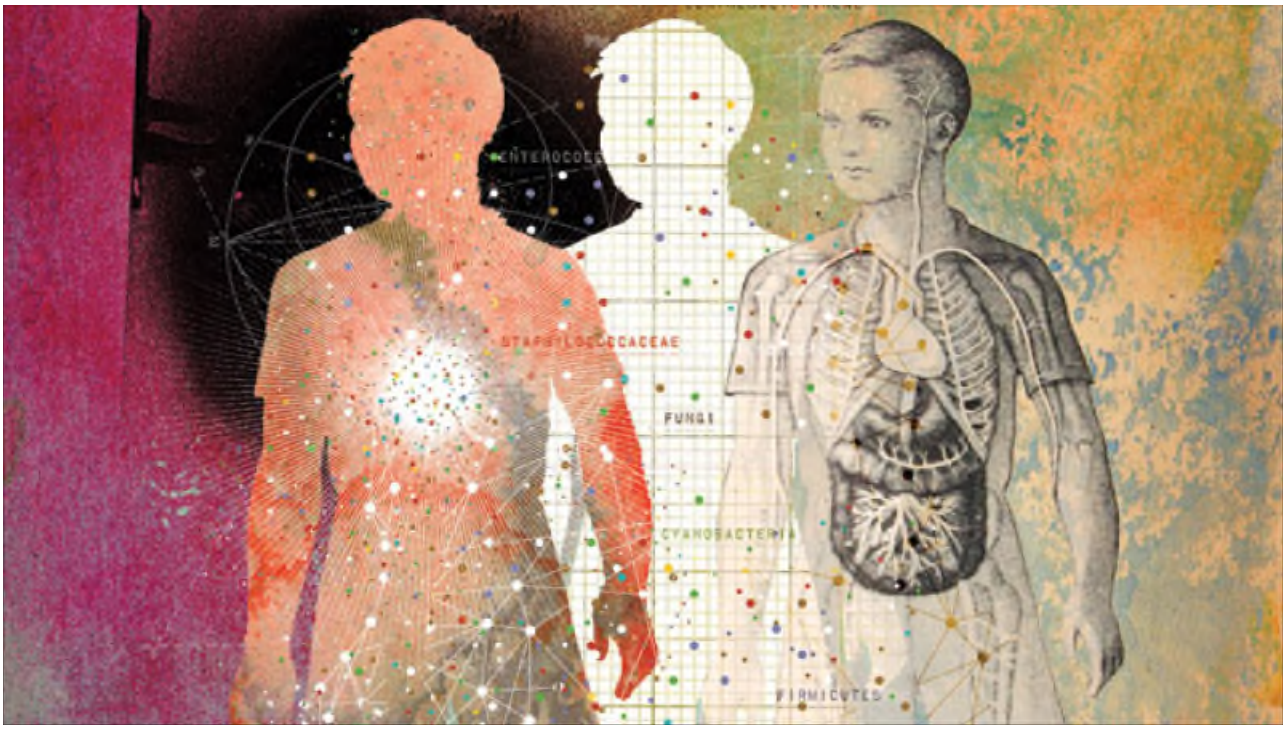
The Sum of Our Parts

Putting the microbiome front and center in health care, in preventive strategies, and in health-risk assessments could stem the epidemic of noncommunicable diseases.

By Janice Dietert, and Rodney Dietert | July 1, 2015



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Looking across generations at how health concerns have changed over the past century is an enlightening exercise. For your ancestors living in the roaring ’20s, fear of infectious diseases—including typhoid fever, cholera, and influenza—far outweighed concerns about heart disease or cancer. Autism, Alzheimer’s, attention deficit disorder, and Parkinson’s disease were virtually unheard of. Allergies, then called hay fever, were around, but not common. Ratchet ahead through the rock-and-roll and disco generations and on to the ’80s and ’90s, and the fear of cancer grew enormously, while a number of new diseases began to appear on the radar screen. Asthma, autism, lupus, arthritis, inflammatory bowel disease, attention deficit disorder, celiac disease, multiple sclerosis, obesity, and diabetes, among others, became common concerns. Fast-forward another two decades to present day, and it is not a matter of whether you, your friends, or family members have one of these ailments, but which ones and how many.

