Review Article

THE GUT MICROBIOME AND THE BRAIN

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ABSTRACT

The enteric nervous system and the central nervous system are no longer viewed as being separate entities. They are connected to each other by the vagal nerve which allows for bi-directional communication between cells on opposite sides of the body. Local cells in the gut can also activate the release of cortisol from the hypothalamic-pituitary-adrenal-axis (HPA) during an immune challenge in order to augment the local immune response. Enteric bacteria have adapted to make use of both the vagal nerve and the HPA in order to create a metabolic niche in which they can survive. They do this by sending neural, as well as, hemocrine signals to the brain which alter behaviour in the host. Feeding behaviour, mood regulation and circadian rhythms can be influenced through cross-talk between gut bacteria and neurons which form part of central circuits. Pathogens can therefore induce a dependency in the host, in which unhealthy foods are sought and irregular sleep cycles are entrenched. This may help to explain the current epidemic of 'fussy eaters' and 'difficult sleepers' in the paediatric population. Of concern is that the emergence of this dysregulated microbiome in children may result from unregulated modern practices such as elective caesarean section and poor antibiotic stewardship. The aim of this article is to foster greater discernment in our modern practices.

INTRODUCTION

In the Middle Ages, Benedetti stated that 'the uncleanliness of the gut had to be fenced off by the diaphragm, as its importunity disturbed the mind, which was the site of reason'.[1] This view that the alimentary tract and brain were disconnected in both structure and function persisted widely until the beginning of the 20th century, even though Galen, the great scholar and anatomist, had previously mentioned that 'the stomach had the ability to feel a lack, which roused the animal and stimulated it to seek food'.[2] Galen suggested that the gut must be part of some reflex arc which involved elevated faculties such as the senses, emotions and purposeful actions, and that the function of this arc was to alter behaviour. His idea that the stomach 'stimulated' the animal, implied that the stomach and the brain must be of the same matter or that signalling relied on the same substrate. His statement was centuries ahead of his time, as we now know that the same embryological cells which form the brain, namely, the neural crest migrate and form the enteric nervous system (ENS) of the gut. The ENS consists of 100 million neurons and weighs about the same as an adult brain.[3,4] It spans the vast length of the gastrointestinal tract and can function independently of the central nervous system (CNS).

In the early 20th century, Ivan Pavlov propagated what he called 'Nervism', which surmised that the nervous system controlled the greatest possible number of bodily functions.[5] He found that secretory fibres of the pancreas and stomach were located in the vagal nerve and in 1904 won the Nobel Prize for his famous work on digestive physiology. He also described 'conditioned reflexes' which demonstrated the effect of sensory or psychic stimulation on secretory glands in the intestines.[6] This was a pivotal step forward, as it not only connected brain physiology to gut physiology but also highlighted the significant impact which psychology and emotion could have on intestinal function.

Shortly thereafter, Starling and Bayliss published a series of lectures describing a 'blood-borne messenger' that could promote growth and influence function in distant organs.[6] The word 'hormone' was subsequently derived from the Greek *hormoa*, which means 'to arouse or activate'. This non-neural mechanism of glandular secretion was a significant discovery at the time. It went against Pavlov's theory that only nerves could activate physiological responses in the body, and opened up the possibility that function was dependent on both the nervous and the endocrine systems.

The picture was now becoming clearer. Pavlov had demonstrated that the vagal nerve and, therefore the brain, was connected to glands in the stomach. This

provided an efferent circuit between the brain and the stomach. Starling and Bayliss had discovered hormones, which enabled these glands to send signals to the brain via the bloodstream, thereby confirming an afferent link.[6] This link created a bi-directional circuit between the gut and the brain which consisted of neural as well as endocrine routes. The culmination of the combined work of Pavlov and Starling and Bayliss proved that Pavlov's conditioned reflexes really existed, and that psychological stress could alter gut function. The question that followed was that of whether the opposite was also true: that is, whether gut function could affect brain function.

If not, then the circuit was one-dimensional. But surely the brain would require feedback from the gut in order to modify future outflow from the brain? If this was the case then the afferent route to the brain would presumably be neural rather than hemocrine, as it was assumed that brain signalling and reflexes depended solely on the generation of electrical currents between neurons. In addition, a neural circuit to and from the brain, utilising the vagal nerve as a common vector, would be more rapid than a hemocrine circuit and would bypass the filtering effect of the blood–brain barrier (BBB).

