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Responsibility and the Microbiome

Kristien Hens and Eman Ahmed

Introduction

The gut microbiome is a diverse ecosystem encompassing trillions of micro-organisms, including bacteria, viruses, fungi, archaea and protozoa. It establishes a symbiotic relationship with the human host via microbiome–host interactions that occur at various levels of complexity and that are essential for maintaining bodily homeostasis (Wu and Wang, 2019). The microbiome's 'cross-talk' with the host physiology is demonstrated via its contribution to a wide range of functions, including digestion, production of metabolites, and development of the immune system (Cryan and Dinan, 2012). The gut microbiome as an ecosystem has thus emerged as a key factor in understanding human health and disease. Although the exact number is unknown, the number of microbial genes present in the human body may equal or exceed the number found in the human genome. Indeed, the genome of these microbes is sometimes called 'our second genome'(Meisel and Grice, 2017).

At this point, the reader may wonder what a chapter on the human microbiome is doing in a volume on epigenetics. There are a number of reasons for its inclusion here. First, it has been demonstrated that there is an interplay between the gut microbiome and epigenetics. Research suggests that gut microbiome metabolites are crucial epigenetic regulators of the host genome. They can induce epigenetic changes in key human genes and ultimately lead to the development of disease (Yuille et al, 2018). For example, changes in the diet seem to influence microbiome composition and affect the regulation of histone methylation and demethylation in the host genome (Krautkramer et al, 2016). A more specific but relatively recent area of research explores the ways in which epigenetic alterations brought about by the microbiome influence the development of cognitive function

and behaviour and the development of neuropsychiatric disorders. Even though the specific underlying mechanisms are not yet fully understood, promising strands of research suggest that changes in the microbiome alter neuroactive signals via the vagus nerve, thus bringing about epigenetic changes in the brain (Kaur et al, 2021). It has also been suggested that neuroepigenetic modifications can occur due to production of short-chain fatty acids by the microbiome. These modifications underlie the pathogenesis of many neuropsychiatric conditions via inhibition of histone deacetylases (Peedicayil and Santhosh, 2021). Hence, if we are asking questions about responsibility in epigenetics, it may be helpful to consider these together with questions related to responsibility in the context of the microbiome.

While epigenetics has challenged the mechanistic view of organisms as primarily built up from genetic blueprints, microbiome studies take this knowledge one step further. Understanding epigenetics shows that we are intertwined with the environment (inside the body and outside) down to the molecular level. Gene expression is as relevant for health and disease as the information in the genes themselves. Furthermore, it has now become clear that our health is closely linked with the microbiome that is found in our gut and elsewhere. Just as with epigenetics, the composition of the gut microbiome is influenced by specific features and circumstances of the host. It has been argued that each individual's microbiome acts as a unique fingerprint (Franzosa et al, 2015). This claim is based on a growing body of literature that explores the influence of several host factors on microbiome composition, such as early-life stressors, mode of birth, diet, lifestyle, the surrounding environment and previous diseases and medications (Dong and Gupta, 2019). The link between lifestyle and the gut microbiome raises complex questions regarding responsibility for one's health.

The gut microbiome modulates the central nervous system via multiple signalling pathways that involve immune, endocrine and neural communications (Fülling et al, 2019). In addition, the microbiome has been recognized as a key regulator of the gut–brain axis. Even though the specific mechanisms of this regulation are not yet known, preclinical and clinical research supports evidence of bidirectional communication between the gut microbiome and the brain. Such communication connects the cognitive and emotional brain centres with gut functions. Hence, the term 'gut–brain axis' has been expanded to 'microbiota–gut–brain (MGB) axis' (Mayer et al, 2014).

Moreover, as with epigenetics, research into the microbiome seems to confirm the plasticity, historicity and environmentality of humans and other organisms (Meloni, 2018; Formosinho et al, 2022). At this point in this volume, we may even wonder whether maintaining sharp boundaries between areas such as genetics, epigenetics, proteomics and microbiome studies makes sense. It may be more appropriate to study the interactions

and even entanglements between these domains rather than seeing them as separate. This may hold true for work in both science and ethics.

In what follows, we first discuss the implications of research into the microbiome for what it means to be human. Starting from a reflection on scientific findings on the relationship between the microbiome and mental states, we discuss what the fact that the human 'self' seems to coexist with trillions of microbes means for an understanding of responsibility. In the second section, we turn the question around, and discuss the implications for responsibility of considering humans as holobionts. We also discuss the implications of what it means to share our microbiome with non-human beings who are close to us. Finally, we reflect on what these findings imply for questions about ethics and responsibility.

