Evolutionary public health 3

Evolution, human-microbe interactions, and life history plasticity

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A bacterium was once a component of the ancestor of all eukaryotic cells, and much of the human genome originated in microorganisms. Today, all vertebrates harbour large communities of microorganisms (microbiota), particularly in the gut, and at least 20% of the small molecules in human blood are products of the microbiota. Changing human lifestyles and medical practices are disturbing the content and diversity of the microbiota, while simultaneously reducing our exposures to the so-called old infections and to organisms from the natural environment with which human beings co-evolved. Meanwhile, population growth is increasing the exposure of human beings to novel pathogens, particularly the crowd infections that were not part of our evolutionary history. Thus some microbes have co-evolved with human beings and play crucial roles in our physiology and metabolism, whereas others are entirely intrusive. Human metabolism is therefore a tug-of-war between managing beneficial microbes, excluding detrimental ones, and channelling as much energy as is available into other essential functions (eg, growth, maintenance, reproduction). This tug-of-war shapes the passage of each individual through life history decision nodes (eg, how fast to grow, when to mature, and how long to live).

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This is the third in a **Series** of three papers about evolutionary public health

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Human beings as products of their evolutionary history

Since the evolution of cellular life (about 3·8 billion years ago) the biosphere has been dominated by the Bacteria, Archaea, and eukaryotic microbes.[1] A consideration of the major milestones in evolution and their relationship to the microbial world can provide insight into the position of human beings in the history and diversity of the biosphere. Animal, plant, and fungal life exist as a patina on this microscopic landscape and represent a very minor portion of the biosphere's diversity. Human beings live in a microbial world, and this has shaped all aspects of our biology (figure 1).[3]

Conventionally, evolutionary perspectives of human phenotypic variability emphasise our genetic variability and diverse components of plasticity. We need to go beyond these perspectives, however, to address how

Key messages

What we know

- Vertebrates are ecosystems, and the microbiota (large communities of microorganisms) and its metabolic products influence the development and function of most, probably all, organ systems.
- There are crucial developmental windows when an appropriate microbiota must be in place to set up metabolic pathways and the immune system.
- Human beings co-evolved with the microbiota, and with organisms that could persist in small hunter-gatherer groups (old infections) and organisms and their genes (by horizontal gene transfer) from the natural environment. The crowd infections are more recent.
- Modern lifestyles reduce these microbial inputs, and this is likely to be a factor in the increased prevalence of disorders of immunoregulation (allergies, autoimmunity, inflammatory bowel disease), and of diseases associated with persistent background inflammation.
- The microbiota influences metabolism and energy extraction from food and so shapes susceptibility to obesity and the metabolic syndrome, while also influencing metabolism and reabsorption of sex steroids that modulate sex-steroid-dependent aspects of life history plasticity.
- In animal models the microbiota has profound effects on cognition and stress responses (gut–brain axis). Substantial evidence suggests that the same is true in human beings.

What we need to know

- A more complete knowledge of the gut microbiota, including fungi and viruses, and more reliable data on their relationship to disease susceptibility.
- Can components of the microbial metabolome, or immunomodulatory components of old infections such as helminths, be identified and exploited to benefit human development and health?
- Does loss of environmental microbial biodiversity due to agrochemicals and monoculture compromise human health by reducing the health benefits of green space?
- Can the microbiota be modulated to combat obesity, metabolic syndrome, chronic inflammatory disorders, or the psychiatric disorders associated with chronic inflammation?
- In view of the many biological roles of the microbiota, what are the benefits and dangers of faecal microbiota transplants? How should donors be selected?

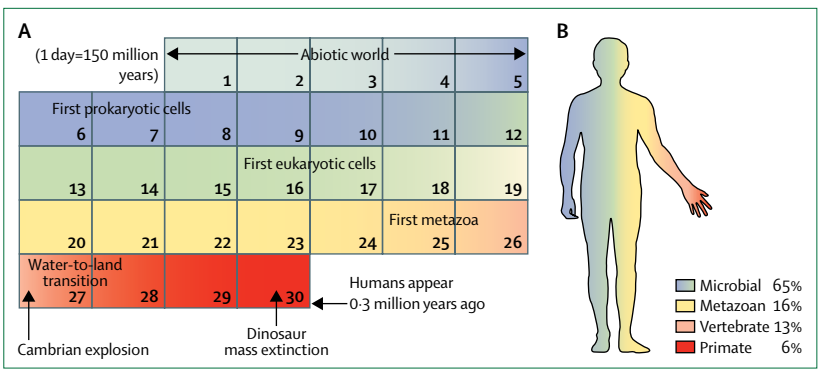

Figure 1: **The position of *Homo sapiens* in geological time**
(A) Earth's history as a calendar month. The first several weeks of this month were entirely microbial. Only in the last 4 days do animals and plants enter the microbe-dominated biosphere, and only in the last 30 min of the last day do humans appear. (B) The microbial signature of the human genome.[2]