However, this theory posed a problem. In order for neurotransmission to occur between the ENS and the CNS, a soluble factor would have to exist which could be secreted by an enteric neuron and which could bind to the receptor of a central neuron. The opposite would also have to be possible. Approximately 50 years after the work of Starling and Bayliss, neuropeptides were discovered.[7] The first major problem concerning bi-directional flow had been resolved, but the resolution involved only the neurological system. Could a similar bi-directional flow occur by means of a blood-borne route?

The focus now shifted to hormones. It was discovered that certain hormones produced by the stomach and the pancreas, in response to food intake, could easily gain access via the blood to specific regions of the brain that lack a BBB, such as the lamina terminalis and the area postrema. These regions are known as 'circumventricular organs', and are closely connected to central feeding and satiety centres located in the hypothalamus.[8] The fact that a hormone can bypass the BBB greatly diminishes the transit time for signalling from the gut to the brain, and greatly enhances the efficacy of the hemocrine circuit in comparison to the neural circuit. Hormones represent another example of how gut function can influence brain function. Of greater significance, however, is the fact that the gut is also able to alter human behaviour directly by controlling food intake during periods of metabolic stress.

The hypothalamus has strong connections to the amygdala and the limbic system in the brain, which is responsible for the processing of emotions in response to stress. As the hypothalamus is the central control centre between feeding centres and the limbic system, anxiety can be associated with decreased food intake or availability. Therefore the gut is also able to alter behaviour indirectly by creating a sense of personal awareness and by driving exploratory behaviour to either find more food or to sample different types of food. The outflow tract for this response, to either nutritional or emotional stress, is the hypothalamic–pituitary axis (HPA).The major stress hormone in the body is cortisol-release factor (CRF), which is converted to cortisol in the adrenal glands. The fact that hormones from the stomach and pancreas can result in cortisol being released back to the gut is important, as metabolic stress is often accompanied by immune stress or inflammation. With a link between gut hormones and central feeding centres and the limbic system, gut physiology was now also seen to have a plausible effector system, in the HPA and the release of cortisol.[9]

The unravelling of the complexity of the brain–gut axis was nearing its final stages. It was now understood that there are two parallel circuits – one neural and the other endocrine – which can function both independently of each other and in a bi-directional manner. The effector system of the neural circuit is the vagal nerve, and that of the endocrine circuit is the HPA system.[10] Activation of these circuits can be simultaneous, and results in changes in peristalsis, glandular secretion and cortisol release in order to maintain local gut homeostasis. This enables the brain to become 'aware' of subtle changes in the micro-environments of the gastrointestinal tract through signals from the gut, and it enables the gut to alert the brain and alter feeding behaviour during metabolic or immune stress. This bi-directional effector system is highly effective, but the theoretical understanding of the brain–gut axis was not yet perfect. Other challenges remained.

The object of any biochemical system is to be as energy efficient as possible, in the shortest time possible. In an optimal system, a hormone would stimulate a nerve and a nerve would in turn activate an endocrine cell. By directly connecting the parallel effector systems, a smaller stimulus from the gut would generate a greater and more diverse response from the brain, over a shorter period. This would be particularly beneficial during low energy states, such as food deprivation or illness. Helpfully, not long after the discovery of neuropeptides, peptide hormones were discovered. These factors are produced and secreted by both neurons and endocrine cells, and can act on both neural and non-neural substrates.[11] This modification in our understanding of function resulted in a change in the perceived architecture of the brain–gut axis, which was now known to be a unified system instead of two separate systems functioning in tandem. Pavlov, Starling, Bayliss and multitudes of others would probably at this stage have breathed a sigh of relief, thinking that their work had finally been done. However, perhaps the most fascinating

aspects of the brain–gut axis still lay before us.

For ideal gut homeostasis, a local effector response to stress would be triggered at the same time as the distal response from the gut–brain axis. As the intestinal lumen represents the ever-changing external environment, both local barrier holding mechanisms and immune cascades would have to be activated immediately in addition to the central response. In order for this to occur, local enteric and immune cells would have to hold receptors identical to these cells dispersed throughout the brain–gut axis.[12] This would allow neurons to activate immune cells, immune cells to cross-talk with enterocytes and enterocytes to stimulate glands. Such receptors would also enable certain cell types to diversify; for example, neuro-endocrine cells could be activated by nerves and release hormones into the bloodstream. Receptors of this kind have, in fact, recently been discovered on all cell types throughout the brain–gut axis, as well as in the lining of the gut, and this has highlighted the critical role that the gastrointestinal tract plays in immunity and atopy.