Impact of knowledge about the microbiome on what it means to be human

A healthy gut and a healthy mind?

The fact that new information regarding the microbiome may challenge an atomistic view of human beings, just like epigenetics does, seems straightforward. But what does it mean that we are entangled not just with the external environment but also inhabited by and maybe even governed by other creatures? Let us look at the relationship between the microbiome and the human mind. The gut–brain axis is a focus of much present-day research. Indeed, microbiome studies are often undertaken as part of biomedical research to investigate the relationship between microbes and health status or mental wellbeing. We first discuss some of these findings.

Use of probiotics, antibiotics or faecal transplants to manipulate the commensal gut microbiota has been found to influence the behaviour of rats. These findings support the evidence that gut bacteria influence brain processes (Cryan and O'Mahony, 2011). Use of germ-free rats and mice has also enabled researchers to investigate how the gut microbiome influences the animals' behaviour (Cryan and O'Mahony, 2011). These advances in microbiomics have led to a better understanding of microbiome–host interactions. Moreover, many studies over the last decade have led to an increasing recognition of the role of the microbiome in the development of neuropsychiatric conditions in humans, including anxiety, depression and schizophrenia (Grochowska et al, 2018). These conditions are often associated with a 'dysbiotic' microbiome. Dysbiosis is an imbalance in the gut microbiome composition that favours the abundance of proinflammatory and pathogenic species and decreases microbiome diversity (Floch et al, 2017). Some studies have suggested using microbiome compositions as biomarkers for neuropsychiatric conditions (Zhu et al, 2020). However, many philosophical and scientific questions remain. Autistic people, for example,

often experience difficulties in eating, which in itself will influence the microbiome's composition. Hence, the idea that there is a one-way causal pathway by which microbes determine our mental states seems naive. After all, how we feel or how we experience the world is highly likely to influence what we prefer to eat and hence the composition of the microbiome as well.

Perhaps research on the microbiome challenges simple causal explanations in psychiatric and developmental conditions even more than findings in epigenetics do. Those responsible for science communication should not shy away from conveying these complexities to the general public. It also means that responsibility for one's own or other people's mental health is more complex than what certain lifestyle coaches may suggest. Indeed, research in epigenetics and in microbiomics gives us powerful reasons to adopt a complex view of mental states, with feedback loops and sensitivity to external influences, genes, and what goes on in our gut. Moreover, we may question the concept of a 'normal' versus a dysbiotic microbiome. Just as others have argued in the case of epigenetics, the dynamic and reactive nature of the microbiome may challenge the notion of normality here (Dupras and Ravitsky, 2016).

The French philosopher and medical doctor Georges Canguilhem questioned the idea that pathology can be measured by looking at the body's internal states alone (Canguilhem, 1989). Pathology, according to Canguilhem, arises if there is a mismatch between organism and milieu to such an extent that the organism cannot proactively adapt its environment and itself to suit its needs. In this respect, we may challenge the idea of an 'abnormal' microbiome. This challenge becomes still more pressing if we look at the relationship between the microbiome and certain psychiatric conditions. It has been argued by philosophers and psychiatrists alike that to rely on concepts of normality to compare neurodivergent with neurotypical people is problematic. There may not be such a thing as an unhealthy microbiome, only one that is not adapted to its current environment. This is similar to the mismatch hypothesis in epigenetics, which suggests that there is no absolute way of defining a good or bad epigenome, just one that is adaptive or mal-adaptive in a specific environment. At the same time, the propitious findings of microbiome research, such as the correlation of certain microbiomic states with psychiatric diagnoses and the importance of the microbiome in shaping the immune system (Postler and Ghosh, 2017), show how our minds are closely interlaced with the micro-organisms inhabiting our guts.

The microbiome and the human self

In Chapter 1, Kristien Hens argues that epigenetics throws the enlightenment idea of the atomistic and autonomous individual down the drain, as it

demonstrates, at a molecular level, that organisms are deeply entangled with their environment. Indeed, (primarily Western) conceptual certainties about the biological basis of our identity and sense of self are being challenged in light of post-genomic research findings. Microbiome research, as a post-genomic science, may even have more profound ontological implications (Suárez and Triviño, 2019). After all, what is a human being if it not only carries trillions of other organisms but is primarily composed of these organisms and even influenced by them when it comes to personality, responsibility and wellbeing? The gut microbiome is an indispensable component of the physiological functioning of the host. In Chapter 4, Anna Smajdor shows how epigenetics challenges the idea that what primarily matters for identity is an individual's unique combination of genes. Given that an organism's microbiome is unique and influences phenomena that we usually associate with identity, such as personality, it adds a further element to the question of identity and uniqueness.