In less than 100 years, leading diseases and causes of death have shifted dramatically away from infectious diseases and heavily toward noncommunicable diseases (NCDs), not just in developed countries, but around the globe. NCDs are now the number one killer worldwide, accounting for 63 percent of all mortalities.[1] There is no question that environmental variables, including exposure to cigarette smoke, certain dietary factors, and chemicals such as heavy metals, pesticides, endocrine disruptors, or particular drugs, increase one’s risk of developing an NCD. Psychosocial stressors also play

a role. But any assumption that the ongoing NCD epidemic is due solely to external factors would be missing a key part of the story: the human microbiome. In reality, the NCD epidemic is as much about the ways we have altered our microbiomes in recent decades as it is about our changing external environment.

Commensal microbes that live on and in us are critical for our health. By cell numbers, we are approximately 90 percent microbial, and the vast majority of the genes expressed in our superorganism are not on our mammalian chromosomes but in the bacteria, archaea, and single-celled eukaryotes that call the human body home. Normally, a robust microbiome would be part of our inheritance, a legacy passed, largely maternally, from generation to generation. But recently that chain has been broken, usually more than once. The increase in cesarean deliveries, the reduced prevalence and duration of breastfeeding, overuse of antibiotics both as prescription drugs and in agriculture, modern urban living surrounded by sanitizers, and a general tendency to limit contact with the environment have changed our relationship with the microbes that are an integral part of our biology. In today's world, our best chance of acquiring microbes might be from touching our computer keyboards and cellphones or frequenting shopping malls, hotel rooms, or doctors' offices—and many are not bugs you want in and on your body.

Our microbial gatekeeper

The human microbiome plays a critical role as a filter between us and the world. In fact, it is the microbiome that determines our actual exposure to the environment. Substances such as foods, drugs, and environmental chemicals—collectively termed xenobiotics—must first pass through the layers of microbiota on the skin, in the gut, and in the airways where, depending upon the microbes present, the chemicals will be sequestered, excluded, or metabolized before they ever enter our cells. The common gut actinobacterium *Eggerthella lenta*, for example, can significantly change the potency of the cardiac drug digoxin.[2] Likewise, microbiome composition affects the toxicity of certain environmental chemicals such as arsenic, with some sulfur-reducing gut bacteria able to generate highly toxic, thiolated species of arsenic, thereby increasing health risks following exposure.[3] And, of course, diverse gut microbes are critical components of our gastrointestinal system, helping us process the otherwise hard-to-digest foods we eat.

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There is also a flip side to the xenobiotic-microbiome relationship: the external environment affects the composition of our microbial populations. Even some xenobiotics that were previously thought to be safe may need to be reexamined in light of effects on the microbiome. For example, commonly used food emulsifiers such as polysorbate 80 and carboxymethylcellulose have been reported to adversely affect the microbiome of rodents, predisposing them to chronic inflammation and elevated risk of metabolic syndrome. In one study, mice that drank the emulsifiers in water showed reduced overall diversity of the gut microbiota, decreased representation of generally beneficial Bacteroidales species, and higher numbers of some potentially pathogenic bacteria, such as Ruminococcus gnavus.[4] In some rodent strains, exposure to the emulsifiers also thinned the mucus barrier, reducing the physical distance between bacteria residing on the surface of the barrier and gut epithelial cells by more than 50 percent. Such alterations can affect the interactions between bacteria and cells of the innate immune system, increasing the risk of inflammation-driven disease. Not coincidentally, microbiomes that have been impoverished or unbalanced by environmental factors often have a skewed bacterial metabolism, affecting their host's energy utilization, hormone status, and control of inflammation.

Thus, it should be no surprise that altered microbiomes and elevated risk of NCDs go hand in hand. Myriad studies have linked specific NCDs to an altered diversity of gut microbiota in early life, with possible risk factors including maternal and infant diet, birth delivery mode, perinatal environmental toxicant exposures, and psychosocial stressors.[5,6] Many disease-associated microbiomes can serve as a type of fingerprint, reflecting the underlying disease condition. In some cases, these skewed, limited-diversity microbial communities may help cause or promote the disease; in others, they may be a consequence.

