COMMENT

The theory of disappearing microbiota and the epidemics of chronic diseases

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In recent decades, the incidence of many apparently unrelated chronic diseases has markedly increased. Here, I theorize that losses of particular bacterial species of our ancestral microbiota have altered the context in which immunological, metabolic and cognitive development occur in early life, which results in increased disease. This ominous trend suggests that we must refocus efforts to understand and reverse the underlying circumstances that are responsible for our disappearing microbiota.

In the present era, medical scientists have been confounded by the increasing incidence of multiple diseases across the world, beginning first in developed countries, and gradually spreading to other areas as they develop. These include the rises in cases of obesity, asthma, hay fever, food allergies, inflammatory bowel disease, juvenile (type 1) diabetes and autism, among many others. Are these diseases, which affect different body systems, unrelated or can a unified theory explain the increased incidence of all of these?

I believe that the latter possibility is true, and that the central theory to explain why these diseases have arisen and by what mechanism is based on modern changes in early life events that are related to the human microbiome. According to this theory, the microbiome of humans and of other animals is not accidental, but has been selected over long time periods to optimize host reproductive success through interactions between the microbiota and host physiology[1]. Early life is the crucial period during which the adult microbiome becomes established[2], and development of the host and of the microbiota occur together in a conjoined manner through a dynamic equilibrium that follows a well-choreographed path. In early life, the context is set for the important developmental decisions that are required for the immune system to distinguish between what is self and what is not self, for metabolic organs to partition how much energy to expend or to save, and for the brain to determine how to respond socially to a person who might be either a friend or a foe.

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Causes of the disappearing microbiota

I have proposed that this developmental equilibrium has been disrupted by elements of modern life that have led to the loss of crucial microbial taxa, and to the loss of their roles in shaping human physiology[1,3]. This theory of disappearing microbiota can help us to understand the increased incidence of a wide variety of diseases. Several factors should be considered to help understand the loss of microbial richness in the populations in industrialized countries.

First, strong evidence is emerging for the importance of vertical transmission of the key microbiota taxa from mother to child[4]. Such a pattern of transmission suggests that if there are extinctions of microbial taxa in one generation, this loss would be passed down to the next generation, unless there are opportunities for the missing taxa to be regained by horizontal transmission[3]. One example of a cause of decreased vertical transmission of the microbiota is the caesarean section. In the United States, one-third of babies are born by caesarean section; in many countries and populations, the proportion exceeds one-half. For such births, the intergenerational transfer of microorganisms, which is a conserved feature of essentially all animals, is diminished. Another example affecting the intergenerational transfer of the microbiota is the widespread use of antibiotics during pregnancy.

Second, humans have been sharing their commensal microorganisms with one another since time immemorial; we have bathed in and drank water that contains the microorganisms that are present in our faeces. Good sanitation — in particular, clean water — has been crucial for avoiding infections with high-grade and lethal pathogens, which has contributed considerably to reduced childhood mortality and to improved longevity. However, an unexpected consequence has been the decreased horizontal transmission of commensal microbiota. Clean water is so important to overall health that the idea that it might have some biological costs by reducing horizontal transmission of the microbiota has received scant attention.

Third, in addition to the decreased acquisition of commensal microorganisms from other humans, in each recent generation, there have been multiple insults

to the maintenance of key microbiota taxa in early life. Major factors include antibiotic exposures of infants, and the feeding of formula milk as a replacement for breast milk. Formula milk includes the macronutrients that are necessary for healthy infant growth, but it almost completely lacks many of the micronutrients, such as particular oligosaccharides, that foster the survival of inherited and beneficial microbiota. The composition of breast milk seems to have evolved to favour (select for) those microorganisms that have a well-established commensal relationship, having been passed down over the millennia.

Exposure to antibiotics may have the greatest impact on the early life microbiota — due to both the extent and timing of their use. The importance of intergenerational transmission of the microbiota amplifies the effects of prenatal events, such as the antibiotics given to a mother during pregnancy and just at birth (and even later, as they are excreted in milk). Evidence is accumulating that antibiotic use by young women before pregnancy could also be contributing to health problems in their children. An extension of this might be that any antibiotic dose in a female has some impact on her future children. This is a frightening notion, but we need to understand whether or not it is true, and if so, what is the magnitude of the effect, so that clinicians can make more informed decisions about when antibiotic use is appropriate. Without much supporting evidence, we all originally believed that any disturbance to the microbiota after a course of antibiotics would be temporary, and that everything would soon return to normal. But we now know that the microbiota is not uniformly resilient[5]. In young children in particular, (antibiotic) insults may change the development of the 'adult' microbiota, and not allow its normal maturation[6].