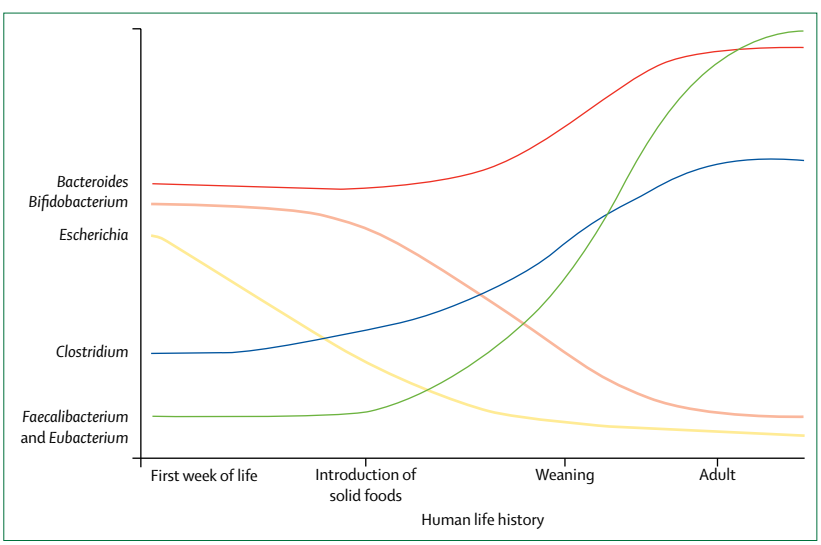

Figure 2: **Development of the adult human gut microbiota**
In the adult, this development is dominated by two phyla: Bacteroidetes (*Bacteroides*) and Firmicutes (*Clostridium*, *Faecalibacterium*, *Eubacterium*), which replace the early dominance of Actinobacteria (*Bifidobacterium*) and Proteobacteria (*Escherichia*). The windows of opportunity for the correct establishment of the immune system, metabolic system, gut–brain axis, and stress responses could occur during the periods of complex change between birth and adulthood. These crucial windows are documented in animal models[9] but not yet in human beings.

microbes shape both phenotypic and genetic variability. Some microbes have co-evolved with us and constitute crucial components of our physiology and metabolism, whereas others such as the more recently evolved so-called crowd infections are new consequences of people's changing lifestyles. Microbes thus shape the allocation of energy between multiple competing functions, as modelled in life history theory (Paper 1 in this Series).[4] The activity of the immune system is energy-intensive, but beneficial microbes such as microbiota must be managed and detrimental ones excluded, while providing energy for other essential functions such as growth, maintenance, sexual maturation, reproduction, and brain activity. Human behaviour, changing lifestyles, and medical efforts shape these consequences. This Series paper aims to explore these issues from a microbiological point of view.

Evolution of eukaryotes

The early biosphere was inhabited only by Bacteria and Archaea.[5] Then about 1·5 billion years ago the eukaryotic cell evolved. Data suggest that this new cell type arose as the result of an endosymbiotic event in which an alphaproteobacterium gave rise to the mitochondrion.[5] Molecular signatures provide evidence that this event occurred only once in evolution—ie, that all eukaryotes have mitochondria derived from that original endosymbiotic incident.[6] The radiation of microbial eukaryotes was accompanied by a vast expansion of genome size and increase in metabolic efficiency.[6] About 540–520 million years ago, nearly 1 billion years later, the Cambrian explosion resulted in the appearance of nearly all of the approximately 38 animal phyla.

Evolution of vertebrates and their microbial partners

Although we tend to think of them as much younger, vertebrates arose early in the evolution of animals, about 500 million years ago, only about 20–30 million years after the Cambrian explosion.[7] Using new genomic tools, bioinformaticians have resolved the trajectory of evolution that lead to human beings into a series of 19 steps in which, with each successive step, new genes arise.[2] This analysis provides evidence that about 65% of our genes originated with Bacteria, Archaea, and unicellular eukaryotes (figure 1), including those genes that enabled animal-microbe interactions. Thus all vertebrates harbour complex communities of microbial partners that probably necessitated the evolution of a complex adaptive immune system.[8]

Biologists have traditionally defined vertebrates as a group with neural crest tissue and ten organ systems. The microbiota (the naturally occurring set of microorganisms that inhabit body organs, especially the gut) is a newly recognised 11th vertebrate organ system (figure 2) that influences all of the other systems and communicates with them through the metabolome (the collection of metabolites). A noteworthy percentage of the metabolic products in human blood is microbial in origin. This finding reveals that each cell of the body that is serviced by blood is now, and has been over evolutionary time, influenced by microbes. Consequently, the signature of microbes can be found in all aspects of human biology, from our molecular makeup to such central functions as our sleep cycles, circadian rhythms,[10] and mental health.[11] Thus an individual vertebrate is a holobiont composed of multiple different microbes and macrobes (bionts) in symbiotic relationships. Organisms that can switch between mutualistic and pathogenic relationships are often known as pathobionts.

