Hay fever.

Health and our microbial partners: The hygiene hypothesis and the old friends mechanism

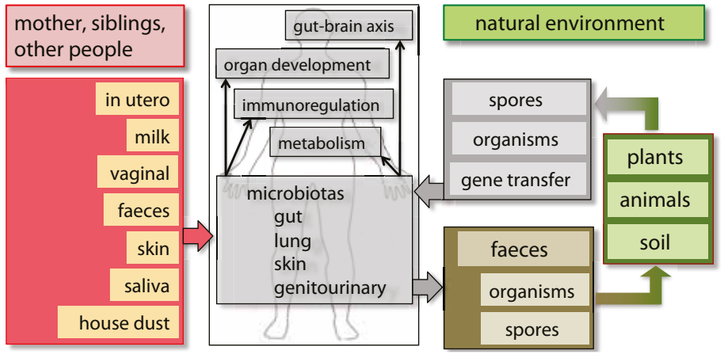
Graham A.W. Rook

Disorders associated with chronic inflammation become more frequent as countries develop economically and adopt the western lifestyle. These disorders include autoimmune diseases, where the immune system is attacking our own tissues (multiple sclerosis, type 1 diabetes), inflammatory bowel diseases where it is driving inflammation in the gut (Crohn's disease, ulcerative colitis), and allergic disorders where it is attacking harmless molecules in food or in the air (hay fever, allergic asthma). Moreover, in high income settings there are also many superficially healthy people who have persistent systemic background inflammation, easily detected by measuring blood levels of molecules involved in inflammation: this chronic inflammatory state is linked to increased risk of developing heart disease, metabolic disease, and some psychiatric problems such as depression. All of these problems are at least partly due to failure of regulatory mechanisms within the immune system, which should stop it from attacking targets it must not attack (such as our own tissues) and should ensure that the system is turned off completely when it is not needed. So why is the modern lifestyle accompanied by inappropriate activity of the immune system?

Immune system memory

The "hygiene hypothesis", applied initially only to allergic disorders, suggested that hygiene, by reducing exposure to infections early in life, contributes to defective immune function. We now know that it is not that simple, and hygiene is not the main problem. Many scientists now prefer the terms "old friends" mechanism, or "biodiversity hypothesis". Like the brain, the immune system needs data input, particularly in early life, in order to function correctly. The relevant data come from exposure to three main categories of organisms. These are: symbiotic organisms (microbiota) that live in and on us (particularly the gut microbiota); organisms and spores from the natural environment; and, possibly, some infections that were continuously present from soon after birth in evolving human hunter-gatherers (for example parasitic worms). How does exposure to these organisms enhance regulation of the immune system, and why is this failing in modern urban settings?

Graham A.W. Rook
Centre for Clinical Microbiology,
Department of Infection,
University College London, UK



Intricate relationship between human and natural environments and the consequences for microbiota in the individual.

Friends in the gut

The gut microbiota contains many more microorganisms than there are human cells in our bodies and plays many vital physiological roles. The immune system has the complex job of maintaining, tolerating and "farming" the microbiota while simultaneously excluding organisms that cause disease (pathogens). Thus the immune system and microbiota develop together, particularly during early childhood. Some species of bacteria within the microbiota drive the formation within the immune system of specialised cells (regulatory lymphocytes) that "police" the immune system and help to suppress inappropriate immune responses. Other bacteria release small molecules that have systemic anti-inflammatory effects, so the microbiota needs to contain the bacterial strains that fulfil these functions. However, the microbiota comes mostly from the child's mother. Some transfers occur while still in the mother's womb before birth, and lots more during passage through the birth canal. Then more strains are transferred in breast milk, which contains some gut microbiota, and through day-to-day contact and kissing. The problem is that this transfer of microbiota can be interrupted by caesarean section, by not breast feeding, and worst of all, by administering antibiotics during pregnancy or during the early months and years of life. Antibiotic use at these times distorts the microbiota and is associated with increased risk in later life of several of the conditions listed above, notably allergies, metabolic problems and obesity. Similarly, monotonous western fast food diets distort the microbiota and lead to reduced diversity and even to extinctions of crucial species. This matters because low gut microbiota biodiversity is a characteristic of illness. Diets rich in fibre (plant polysaccharides) and various small molecules from plants (polyphenols) help to maintain this biodiversity.

Outdoor friends

What about organisms from the natural environment? The air we breathe (about 10,000 litres per day for an adult) contains numerous microorganisms. When these impact the cells lining the airways in early childhood, they activate regulatory path-