Thus, despite the immense benefits that antibiotics have brought, it may be that they not only temporarily perturb the microbiota, but can also lead to the extinction of some microbial taxa, with additive effects on host physiology. Studies in mice have shown that short-term, low-dose antibiotic exposures early in life that lead to only transient effects on microbiota composition may have long-term effects on host phenotypes, such as adiposity and the levels of immunological mediators[7]. One explanation for why this occurs is that antibiotics alter (select) the microbiota at a crucial time window during development, when equilibria are being established, and that even with full resolution of the microbiota composition, the damage to other physiological processes, such as the immune system, has already occurred. We know that severe infections during early childhood stunt the height trajectory of children, from which recovery is limited. Similarly, exposure to therapeutic antibiotic doses early in life may cause profound and sustained microbiota perturbations, which can lead to altered immunity[8].

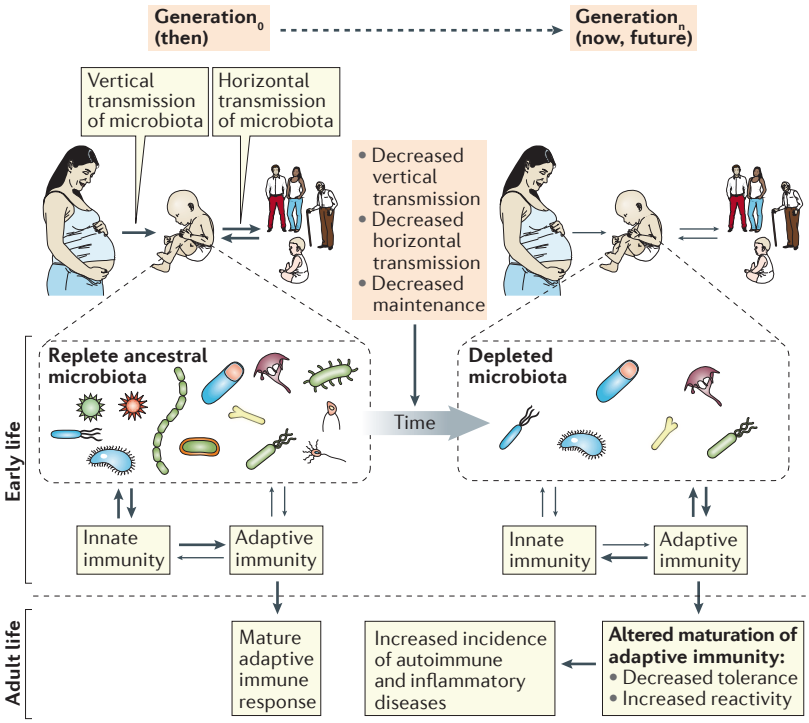

Figure 1 | **A model for the interaction of the inherited microbiota with early life immunological development in past and present children.** In the past (Generation$_0$), a replete vertically and horizontally transmitted microbiota interacted primarily with the diverse elements of the innate immune system, which in turn signalled to adaptive immune cell populations. Over time, this co-evolved dynamic equilibrium led to developmentally normal maturation of adaptive immunity. Over succeeding generations, there has been a major shift in the equilibrium. Our children (Generation$_n$) have been progressively losing microbial diversity, and the remaining constituents of the microbiota are less able to signal to the innate immune constituents that have been selected in and for the context of the replete ancestral microbiota. The emergent 'modern' opportunistic microorganisms trigger adaptive immune responses to a greater extent than do the ancestral microorganisms. With these shifts in the equilibria, the maturing adaptive immune system becomes less tolerogenic and more reactogenic. I believe that such changes fuel the current epidemics of autoimmune and inflammatory diseases, sometimes with prolonged latency.