For example, there are approximately as many microbial cells as human cells in the body (Sender et al, 2016). These findings have implications for our understanding of human identity. Natural sciences have traditionally relied on a biological view in which the human genome, brain and adaptive immune system constitute an individual self (Rees et al, 2018). However, what makes human beings human is something that philosophers have tried to answer for a long time. We suspect that 'half microbial' is more than they bargained for. We can circumvent the implications of the above findings by no longer seeing these microbes as separate, external organisms that are part of the environment that just happens to be in our gut. Instead, we could consider them as part of us. After all, there are many examples in the history of life itself of unicellular organisms merging with other organisms, mitochondria being a famous example.

We may wonder, however, why we as philosophers are so hung up on personal identity and the human as a discrete and well-circumscribed entity. Personal identity has been linked to numerical identity: numerically, human beings remain one and the same over time. However, research into the microbiome may support the view that human beings are more 'ship of Theseus-like' than we usually think. Like the ship of Theseus, all of a human being's material components, such as cells and also microbes, are gradually replaced throughout one's lifetime. At the same time, personal identity has been firmly linked to the unique set of genes that we acquire at conception, with the exception of the case of monozygotic twins. This has influenced how we think about responsibility towards future people, Derek Parfit's non-identity problem being a case in point (see Chapter 4). Indeed, giving up on a fixed sense of identity seems dangerous, and risks undermining the fundamental prerequisites of morality. Questions of moral responsibility seem to imply a specific answer to the question who is

responsible for whom. At the same time, we may also ask ourselves whether we are missing opportunities to think about responsibility differently if it is so firmly linked to a numerical or genetic interpretation. After all, social sciences and humanities have investigated personal identity by looking at the various ways people have understood themselves. Individuality may be understood as inherent in the continuity of a person's past, present and future (Rex and Mason, 1986). The fact that our 'self' is partly microbial may not conflict as much with the narrative self as with a personal identity based on old-fashioned ideas about biology and genes.

Microbes and environmental entanglements

The examples given above suggest that the relationship humans have with their microbiome is one of symbiosis. Not only do gut bacteria help us digest food, but they are also tightly intertwined with our personality, to the point that the gut has been called 'the second brain'. This collective interaction between the host and microbiome has been called the 'holobiont'. According to Bosch and Miller (2016, p 1), a holobiont is 'an association comprised of the macroscopic host and synergistic interdependence with bacteria, archaea, fungi, and numerous other microbial and eukaryotic species'. We may conceive of the microbiome as an environmental factor that influences us, while, at the same time, we are our microbiome's environment. However, even when thinking about epigenetics, the concept of environment is problematic. Epigenetics is often conceptualized as the molecular 'link' between genes and the environment. Such conceptualization assumes that, as causal agents, genes and environment operate at the same level. For example, a health problem may be due to the environment, genes or a combination thereof. This distinction does normative work: if one's health problem is caused by an environmental factor, it is often assumed that one's responsibility to do something about it is greater than in the case of a genetic cause. Nevertheless, the environment is many things. It is the intracellular environment, the environment within the body, the local environment, or even something beyond. We may see the workings of organisms not as 'genes versus the rest' but as a dynamic and interacting system in which genes are but one aspect. The microbiome challenges the dichotomy of genes versus environment even more: now, a factor *within* the body is added. At the same time, the concept of the environment may in itself have the connotation of being external and fixed, as Formosinho and colleagues have argued in their excellent paper (Formosinho et al, 2022). They state that 'microbiome research introduces challenges regarding usage of the term environment: what constitutes an environment, for whom, and with which consequences for health?' (Formosinho et al, 2022, p 148) They situate microbiome research in 'a history of reaching for a more scientific

medicine; a more controlled, precise and generalizable knowledge that would separate the body from the environment and locate it instead in the aperspectival "view from nowhere" of the clinic' (Formosinho et al, 2022, p 152). The microbiome further complicates this aperspectival view. Formosinho and colleagues propose 'environmentality' as 'the state or quality of being a causal context for something else', a 'firmly perspectival concept aware of its own situatedness and the situatedness of its object of study' (Formosinho et al, 2022, p 152). For them, environmentality is an epistemic tool that has 'helped us trace lines of relationality across scales, back in time, through flesh and across organismic boundaries' (Formosinho et al, 2022, p 155). As such, the concept also seems suitable as a way of looking at epigenetic research.

