Defined by Joshua Lederburg at the turn of the 21st century, the microbiome may have an important impact on human health. The microbiome has existed since the dawn of multicellular life, thought to be about one billion years ago. Hosts and microbes have co-evolved with the result that we derive many benefits from our microbiotic guests. For example, it is estimated that the Bacteriodes species in the human colon synthesises half of our requirement for vitamin K, and gut bacteria help us deter invading organisms by contributing to the innate immune system and denying pathogens space to colonise. The widespread use of antibiotics and antimicrobials can disrupt the natural balance.

The microbiome is also believed to have implications for a wide range of diseases, from autoimmune conditions such as diabetes, rheumatoid arthritis and inflammatory bowel disease to some cancers and even depression.

This is an important emerging area of research which requires further robust studies to clearly distinguish between correlation and causation.

The following case studies represent some of the research being done by the MRC relevant to this area.
Declining *Helicobacter pylori* infection and obesity

Around half of the world’s population are infected with *Helicobacter pylori* (*H. pylori*), a lifelong and typically asymptomatic infection of the stomach. It presents no symptoms or complications in 85 per cent of cases. In the other 15 per cent, however, it can cause stomach ulcers and indigestion, and for a very small number of people, increase their chances of stomach cancer. However, with the increase in antibiotic use, rates of infection are falling. Studies have shown that less than six per cent of children born today in the US, Sweden and Germany carries the organism.

*H. pylori* has been around in humans and humanoids for at least 50,000 years. So from an evolutionary perspective, this suggests that should be a reason for bacteria that can cause illness to still exist.

MRC researchers have shown that circulating levels of the ‘hunger hormone’ ghrelin are lowest in those infected with *H. pylori*. Ghrelin is the first appetite-enhancing hormone to be identified. It has been demonstrated that, usually, circulating levels of ghrelin are highest before a meal, stimulating appetite, and then decrease afterwards.

The study concluded that the relationship between ghrelin and *H. pylori* required further investigation. However, these findings are supportive of a potential link between declining *H. pylori* infection and an increase in obesity levels.

Treatment of *Clostridium difficile* with faeces

MRC-funded researchers have demonstrated that transplanting faeces from healthy mice into *Clostridium difficile* (*C. difficile*)-infected mice rapidly restores a diverse, healthy microbiota and subsequently resolves the disease and its contagiousness.

*C. difficile* is a Gram-positive bacterium that is the major cause of antibiotic-associated diarrhoea and a significant healthcare-associated pathogen. The first line treatments are antibiotics vancomycin or metronidazole, although in 20–35 per cent of cases, a relapse of the disease follows completion of the antibiotic course.

A recent study has shown that narrow-spectrum antibiotic fidaxomicin causes less damage to the microbiota and results in a lower rate of disease recurrence compared to treatment with vancomycin. *C. difficile* has therefore been subsequently linked to a general imbalance of the intestinal microbiota (known as dysbiosis).

This study identified a simple mix of six phylogenetically diverse intestinal bacteria which re-established a health-associated microbiota and cleared the *C. difficile* infection from the mice. The researchers demonstrated that diversity of species is important, as when administered individually, the intestinal bacteria strains failed to trigger a response.

Species composition is also key; as other mixtures failed to successfully resolve the disease. This study has demonstrated a rational approach to harness the therapeutic potential of health-associated microbial communities to treat *C. difficile* disease and potentially other forms of intestinal dysbiosis.

Infection with *Helicobacter pylori* and protection against tuberculosis

Researchers at the MRC Laboratories in The Gambia, in collaboration with scientists in the US, have found that infection with *H. pylori* may protect the host against other pathogens, such as tuberculosis.

They compared rates of *H. pylori* in blood samples from TB cases and household contacts recruited from TB case-contact studies carried out in The Gambia and Karachi, Pakistan. They found that *H. pylori* is associated with an enhanced immune response to specific TB antigens. The researchers also observed that TB-infected household contacts who did not develop the active form of the disease were more likely to have concurrent *H. pylori* infection.
This suggests that infection with *H. pylori* might induce a continuous immune response, enhancing the host’s response to a range of infectious challenges. Alternatively, infection of *H. pylori* in childhood could permanently differentiate immature T-cells into a lymphocyte-like phenotypes.

This study raises the possibility that the human microbiome can be manipulated to modulate disease risk from tuberculosis as well as other common human pathogens.

Changes to the gut flora following helminth infection – implications for immunity

Worm parasites — helminths — are capable of infecting the gastrointestinal tract of a broad range of animals, including humans. Helminth infection is associated with pronounced effects on the health of the infected individual host, such as malnutrition, anaemia, internal bleeding, mental impairment and seizures. An example of such a parasite is the human whipworm, which causes a parasitic infection in the tissue of the appendix, colon and rectum and infects around one billion people worldwide.

Professors Ian Jackson and Richard Grencis at the University of Manchester are studying the interaction between the whipworm and the host’s immune system to understand the mechanisms by which the host attempts to eradicate the worm. To do this, they are using a model system in the mouse.

Changes to the gut flora of the infected animal. They are currently examining these changes to understand the subsequent functional implications for the host; whether the changes in gut flora provide a new ecosystem that is more beneficial to long-term worm survival and whether they have implications for the way immune responses to other infectious agents are mounted.

Infant exposure to antibiotics may cause increased body mass in later life

Knowledge of the importance of the microbiome raises issues about antibiotic use in children as exposure may disrupt microbial ecology. Early life appears to be critical for gut colonisation as the infant builds up their gut bacterial community, through contact with the mother’s own microbiota during childbirth and feeding.

It has previously been demonstrated that intestinal bacteria play a role in the metabolism of animals. US farmers have exploited this principle for decades by giving domesticated animals low-doses of antibiotics to fatten them.

A study using data from the MRC-funded Avon Longitudinal Study of Parents and Children has found that exposure to antibiotics during a child’s first six months was associated with a later increase in body mass of that child. At the age of 38 months, children who had been exposed to antibiotics during this period were 22 per cent more likely to be overweight than children who had not been exposed.

The researchers have data that show dramatic changes in the gut flora of the infected animal. They are currently examining these changes to understand the subsequent functional implications for the host; whether the changes in gut flora provide a new ecosystem that is more beneficial to long-term worm survival and whether they have implications for the way immune responses to other infectious agents are mounted.

End notes

1Blaser M. Antibiotic overuse: Stop the killing of beneficial bacteria Nature 476, 393–394 (25 August 2011) doi:10.1038/476393a