The next breakthrough came when these same receptors were discovered on the surfaces of enteric bacteria.[13] This implies that bacteria in the lumen of the gut and, therefore the environment, can manipulate the function and, importantly, the constitution of the brain–gut axis. It also reveals that a change in behaviour and diet in the host could have the effect of selecting and supporting different populations of bacteria. This symbiosis suggests that beneficial bacteria could drive the host to seek high-quality food and explore a broader range of foods, whereas pathogens could thrive on poor-quality foods, leading to bacterial overgrowth and disease from direct mucosal injury and a diet high in fat.[14]

The fact that bacteria can alter an individual's lifestyle was unnerving. The era of probiotics exploded, and slogans such as 'You are what you eat!' became widespread. Later, these receptors that connected bacteria to the brain–gut axis were found on a variety of viruses, fungi and protozoa. The concept of the gut microbiome was born, and the brain–gut axis then became the microbiome–brain–gut axis. Each individual harbours trillions of micro-organisms, a unique microbial fingerprint which can function as a separate organ in the body. Specialised microbiomes have been found in other parts of the human body, for example, in the mouth, on the cornea of the eye and in the lungs. In addition, the vagina specifically harbours a unique and site-specific microbiome.

This suggests that the relationship between humans and bacteria could be far more dynamic and significant than originally thought.

This knowledge about the microbiome was developing at about the same time as the 'clean-earth' theory. Why were children from sterile environments in First World countries developing a broader spectrum of autoimmune diseases, such as rheumatoid arthritis, type-one diabetes and multiple sclerosis, at increasingly younger ages? Could immune dysregulation from a disrupted microbiome cause disease in adult life?[15] If so, then the questions arise of when this dysbiosis occurs and whether modern lifestyle practices are to blame.

Any organ in the body needs to mature with regard to structure and function, and undergoes critical periods of development, at which times it is particularly vulnerable to environmental stressors. An insult during a critical window of organogenesis often leads to a permanent loss of function which can persist into adult life.[16] As the gut microbiome is intimately interwoven with the structure and function of the gastrointestinal tract and, as it is passed on to the foetus from the mother during passage through the birth canal, the gut microbiome can be seen as an environmental factor which directly impacts the organogenesis of the gastrointestinal tract. The bacterial colonies establish themselves along the length of the alimentary canal over the first three days after birth. They then proliferate and mature over the subsequent year of infancy. This coincides with a critical window during which immune tolerance and T-cell skewing are also established in the infant's gut. During caesarean section, bacteria from the mother's skin are transferred to the foetus instead of vaginal and faecal flora. This creates immediate dysbiosis and immune dysregulation, the effects of which persist into adulthood. Since brain cells undergo proliferation and differentiation in primary and association areas at the same time as cells in the gut, dysbiosis can also alter brain functions, such as memory and learning, mood and behaviour (see Table I).

BENEFICIAL BACTERIA CAN ENHANCE MEMORY AND LEARNING

Brain-derived neurotrophic factor (BDNF) is a growth hormone for brain cells. It is produced by bacteria in the gut and then transported to the hippocampus in the brain. The hippocampus is involved with learning and the processing of thoughts and experiences into long-term memory.[10] This places an enormous burden of neuronal activity on the hippocampus, which is then dependent on BDNF for synaptogenesis and neuroplasticity.[17] A depleted source of BDNF cannot adequately support the metabolic demands of the remaining hippocampal neurons, which are subject to high levels of turnover and energy expenditure.

BDNF also matures cells in different parts of the brain. This is important for neurodevelopment, as one part of the brain is often dependent on the function of another. An example of this important role of BDNF can be seen in the relationship between the hippocampus and the HPA.[18] Stress causes the release of cortisol from the HPA. This is extremely toxic to immature hippocampal neurons. Dysbiosis not only causes chronic activation of the HPA