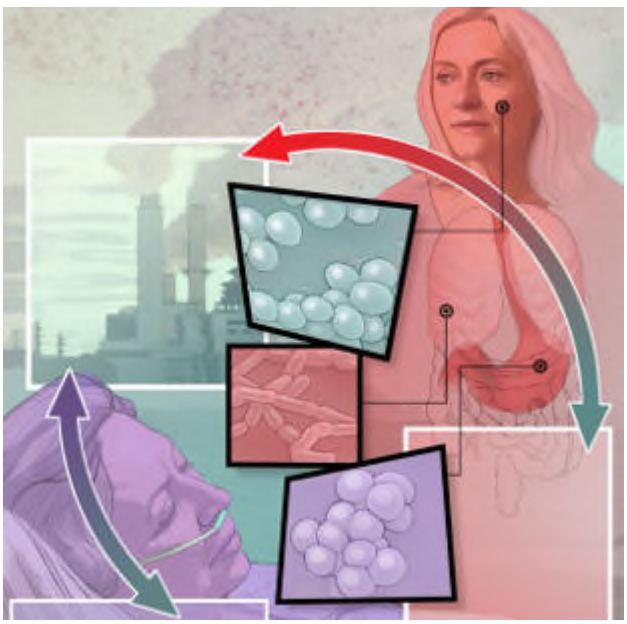
And if the status of the microbiome appears to affect the outcome of xenobiotic exposures and risk of NCDs, the reverse appears also to be true. Having an NCD appears to influence the composition of the microbiome and the body's susceptibility to some xenobiotics. In recent studies, Yale toxicologist Gary Ginsberg, also of the Connecticut Department of Public Health, and others demonstrated that NCDs, such as cardiovascular disease, obesity, or chronic kidney disease, affect one's vulnerability to certain heavy metals.[7]

Given the intimate relationship between the human immune system and the microbiome, it is not surprising that alterations in our microbial makeup can greatly affect health.

The current gold-standard model for assessing environmental health risks was developed in 1987 by the US National Research Council during a time when the role of the microbiome was largely unknown. In effect, toxicologists and risk assessors have been missing the impact of the microbiome for decades. This year, one of us (R.D.) and Ellen Silbergeld of the Johns Hopkins Bloomberg School of Public Health proposed a new health-risk assessment model that places the microbiome as the filter between the external environment and the human body's own cells.[8] The new model relies on biomarkers that correlate with microbiome composition—such as volatile organic compounds (VOCs) and short-chain fatty acids—to help to connect environmental exposures, microbiome status, and risk of NCDs.

Microbial role in immunity

In addition to playing gatekeeper between our mammalian cells and the external environment, the human microbiome is critical to the maturation and function of our immune system, affecting the entire spectrum of immune processes. Commensal microbes have been shown to influence, for example, the body's overall cytokine milieu; the balance among T regulatory cells and inflammation-promoting Th17 cells; T cell–driven adaptive immune responses; macrophage and dendritic cell function; and natural killer T-cell activity, among other immunomodulatory properties. Given this intimate relationship between the human immune system and the microbiome, it is once again not surprising that alterations in our microbial makeup can greatly affect health.



Microbiome-based immune programming largely takes place during a critical window early in

postnatal development and extends well beyond the gastrointestinal tract, affecting immune-cell reservoirs in the bone marrow and spleen as well as the functional capacities of resident immune-cell populations in distant organs and tissues. Microbiome-driven immunomodulation occurs via cell surface receptor signaling—involving Toll-like and NOD-like (nucleotide-binding oligomerization domain) receptors, among others—and also through epigenetic regulation, driven by microbe-produced short-chain fatty acids, that can affect the expression of hundreds of genes related to immune function.

