involved in a feedback loop of interregulation with innate immune lymphoid cells bearing the retinoic acid receptor-related orphan receptor γt.

Li et al. (2014) recently reviewed the factors connected with early-life microbiota and risk of childhood illnesses. Risk of both infectious and noncommunicable diseases is affected. For example, Madan et al. (2012) reported that the pattern of gut microbial colonization in premature infants is predictive of the risk for neonatal sepsis. For noncommunicable diseases and conditions, Mejía-León et al. (2014) reported that children in Mexico at the time of diagnosis with type 1 diabetes had altered gut microbiota with higher levels of the genus Bacteriodes and lower levels of Prevotella compared with controls. Following two or more years of treatment, the ratios in the children with type 1 diabetes were more similar to those of the controls. Additionally, Soyucen et al. (2014) reported reduced

Bifidobacterium colonization in recently diagnosed children with type 1 diabetes compared against controls.

There is evidence suggesting that during infancy, gut microflora can exert a major influence that extends to the brain and affects behavior (Douglas-Escobar et al., 2013). At least one pathway for these effects is through the actions of specific bacterial metabolites (e.g., short-chain fatty acids, such as butyrate and propionic acid) exerting effects on the developing brain and nervous system. Evidence suggests that propionic acid can promote microglia activation, altered gene expression, neuroinflammation, increased oxidative stress, and mitochondrial dysfunction (MacFabe et al., 2007; Al-Lahham et al., 2010; Tang et al., 2011; Aldbass et al., 2013; den Besten et al., 2013). MacFabe and others have reported that gut microbial dysbiosis in children may contribute to elevated risk of autism (Hsiao et al., 2013; MacFabe, 2013). Additionally, using a rat model, Foley et al. (2014) demonstrated that pre- and postnatal exposure to an enteric fermentation metabolite of bacteria, propionic acid, could alter the development and behavior of adolescent rats producing repetitive-like and antisocial sexually dimorphic behaviors consistent with those of autism spectrum disorders.

Exposure to environmental chemicals is thought to be a potential route to microbial dysbiosis. For example, Snedeker and Hay (2012) recently discussed the potential for obesogenic chemicals to increase the risk of type 2 diabetes via a disruption in gut microbial ecology. Although a new area of investigation, several environmental chemicals have been reported to disrupt normal gut microbiota. These include arsenic (Lu et al., 2014), cadmium (Liu et al., 2014), chlorpyrifos (Joly et al., 2013), glyphosate (Shehata et al., 2013), particulate matter (Kish et al., 2013), and polychlorinated biphenyls (Choi et al., 2013).

CONCLUSIONS

A new opportunity exists in OB/GYN and pediatric care medicine to blunt the epidemic rise of noncommunicable diseases (NCDs). Because most NCDs have their origins in early life (pre- and postnatal) environmental experiences (e.g., the Barker hypothesis; Barker, 1991), medical decisions made early in life can have far reaching implications for health risks with each passing decade as the child ages. As detailed in this review, these decisions require a new view of the patient. We are no longer treating a human mammal. Indeed, the fully formed infant with a robust and diverse microbiome is majority microbial and needs to be medically managed as such for optimum health. The ramifications are that all risk–benefit decisions (e.g., VD vs. CD, diet, exposure to drugs and chemicals) need to be recast with a higher priority given to what is best for installing, preserving, protecting, and/or restoring the microbial part of the human superorganism child. It will be useful to begin management of the microbiome during pregnancy, at birth, and continuing through early infancy to ensure that each child has the best opportunity to be fully formed. Given our present knowledge of the microbiome, there is no reason for children to go through life missing that which connects us to our environment, protects us from dysbiosis, helps to effectively metabolize medications, and can reduce the risk of noncommunicable diseases.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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