TABLE I: KEY LEARNING POINTS SUMMARISING THE RELATIONSHIP BETWEEN THE GUT MICROBIOME AND THE BRAIN

- After discovery of the relationship between the brain–gut axis and the importance of the microbiome in this process this relationship became known as the 'microbiome–brain–gut axis'.
- The gut microbiome is intimately interwoven with the structure and function of the gastrointestinal tract, and as it is passed onto the foetus from the mother during passage through the birth canal, the gut microbiome can be seen as an environmental factor which directly impacts the organogenesis of the gastrointestinal tract.
- This coincides with a critical window during which immune tolerance and T-cell skewing are also established in the infant's gut.
- During caesarean section, bacteria from the mother's skin are transferred to the foetus instead of vaginal and faecal flora. This creates immediate dysbiosis and immune dysregulation, the effects of which persist into adulthood.
- Brain-derived neurotrophic factor (BDNF) is a growth hormone for brain cells. It is produced by bacteria in the gut and then transported to the hippocampus in the brain. The hippocampus is involved with learning and the processing of thoughts and experiences into long-term memory by synchronising critical windows of maturation in both the hippocampus and the HPA.
- Dysbiosis has a number of critical effects on the brain including abnormal synthesis of neurotransmitters and hormones and enhances brain sensitivity to various stressors.
- In addition, pathogenic bacteria may contribute to increased brain inflammation, with many other consequences.
- Consequences of dysbiosis have been associated with behavioural abnormalities including 'fussy eating and sleep disturbances as well as problems with memory, mood and learning'.

but also leads to an overactive HPA. But by synchronising critical windows of maturation in both the hippocampus and the HPA, BDNF protects immature hippocampal neurons from the damaging effects of cortisol.[19]

The maturation of brain cells and cells from the gut must also be synchronised in order for them to be mutually beneficial. Enteric bacteria decompose dietary fibre into short-chain fatty acids (SCFAs), which are largely absorbed by the colon. These SCFAs not only form a substrate for other metabolic pathways, but can also function independently as chemical messengers that can gain access to the central nervous system and stimulate the production of BDNF in the hippocampus.[20] In this way, SCFAs offer both a degree of neuroprotection and provide a tangible and sustainable link between diet and brain function in the form of memory and learning.[21] SCFAs also function as neurotransmitters and are involved in plasticity through the formation and maintenance of synapses.[22]

BACTERIA CAN AFFECT OUR MOOD AND SOCIAL BEHAVIOUR

Hunger centres in the brain are closely associated with anxiogenic regions within the limbic system. Because of this relationship, the unavailability of food causes anxiety. The limbic system relays afferents to the basal ganglia that are involved with the initiation of exploratory behaviour in young children, but anxiety in a young child suppresses exploratory behaviour, not only in relation to finding more food, but also with regard to the willingness to experiment with unusual tastes and consistencies. The stress of hunger coupled with anxiety and social isolation drives the chronic release of cortisol via the HPA.[23] Malnutrition and psychosocial deprivation can therefore result in the shrinkage of hippocampal neurons, along with poor school performance and intellectual disability.[19]

Favourable gut bacteria produce Neuropeptide-Y (NPY). NPY is a neurotransmitter which has receptors throughout the CNS.[24] It counteracts the immunosuppressive effect of cortisol by activating feeding centres in order to increase food intake during periods of immune suppression during which there are greater nutritional demands.[25] NPY also suppresses anxiogenic regions in the limbic system and drives exploratory behaviour through a direct effect on the hippocampus, which has a similar function to the basal ganglia in this regard.[25]

However, stress resilience does not rely only on interoceptive information from within the individual. Stress also encourages affiliative behaviour and group cohesion, in order to secure communal resources. Through modulation of vagal tone, beneficial bacteria can alter cardiac and respiratory output towards a state of calmness. *Lactobacillus reuteri* up regulates gamma-aminobutyric acid (GABA) receptors in the CNS, thereby increasing parasympathetic tone. This creates physical calmness through direct inhibition of the HPA, as well as emotional calmness through negative feedback from the HPA to the limbic system.[7] Increased vagal tone also regulates facial expression, which is another prerequisite for effective social cohesion. Bacteria can therefore contribute to the autonomic substrate necessary for effective social behaviour.[26] Galen was indeed correct when he postulated that the stomach was able to rouse the animal and stimulate it to seek food.

HARMFUL BACTERIA CAN INFLUENCE WHAT WE EAT

Our gut bacteria not only are able to inform our brains about whether or not food is available, but can also inform us about the nature of the food in our intestines and which foods we should be eating. The term 'commensal' is derived from the Latin *cum mensa* which means 'to eat together'.[7] Gut bacteria are able to process and 'taste' luminal contents through a reaction called 'chemo-sensing', whereby glucose and L-glutamate molecules bind to receptors on the surface epithelium and initiate downstream signalling, resulting in the activation of deeper-lying enterochromaffin cells.[27] Neuropeptides are released and an 'interoceptive map' of the luminal contents is transmitted to the solitary tract nucleus in the brain stem via the vagal nerve. This enterosensory information is then relayed to associated feeding centres and limbic regions. As diet is the major

driver of diversity and health in the microbiome, beneficial gut bacteria can, as it were, persuade the child to sample better quality foods in order to flourish.[28]