THE MICROBIOME CONNECTOME: The human microbiome plays an integral role in our relationship with the external world, and both the composition of our microbial communities and our environmental exposures influence our risk of contracting certain noncommunicable diseases (NCDs). Conversely, some NCDs can impact our microbiome status and our reactions to certain xenobiotics. The microbiome is also intimately involved in the function of the human immune system, further affecting health and disease. The interplay between our internal and external environments must be considered when evaluating health risk factors.
See full infographic: JPG

Germ-free (gnotobiotic) mice provide a sobering model for what happens to a developing human immune system in the absence of microbiome-based training.[9] When microbiota are absent, normal postnatal immune maturation is blocked, and tissue homeostasis is never fully established. Lymphoid deficiencies occur in both the body's mucous membranes and its systemic tissues, such as the lymph nodes and spleen. Germ-free mice also develop imbalances among specialized immune cell populations that result in improper immune responses when challenged with injury or a pathogen. Depending on the nature of the challenge, defective host immune responses may include increased susceptibility to certain infections, reduced vaccine responses, and/or inflammation-induced tissue pathologies, such as asthma or colitis.

Not surprisingly, perinatal treatment with antibiotics can compromise the microbiome, depleting or eliminating the microbial signals needed for a newborn's postnatal immune development. The result can be an immune profile that bears worrying similarities to those of germ-free mice. For example, antibiotic-induced disruption of the neonatal microbiota can result in aberrant immune maturation with altered cytokine production, the creation of a proinflammatory state, shifts in both host and microbial metabolism, and altered epigenetic programming.[10] And the results can be long-lasting. Antibiotic administration in infants is associated with higher risk of asthma later in childhood, a risk that scales with the number of rounds administered.[11] Increased use of antibiotics in infants is also associated with a higher risk of childhood obesity,[12] and some investigations have reported an association between antibiotic use and an elevated risk of celiac disease. It is likely only a matter of time before more links between disease and an infant's compromised microbiome are revealed.

A better understanding of normal microbiome maturation may inform potential microbial-manipulation therapies, in which life stage–specific adjustments to the microbiome can improve health outcomes.

Self-completion

Given the undeniable importance of commensal microbes in both training our immune systems and serving as a barrier between ourselves and the outside world, one of us (R.D.) has posited that a complete microbiome, seeded at birth, is absolutely critical for a healthful life, an idea called "the completed self hypothesis."[13] Single-celled organisms from all three domains of life—eukaryotes, archaea, and bacteria—join our mammalian cells to create a superorganism. Inadequate or inappropriate seeding of the microbiome is in many ways the equivalent of being born with a serious birth defect,

resulting in inappropriately matured physiological systems.[14] In the absence of effective microbiome-based training, the immune system does not learn what is safe outside of the body, resulting in haphazard, inappropriate reactions to innocuous environmental factors—allergens such as pollen, mold, cat dander, and peanuts. It also fails to properly recognize and ignore internal targets, resulting in autoimmune and inflammatory responses that are misdirected, ineffective, and sometimes never-ending. Such reactions can eventually compromise the function of our own tissues and organs.

A newborn's microbiome is largely inherited from the mother, with birth being the most pivotal step in seeding. During vaginal delivery, the passage of the baby down the birth canal allows exposure not only to the vaginal microbiota but also to a film of maternal intestinal flora. This process is thought to provide direct seeding of the newborn's gut with maternal microbes. Skin-to-skin seeding is also important at birth. When natural childbirth is interrupted—for example, by cesarean delivery—the baby is seeded by default with microbes from the local environment, typically from the largely sterile hospital staff and equipment. Invariably, this results in incomplete and/or inappropriate infant microbial seeding. Indeed, numerous studies have suggested that cesarean-delivered babies typically have altered immune profiles and are at an elevated risk for NCDs such as asthma, type 1 diabetes, and obesity. A recent study of 98 Swedish infants and their mothers, for example, found that cesarean delivery significantly blocked vertical transmission of the maternal microbiome to the infant.[15] Additionally, the microbiome transition toward an adult-type profile was shaped by the infant's feeding pattern after birth, including both breast-feeding and the transition to solid foods.

Disruptions to complete microbiome transfer can also occur before birth, as the mother's microbial makeup is influenced by her diet, environmental exposures, and health. Microbiota originating from a mother afflicted with one or more NCDs or from a mother who was treated with antibiotics during pregnancy are likely to differ from the microbiota transferred from a mother who is NCD- and antibiotic-free.