Immune effects of the disappearing microbiota

This combination, of a loss of commensals in one generation (for example, owing to antibiotic use or formula milk feeding) and the diminution of both vertical and horizontal transmission, suggests that microbial extinctions become fixed and cumulative across generations[3]. Therefore, the microbial disappearances are increasing and the loss of diversity is steadily worsening. There is already evidence to support the worrying notions of microbial extinctions[9] and of cumulative effects over generations[10].

These ideas are particularly relevant to immunology, because early life is the period when the adaptive immune responsiveness of a host develops, and when important decisions regarding responsiveness versus tolerance are made[11]. In immunology, as in all of developmental biology, context is crucial. Although innate immunity has evolved, in part, to defend against high-grade pathogens, more subtle interactions (for example with commensal microorganisms) and those innate responses requiring amplification benefit from an engaged adaptive immune response. The frontier regulating the development of adaptive immunity may be the most context specific, and carries the greatest long-term consequences.

A growing body of evidence indicates that both the prenatal (maternal) microbiota[12] and the early life (infant) microbiota have crucial roles in the later development of adaptive immunity[13]. Important interactions between innate and adaptive immunity may also be relevant here (FIG. 1). With the decline of the ancestral microbiota, the net early life interactions with innate immune elements may have shifted away from the commensal taxa. Thus, the signals that the major adaptive immune cells receive from their two principal inputs — the microbiota and innate immune cells — will have shifted, creating an altered context for their next developmental steps. Over many millenia, the composition of the early life microbiota has been a 'key' that has (selected for) shaped the structure of its 'lock', innate immunity. Now with the key changing, the lock no longer closes optimally. Thus, effects cascade. Ongoing selection will lead to a restoration of (a new) equilibrium but predictably that will require many generations, and in the interim, much cost in human health.

I speculate that a net reduction of the tolerizing context associated with the ancestral microbiota results in heightened responses to opportunistic organisms and adventitious stimuli. This would lead to a tone of heightened immunological reactivity that could manifest as disease immediately and also later in life, sometimes with considerable latency. The remarkable aspect of vertebrate life is not that we respond to pathogens, but that we so easily tolerate the overwhelming numbers of commensal microorganisms that we host. With the work highlighted in this issue of *Nature Reviews Immunology*, it becomes more clear that the interactions of the early life microbiome with the host are setting the immunological tone for the remainder of the host's lifespan.

Perhaps the most profound effects focus on the development of immunity in the gut, although microbial dynamics in the skin, mouth and vagina all might contribute to overall immunological tone and to site-specific effects. An important concept for all of these sites concerns the timing of developmental windows[11]. At which point in life are the major immunological decisions made and when does the developmental window close? Although there is unlikely to be an absolute answer, as this window is probably to some degree specific to each individual, there probably will be a time-gradient of opportunity to permit interventions.

Future directions

One crucial issue lies in understanding the actual role of the microbiota in the causation of immunological diseases. Once disease is manifest, any microbial abnormalities that are detected could be a consequence of the disease and/or of the pharmacological agents that are used to treat the disease, rather than its cause. Because of the difficulties in obtaining relevant specimens from at-risk individuals (and low-risk controls), using relevant animal models to examine the microbiota and pathological mechanisms before disease onset is crucial. Recent studies in this respect point to roles for both an abnormal microbiota and specific mechanisms in the host that can deepen our understanding of autoimmune diseases, such as type 1 diabetes[14,15].

Understanding the threats and stopping the damage to the next generation are the first orders of business. With deeper knowledge of immunological development, for example, we might be able to define the best location, timing and mechanism to intervene. Interventions could be drugs, prebiotics or validated probiotics, or combinations of these compounds, and even some vaccines. With a disordered microbiome, opportunistic organisms may have disproportionate roles, by suppressing developmentally beneficial microbiota taxa. In such cases, specific vaccines, and even specific (truly narrow-spectrum) antibiotics, could be useful.

I believe that ultimately we will have to restore our lost microbiota to optimize human health and to reverse the disease epidemics that are increasing around the world. This long-term scientific challenge will require immunologists and medical scientists to work in the interstices of microbiology. For immunologists, armed with the discoveries of modern science, it will mean a return to their historical nineteenth century roots in microbiology. In the interim, with the emergence of the microbiome as an unanticipated force of nature, these new ideas must be accommodated into the immunological canon.

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Competing interests statement

The author declares no competing interests.