However, a diet rich in fat and processed carbohydrate selects pathogens and promotes bacterial overgrowth, resulting in a breach of barrier mechanisms.[29] Bacteria come into contact with immune cells in the lamina propria and set off multiple inflammatory cascades. Cytokines and other mediators are released into the blood and overwhelm the brain via circumventricular organs which lack a blood–brain barrier. These regions activate the arcuate nucleus in the hypothalamus, which induces satiety and creates a psychological and emotional aversion to the consumption of food, particularly that which is rich in fibre, through its connections with the limbic system.[30]

Inflammatory mediators (interleukin-1, interleukin-6, tumour necrosis factor-alpha) also heighten the child's felt experience of illness (nausea, pain) through stimulation of nociceptive centres in the frontal cortex, where the perception of illness is generated.[18] In such cases the parasympathetic tone generated by a healthy microbiome becomes dominated by sympathetic overdrive, and the child perceives a feeling of unwellness after ingesting unfamiliar and bitter foods such as vegetables and certain fruits. As tumour necrosis factor-alpha is also involved in neuroplasticity, feeding refusal can persist for years even once the immune stimulus has subsided.[31] This may help to explain what appears to be a contemporary epidemic of fussy eaters among preschool children.

This increased brain inflammation caused by pathogenic bacteria has many other consequences. Cytokines activate microglia and astrocytes, immune cells in the brain which in turn release more cytokines, resulting in a 'cytokine storm'. Cytokines antagonise BDNF in the hippocampus, which apart from memory storage and learning, also serves as an 'immune switch' for global immunity, thereby perpetuating the immune dysregulation.[32] Pathogenic bacteria also release mediators that recruit peripheral tryptophan metabolism, which is a precursor for the formation of serotonin. The body's pool of serotonin is depleted, altering the brain's neurochemistry into an anxiogenic state.[33] Incidentally, it is worth noting that more than 50 per cent of patients with Crohn's disease suffer from anxiety and depression.[32]

Pathogenic bacteria release amino-acid sequences called 'microbe-associated molecular patterns', which act on toll-like receptors throughout the brain–gut axis.[34] Lipopolysaccharide (LPS), an example of such an amino-acid sequence, augments the stress response through the HPA by stimulating anorexia and depressed mood in limbic and feeding centres. It also provokes an autoimmune response in the brain resembling autoimmune encephalitis. Antibodies directed against LPS cross-react with neural antigens, causing demyelination of networks involved in stress resilience. Similar autoimmune antibodies have been detected in older anorexia nervosa and bulimia nervosa patients.[35]

FUNCTIONAL DISORDERS

Nociceptive signals from the gut, such as nausea, pain and abdominal discomfort, are up regulated by the release of substance-P in the enteric plexus. They are then transmitted to the brain via the vagal nerve and terminate in the *stria terminalis*, which is also a fear-processing circuit in the limbic system.[36] An emotional connotation is imprinted on to visceral information, which heightens personal awareness of the stressor at hand. Sensory afferents are also relayed to the frontal cortex in order to alert the individual to the ingestion of potentially toxic substances. The combined sensory and autonomic input facilitates intestinal purging and avoidance of the offending agent.

Campylobacter jejuni can activate this response at subclinical doses.[37] The young child becomes hyper-sensitive to the feeling of being unwell and associates this experience with the sampling of new foods, which further aggravates feeding refusal. This once again illustrates how easily aberrant thought patterns and emotions can be amplified and ingrained in the feeding behaviour of young children. Not only can they feel unwell when eating healthy food but they can also become, as it were, addicted to eating fat and refined sugars. Pathogenic bacteria break down starch and release metabolites resembling opiates and endorphins. These pleasure signals are then carried to the brain by the vagal nerve, resulting in cravings and a dependency on sweet, as opposed to bitter or savoury, food. Populations of taste receptors for the sensation of sweetness are up regulated on the surface of the tongue and aberrant psychology becomes experience. Not surprisingly, then, dysbiosis has been associated with obesity and type-2 diabetes in later childhood.[22]

