The microbiome:

what it means for medicine

It is impossible not to notice the enormous surge in human microbiome research currently underway around the world. For the past decade, new molecular methods have started to unlock the secrets of this unseen universe, and suddenly it is dawning on us that human individuals are not the dominant life-form in the symbiosis of our existence. It is often quoted that humans are 10% human and 90% microbial when a comparative count of cell numbers is taken into consideration,[1] but perhaps more astonishingly, it is now clear that our human microbiome, the collection of genes encoded by our microbial passengers, is at least one hundred-fold greater than our own genome. The diversity of the human 'microbiota' is enormous, with approximately 500–1000 species existing in our gastrointestinal tracts alone. We are the vessels for this community of microbes (including bacteria, viruses, and yeasts) living on us and in us, and as we start to unravel the multitude of roles that this microbiota fulfils, it is becoming clear that our microbes play a far more relevant and important role in the maintenance of our health than we have ever stopped to consider before.[2] Therefore, it stands to reason that we are at a pivotal point in our attitude towards microbes in a medical context.

ADJUSTING OUR PERCEPTION OF 'GERMS'

From an early age most of us are taught that 'germs are bad' and that we need to avoid them wherever possible. For clinicians, there is further reinforcement of this concept, from the threat of the relatively small but significant number of microbes that are pathogenic to us. Infectious disease continues to be a major threat to health despite the medical advances we have made in the past few decades. The success of antibiotic therapy heralded a new era in our collective consciousness that, in the words of the US Surgeon General, William Stewart, in 1967, boldly suggested that it was time to 'close the book on infectious disease'.[3] The medical over-confidence that followed saw the use of antibiotics spread from the treatment of life-threatening infections to the treatment of less serious disease, from mild otitis media to acne. Now in 2014 we have realised the error of our ways, as we witness the widespread and increasing emergence of antibiotic-resistant microbes. Quite rightly, this is forcing a re-examination of the circumstances of antibiotic administration in both medical as well as environmental practices (for example, farming, where the Food and Drug Administration estimated the annual amount of non-therapeutic antibiotics administered to animals in the US in 2011 alone as 24.6 million lbs (almost 13 500 tonnes),[4] and encourage restriction on the use of these drugs wherever possible.

However, the continuing study of the human microbiome is suggesting another, far more ominous side effect of antibiotic use: the concomitant loss of our resident microbiota. Our resident microbes are engaged in a complex partnership with our human selves that has co-evolved with us over millennia. These microbes have recently been revealed to have functions beyond their clear role as niche dwellers that competitively exclude pathogens.

These functions vary widely across body sites and between resident microbes. The microbiota is known to 'educate' the immune system, steering it away from needless attacks on commensal microbes such that its efforts can be concentrated on real threats. The gut microbiota also plays a role in breakdown of complex dietary compounds, provision of key molecules and micronutrients essential to health (such as B vitamins), and even makes (as yet poorly understood) contributions to mood, behaviour and sleep patterns.[5,6]

CONSEQUENCES OF COLLATERAL DAMAGE IN ANTIMICROBIAL THERAPY

Antimicrobials, and in particular those that are broad-spectrum in nature, are never simply targeted towards pathogens; in the battlefield of infection these drugs inflict heavy collateral damage on the indigenous microbiota. Fortunately, the microecology of the healthy human microbiota is highly diverse and carries 'functional redundancy', the capacity for multiple microbes within the same ecosystem to carry out the same tasks.[7] Consequently, it has a moderate ability to withstand antibiotic-inflicted stress and to recover from it. However, because we all have a microbiota that is uniquely shaped by our environment and by other factors that are less well understood, this exclusivity means that it is not yet possible to predict individual responses to antimicrobial exposure. Furthermore, evidence indicates that disturbance of our microbial ecosystems at critical points in development (in particular, early childhood), may result in long-lasting damage that is not easily reversible and may lead to later susceptibility to chronic diseases such as inflammatory bowel disease, asthma, atopy, diabetes, obesity, and even autism.[8–10]