At the same time, microbiome findings raise questions about the status of human beings as holobionts, the status of human beings in general, and even what it means to belong to a particular species. It has become apparent that, through epigenetics and the microbiome, human beings are deeply entangled with the environment inside and outside their skin. Given the link between the gut microbiome and our brain, it is tempting to assume that, although we are partly microbes, at least the specific ecosystem of microbes with which we are populated must surely be distinctly human. However, studies have shown that owners of companion animals such as dogs, share gut microbiomes with their pets (Coelho et al, 2018). Moreover, a recent study has suggested that urban populations of coyotes, crested anole lizards and white-crowned sparrows share more similar gut microbiota with humans than with non-urban members of their own species (Dillard et al, 2022). We discuss what this might mean later on.

Microbes, ethics and responsibility

Contributors to this volume have discussed a number of important questions that epigenetics may raise concerning individual, collective or parental responsibility. As shown above, findings generated by research into the microbiome may raise similar questions. For example, we could ask what the implications of these findings are for parental responsibility. Should we conclude that parents have an even bigger responsibility to feed their children healthy food if this gives them a 'healthy microbiome'? Should Caesarean sections only be seen as a last resort because of the importance of vaginal microbiome transmission to babies (Hoang et al, 2021)? As many have argued with regard to epigenetics, such conclusions tend to neglect the contexts that influence people's decisions or limit their opportunities to make decisions at all.

Moreover, just as with epigenetics, the link between the microbiome and health and disease is complex. A healthy microbiome may be regarded as

such more because it adapts effectively to particular environments than by virtue of its intrinsic properties. This insight may suggest that the balance tips to more collective and forward-looking responsibility (see also Chapter 2 for a discussion of those concepts in an epigenetics context). Such collective forward-looking responsibility then implies the need to ensure that the environment we have is one in which organisms can flourish. In what follows, we do not provide an overview of all responsibility issues that may arise with the increasing knowledge about the microbiome. Instead, we focus on two domains. First, we hint at some points to consider for medical ethics. Second, we argue that microbiome research is yet another proof that medical ethics, or bioethics, and environmental ethics, should not be seen as separate endeavours, but should always be undertaken in synergy.

The microbiome and medical ethics

Medical ethicists who have considered ethical issues related to the genome have often covered issues related to privacy, confidentiality, consent and the return of test results. Similar issues may arise when considering epigenetic and microbiome research. For example, epigenetic and microbiome data may contain sensitive information that could identify the donor. Moreover, they may contain not only genetic, but also phenotypic, information, which may be even more interesting for insurance companies. They may contain more relevant information about the health of the subject in question than mere genetic data. Genetic data are currently governed by strict regulations. At the same time, stool samples are considered waste and are not subject to the same scrutiny. Given the increasing knowledge in the field of the human microbiome, it may be at least as necessary to reflect on responsible management of stool samples as on the management of genetic biobanks.

In addition to research on stool samples, treatments such as faecal transplants to treat metabolic diseases or even psychiatric conditions should be approached with due care. The impact of mental health issues on people's wellbeing is the focus of significant attention. Being able to manipulate the gut microbiome and hence influence one's mental health seems promising in that light. However, there are several reasons why one should tread carefully. Microbiomegutbrain findings are often interpreted as simple biological explanations for psychiatric conditions but the truth may well be more complex.

Microbiome explanations for psychiatric conditions may add to the idea that 'it is all in your biology'. Biological explanations of mental health issues can be liberating as they sometimes relieve sufferers from feeling guilty. Indeed, meta-analytical evidence has shown that, when the public accepts biological explanations of mental disorders, this may reduce the moral

responsibility attributed to sufferers by revealing that mental health problems are not the result of bad character or weakness (Schomerus et al, 2012). A more recent meta-analysis has shown that neurobiological explanations that conceptualize a psychiatric disorder as a brain disease tend to have stigmatizing consequences (Loughman and Haslam, 2018), provoking fear and a desire to maintain social distance. For example, people assume that neurobiological explanations imply that the affected person cannot control their actions. As the brain is perceived as the source of free will and actions, any explanation that casts doubt on its integrity risks being understood as an indication that the affected person is unpredictable and potentially dangerous (Loughman and Haslam, 2018).