Apart from fussy eating, another apparent epidemic which seems to be affecting young children is that of difficulty sleeping. Bacteria can influence food intake and intestinal function. However, these processes are also subject to circadian rhythms, and therefore sleep patterns. If bacteria are able to manipulate the sleep–wake cycle, then bacterial overgrowth might be a common aetiology or be, at least, contributory to both epidemics. Cortisol has an important role in the sleep–wake cycle. Levels peak early in the morning in order to increase alertness and prime energy homeostasis for the day ahead, and then wane at night before the child goes to bed. Dysbiosis creates an overactive HPA, which results in deregulated cortisol secretion and disturbances in the sleep–wake cycle.[38]

Bacteria also have their own daily rhythms, which are mostly affected by diet and the timing of eating. Pathogens

manipulate diet through feeding centres and the limbic system, and the timing of eating through the sleep–wake cycle. Melatonin metabolism may provide another link between feeding behaviour and sleep patterns.[39] The gut produces 400 times more melatonin than the pineal gland.[39] This melatonin is involved in the regulation of intestinal homeostasis as well as food intake, which demonstrates that it can function independently in the central nervous system. Melatonin from enteric bacteria may also facilitate sleep directly through central mechanisms, although this has not yet been proven.[40]

Enteric bacteria not only influence the sleep–wake cycle but they can also have a significant impact on the quality of sleep, especially in infants and young children. Lactobacillus and Bifido bacteria, which are transferred from the mother to the foetus during normal delivery as well as breastfeeding, convert glutamate – an excitatory neurotransmitter in the brain – to GABA, an inhibitory neurotransmitter.[41] Increased GABA neurotransmission creates a blanket of parasympathetic tone over the central nervous system, thereby facilitating sleep onset and maintaining a deep level of slow-wave or REM (rapid eye movement) sleep. Blood supply increases during slow-wave sleep, which results in improved oxygenation and nutrient delivery to distal brain regions. Greater parasympathetic tone also reduces anxiety in the limbic system, which reduces separation anxiety and recurrent arousals at night.[41]

Enteric bacteria are implicated in multiple aspects of sleep physiology, which reflects the importance of a healthy microbiome for sleep in early infancy. Symbiotic bacteria produce benzodiazepine receptor ligands that enhance sleep through calmness, as well as neurotransmitters such as dopamine and serotonin that also regulate sleep–wake cycles.[37] A fascinating discovery in the microbiome–brain–gut axis was that enteric bacteria could produce identical neurotransmitters to those found in the brain. Symbiotic bacteria do not recruit tryptophan metabolism. Tryptophan is not only a precursor of serotonin and dopamine but also a sleep-inducing amino acid, and its concentration is elevated in evening breast milk.

Symbiotic bacteria activate nociceptive opioid and cannabinoid receptors in the gut, thereby desensitising visceral pain and reducing the abdominal discomfort and persistent crying associated with infantile colic.[42] They also produce SCFAs which stimulate the secretion of gut peptides by L-cells in the gut, thereby down regulating hunger centres before the infant goes to sleep at night.[43] It becomes apparent that sleep physiology and digestive physiology are intimately interwoven in infancy, and that the gut microbiome plays a significant role in maintaining equilibrium between the two.

CONCLUSION

Human cells make use of bacteria in order to function effectively. Bacteria transmit signals to the brain which influence essential physiological functions such as feeding behaviour and the regulation of satiety, mood regulation and other circadian rhythms including the sleep–wake cycle. Trillions of organisms, bacteria, viruses, fungi and protozoa share our food and instruct our brains to go out and find more, if resources are limited.[44] They programme our minds in many different ways in order to alter our behaviour so that we can maintain metabolic homeostasis. By manipulating our appetite and emotions, bacteria can make us eat more food of greater nutritional value. By heightening self-awareness and the need for self-preservation, bacteria can increase our exploratory behaviour and improve our chances of being accepted into a group, so that we have a better chance of survival. These commensals support the host and in the process ensure their own survival by replenishing the metabolic niches in which they flourish. This dynamic and symbiotic relationship has become so successful that there are three non-human cells for every human cell in the body.[44]

The normal microbiome of, particularly, the neonatal and infant gut, is critical to immune development and disease tolerance.[45] A number of threats to microbial diversity and normality in the gastrointestinal tract exist in early life. Early elective caesarean section results in aberrant bacteria from the mother's skin being transferred to the baby's gastrointestinal tract.[46] The unconstrained use of broad-spectrum antibiotics has a devastating effect on the gut microbiome which lasts for years.[47] Dysbiosis sets up a process of chronic inflammation and aberrant physiologies that lead to a host of chronic diseases in adult life.[40] Once the healthy microbiome is gone it is difficult to get it back. The fact that the gut microbiome affects learning, memory and mood may foster greater discernment in our modern medical practices.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

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