To understand which microbes are critical for the proper development of a baby's immune system, it is first important to know what a healthy microbiome looks like and what happens to it during normal childhood maturation. Merete Eggesbø of the Norwegian Institute of Public Health and his colleagues have provided a useful picture of normal development of a properly seeded microbiome across infancy in the absence of antibiotic administration and overt disease. They reported that the gut microbes present in four-day-old Norwegian newborns were useful in predicting the composition seen at three months of age (in the absence of medical interventions).[16] The recent study of 98 Swedish mother-child pairs provides further documentation of infant microbiota composition during the first year of life.[14] Going forward, it will be important to collect similar data on normal microbiome development across different regions of the world, as geographic differences do exist among microbiomes. This information can help researchers evaluate the risks and benefits of various birthing, infant-feeding, and treatment practices.

A better understanding of normal microbiome maturation may also inform potential microbial-manipulation therapies, in which life stage–specific adjustments to the microbiome can improve health outcomes. (See "Manipulating the Microbiome" below.) Of course, such therapies should always consider any potential risks, and the ethical implications of microbiome manipulation, as our microbial partners are really a part of our biological identity. (See "Who Are We Really?" *The Scientist*, March 2012.)

For now, we need to rethink the way antibiotic treatments are handled. There has already been a widespread call for priority shifts in the use of antibiotics, designed to slow down the selection of multidrug-resistant bacteria and preserve effective antibiotics for the most serious conditions. But there is another consequence of antibiotic use that has been largely overlooked: a severely altered and/or largely destroyed microbiome. Evidence continues to mount regarding the potential disease outcomes thought to be related to the destruction of the infant microbiome. It's becoming clear that we should not be leaving children deficient in most of their microbiome just to wipe out one pathogenic bacterium. The short-term gain comes at the cost of an increased chance of developing NCDs later in life. That is not to say that antibiotics should not be used, but that antibiotic administration as recently practiced is an incomplete therapy with unacceptable long-term risks. Future treatments with antibiotics should be

accompanied by complementary therapies to restore the commensal microbes that were never intended to be killed.

Indeed, the goal of any medical procedure should be to leave patients with the best possible microbiome. The importance of our microbial partners has for too long been overlooked by the medical establishment. A new treatment standard that takes a complete microbiome into consideration could result in sweeping changes in health care, such that more integration and better personalization are likely outcomes.☐

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MANIPULATING THE MICROBIOME

In contrast to our human genome, our microbial genome is more amenable to adjustment by altering the composition of the microbial communities inhabiting our bodies. Some researchers and doctors have already recognized the power of microbiome manipulation—think probiotics and fecal transplants (*Microb Ecol Health Dis*, 26:25877, 2015). Probiotic mixtures can be ingested to shift microbial balance and metabolism in the gut, translating to potentially useful physiological alterations. Recent reports suggest that probiotics can prevent diarrhea in children taking antibiotics, for example, as well as increase the efficacy and reduce the side effects of anti–*Helicobacter pylori* therapies and aid peanut oral immunotherapy for the treatment of peanut allergy. The more radical approach of fecal transplantation, in which microbiota are installed in the gut via a gastric or nasoduodenal tube, an enema, or colonoscope, or orally administered frozen capsules, has proven successful for the treatment of *Clostridium difficile* infection (*Infect Dis Clin North Am*, 29:109-22, 2015), and other potential uses are currently under investigation. Fecal transplants have also been used subsequent to antibiotic administration to reinstate a healthy microbiome. Identification and selection of donor microbes is likely to be an important future consideration for these therapies.

While microbiome manipulation may have benefits at any age, once certain developmental programming of our physiological systems has occurred, it is likely to be much more difficult to correct underlying dysfunctions. Intervention early in life is the most comprehensive technique, as it allows for self-completion in the newborn prior to most postnatal developmental programming. We believe that no baby should go unseeded or be left to haphazardly acquire the daily menu of microbes from a given hospital environment. If elective cesarean delivery is planned, deliberate seeding of the baby should be considered. Maria Gloria Dominguez-Bello of the New York University Langone Medical Center, for example, has promoted the use of vaginal swabs immediately after cesarean birth to simulate the baby's exposure to maternal microbes in the birth canal, and preliminary results are encouraging (*Trends Mol Med*, 21:109-17, 2015). Potential medical complications should be considered in any decision regarding microbial manipulation therapies. These must be balanced against the immune and other long-term health risks that are created if the baby cannot self-complete as a superorganism.