Having your mental health issues straightforwardly explained through your gut microbiome may have similar effects. At the same time, the nature of the microbiome itself challenges such simplistic causal attributions to 'biology'. Indeed, viewing mental states through a microbial lens diminishes the lines between body and mind and physical and mental health. It undermines a reductionist conception of mental health and disease and introduces a new conception that combines biological, genetic, social and environmental factors. Moreover, the microbiome's dynamic nature may emerge as a more fitting approach to studying mental conditions as it leaves more room for understanding personal and environmental circumstances synchronously with biological factors (Ahmed and Hens, 2021). In this sense, a responsible application of microbiome findings in mental health practice necessarily implies a holistic approach to mental health. Science communicators and the media have work to do to ensure that the complexity of the links between mental health, the brain and the gut is clear, rather than presenting the microbiome as a direct cause for certain issues. Given the still high prevalence of 'gene for psychiatric condition X' language in the popular media, decades after the idea of a gene for a condition has been debunked, there is still a long way to go.

In addition to the danger of continuing a reductionist vision of the causes of mental health issues, there may be issues related to specific treatments. In the first part of this chapter, we challenged the idea of a 'numerical' or 'biological' identity in favour of a narrative one. That does not mean that the former is necessarily less 'real' or more fluid, or that interruptions in biology are not disruptive to that narrative. For example, suppose specific microbiome treatments such as a faecal transplant from a donor without a mental illness could treat mental illness in the recipient. Just like technical approaches such as deep brain intervention, these treatments may profoundly affect how one sees oneself and one's life story. Therefore, applying such interventions responsibly requires paying attention to the stories people tell about themselves and their afflictions. Such treatments should hence also be part of a holistic approach.

Microbes and bioethics as global bioethics

We ended the last paragraph with a plea for a holistic approach to microbiome science and treatment: microbiomes should not be seen as simple causal agents of disease, nor should they solely be targeted as simple biological solutions. The nature of our relationship with the microbiome suggests the need for an appreciation of the complexity of an organism's functioning, the entanglement of human beings and microbiome – if it even makes sense to make that distinction – and of holobiont and the outer environment. Just as epigenetics may be characterized as the molecular link between genes and environment, a link that may even render the distinction between the two obsolete, the microbiome proves that humans and other organisms are not 'standalone' beings. They are composed of various types of cooperating life, which, in itself, is influenced by the immediate environment of the human gut and the human diet, and also by the external environment. Just as with epigenetics, this gives us reason to reassess the scope of the discipline of bioethics.

Nowadays, bioethics is often seen as distinct from environmental ethics. Given the recent findings regarding health and the environment, we may wonder whether this distinction is sustainable or helpful or even a responsible way of practicing ethics. Epigenetics and studies into the microbiome may be a wake-up call regarding what bioethics should be about. We may need global bioethics, to use the words of Van Rensselaer Potter, who mourned that, in the 1970s, bioethics had been reduced to medical ethics (Potter 1988). If we assume that the task of bioethics is to ensure that 'good' is done in medical practice, it may be nonsensical to neglect the broader context in which the good is to be done. This broader context necessarily involves thinking about environmental issues. Moreover, environmental ethics itself has much to gain from looking at microbiome findings.

Discussions about anthropocentric approaches versus ecocentric approaches may become meaningless in the light of the knowledge that we are the environment, and the environment is us. As seen before, an example of this is the finding that the microbiomes of all urban dwellers, be they humans, coyotes or lizards, share more features in common than they do with their non-urban cousins (Dillard et al, 2022). We could take this as a call for a stricter separation between urban humans and wild animals. An all-too-easy interpretation would be that we have colonized these animals with our microbiome. However, these findings could also inspire us to think differently about species boundaries, locality and kinship. In this respect, rather than trying to lay down strict boundaries between ourselves and non-humans, between domestic and wild animals, between society and nature, we could acknowledge that we, humans, coyotes and microbes, are all in this together. Human and non-human health are not necessarily different spheres. We are responsible for ensuring a liveable future for all.

In her brilliant book *Philosophy of Microbiology*, Maureen O'Malley argues that, rather than focusing on plants and (specifically human) animals, philosophers of biology should instead think from the starting point of microbial life (O'Malley, 2014). She points out how cooperation, symbiosis and entanglement have been built into life for billions of years. We conclude with the suggestion that it is not only philosophers of biology who should start from microbial life, but bioethicists too, who have much to gain from 'thinking with' the human as holobiont.

Contributor statement

E.A. and K.H. both contributed to the structure and content of this chapter. E.A. and K.H. both gave feedback on and edited the whole manuscript and agree with this final version.

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