While it is often difficult to understand the extent to which microbiota damage may have concomitant detrimental effects on human health, we can look to a clear example where microbiota collapse is the underlying cause of disease: *Clostridium difficile* infection (CDI). The circumstances that give rise to CDI usually reflect collateral damage on the gut microbiota brought about by incidental antibiotic use, which allows *C. difficile* to proliferate and thrive without a healthy microbiota to regulate its expansion.[11] Because the treatment for CDI is further antimicrobial therapy with either oral vancomycin or metronidazole, it is not surprising that the infection can recur, and a vicious cycle of pathogen expansion followed by antimicrobial suppression (but not clearance) can ensue.[11] The ability of faecal microbial therapy (FMT, or 'stool transplant') to rapidly and effectively clear infection and cure disease, even in recalcitrant cases,[12] is a clear indication of the power of the microbiome in the restoration of health. We and others have made steps to refine this somewhat primitive procedure through the selection of particular health-associated gut microbes for the development of targeted, pure-cultured 'Microbial Ecosystem Therapeutics,' (MET) thereby improving safety, controllability, and overall acceptability.[13,14] MET could be administered alongside nutritional counselling to advise patients on healthy eating for the tailored management and maintenance of their beneficial colonic microbes.

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Harnessing the microbiome to treat disease and maintain health is thus the next step in the journey into a new era of medicine. While physicians have already begun to recognise the importance of antimicrobial stewardship and to adjust their perception of microbes as potentially life saving, there is still much work to be done to educate the general public in this respect. It is time to shift emphasis from the common perception that 'the only good germ is a dead germ', and to instead focus on elucidating the beneficial effects that can be reaped from wise management of our microbiome. Reduced patient insistence on unnecessary antibiotic therapy will be a happy consequence of this new understanding.

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CONCLUSION

Antimicrobials will always have an important place in medicine, but their use may need to become more limited and defined. With more attention focused on targeted approaches to pathogen removal, we can lessen the adverse effects of antibiotics, both in terms of reducing antibiotic resistance and in reducing collateral damage inflicted on our microbiome. In the future, rather than serving as active contributors to the problem by implementing instruments of escalating host-versus-microbe warfare such as antibiotics, physicians may instead be required to be the brokers of peace agreements within the bodies of their patients, through new strategies involving manipulation and 'fine tuning' of the microbiota rather than its destruction.

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REFERENCES

1. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* 2006; **124(4):** 837–848.
2. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; **486(7402):** 207–214.
3. Upshur R. *Ethics and infectious disease.* World Health Organization. http://www.who.int/bulletin/volumes/86/8/08-056242/en/ (accessed 5 Feb 2014).
4. US Food and Drug Administration, Department of Health and Human Services. *Summary report on antimicrobials sold of distributed for use in food-producing animals.* 2011. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf (accessed 5 Feb 2014).
5. Rajilic-Stojanovic M. Function of the microbiota. *Best Pract Res Clin Gastroenterol* 2013; **27(1):** 5–16.
6. Robles Alonso V, Guarner F. Linking the gut microbiota to human health. *Br J Nutr* 2013; **109 Suppl 2:** S21–S26.
7. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; **6(11):** e280.
8. Haahtela T, Holgate S, Pawankar R, *et al.* The biodiversity hypothesis and allergic disease: world allergy organization position statement. *World Allergy Organ J* 2013; **6(1):** 3.
9. Petrof EO, Claud EC, Gloor GB, Allen-Vercoe E. Microbial ecosystems therapeutics: a new paradigm in medicine? *Benef Microbes* 2013; **4(1):** 53–65.
10. Shaw SY, Blanchard JF, Bernstein CN. Association between early childhood otitis media and pediatric inflammatory bowel disease: an exploratory population-based analysis. *J Pediatr* 2013; **162(3):** 510–514.
11. Knight CL, Surawicz CM. Clostridium difficile infection. *Med Clin North Am* 2013; **97(4):** 523–536, ix.
12. Smits LP, Bouter KE, de Vos WM, *et al* . Therapeutic potential of fecal microbiota transplantation. *Gastroenterology* 2013; **145(5):** 946–953.
13. Allen-Vercoe E, *et al.* A Canadian Working Group Report on fecal microbial therapy: microbial ecosystems therapeutics. *Can J Gastroenterol* 2012; **26(7)**:457–462.
14. Petrof EO, *et al.* Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* 2013; **1(1):** 3.