Other components of the microbiota

Although this Series paper focuses on bacteria, which are the most studied components of the microbiota, the microbiota also contains fungi, sometimes protozoa and

helminths, and always far more viruses than bacteria or archaea. Many of these viruses are phages that might influence the composition of the bacterial microbiota. One study[12] has revealed large variations in the rates of turnover of gut bacteria, and suggests that this can be as relevant clinically as absolute abundance. The loss of bacterial biodiversity that is seen in Crohn's disease and ulcerative colitis is accompanied by an increase in the taxonomic complexity of the bacteriophages.[13] Moreover, bacteriophages mediate horizontal transfer of virulence factors (cholera, pertussis, and shiga toxin) and antibiotic resistance.

The gut also contains various eukaryotic viruses that can influence the local immune system and therefore, the microbiota. After a norovirus infection, some individuals develop a long-term distortion of the microbiota with reduced Bacteroidetes and increased *Escherichia coli*.[14] Similarly, some persistent norovirus strains infect Paneth cells bearing a human Crohn's disease susceptibility gene *(ATG16L1)* and drive an abnormal gene transcription pattern that in turn leads to susceptibility to inflammation driven by the microbiota, or experimentally, by dextran sulfate.[15] All of these types of organism might therefore affect human energy metabolism.

Microbiota and life history plasticity

The microbiota influences the development of most organ systems,[3] including the immune system, and it modulates metabolism and development (panel 1; appendix). In this way, the microbiota affect a whole range of life history variables (such as litter size, birthweight, age at sexual maturity, adult weight, and height) that are considered by evolutionary biologists as crucial developmental adaptations to environmental opportunities and stresses.[29,30] Such changes can occur stepwise over several generations.[30]

Epigenetic and developmental mechanisms are invoked to explain these generational effects, but stepwise changes in the relationship between the immune system and the microbiotas provide a key additional explanation. An altered microbiota will drive changes in the immune system and in epigenetic programming, leading to further changes in the immune system and microbiota in the next generation, and so on. The microbiota should be considered part of the epigenetic inheritance of the infant and a potential mediator of life history plasticity.

For example, sex steroids are conjugated with sulphate or glucuronide in the liver and secreted into the gut. These conjugated forms are mostly lost in the faeces, but enzymes expressed by the microbiota can alter the balance of metabolites, and also deconjugate these hormones so that they are reabsorbed. In a mouse model,[31] transfer of adult male gut microbiota to immature female mice resulted in elevated testosterone in the female recipients. These processes are sensitive to modulation of the microbiota by antibiotics. In one study of postmenopausal women,[17] the ratio of oestrogen metabolites that were relevant to risk of breast cancer was found to correlate with composition and diversity of the microbiota. Large changes in the microbiota that occur during pregnancy probably modulate the endocrinological changes that occur.[32] Thus, microbial factors mediate reproductive physiology in each sex, with implications for the risk of various cancers.[33]

Co-regulation of the immune system and metabolism

The gut microbiota defends against pathogen colonisation by production of antimicrobial substances, occupation of ecological niches, nutrient competition, reinforcement of intestinal barrier function, and enhancement of IgA secretion. Some microbiota-derived signals (figure 3), notably those that signal via metabolite-sensing G-protein-coupled receptors (GPCRs) or by inhibiting histone de-acetylase and thus driving epigenetic changes, are equally relevant to metabolism and to immunoregulation.[34] This close link might be due to the large metabolic costs of immune responses that therefore need coordinated regulation of energy harvest.

There is evidence for a crucial window of opportunity during early life, when appropriate and diverse microbiotas must be present for metabolic and immune system pathways to develop optimally for long-term health.[9] The microorganisms in the human gut are well adapted to this environment and are mainly from two dominant phyla: Firmicutes and Bacteroidetes. Diet is a major factor in shaping the gut microbiota.[18] Diets rich in fat and protein enrich bacteria belonging to Bacteroides, whereas diets rich in fibre increase the abundance of Prevotella, which are the two dominant genera within Bacteroidetes.[18,35]

See Online for appendix

Accordingly, one major difference between the microbiome—the collective genomes of the microbiotas— and the human genome is that the microbiome changes to a much larger extent than the human genome over the course of a lifetime and can contribute to life history plasticity. Such changes can have severe consequences. For example, one reason that the malnutrition of kwashiorkor is difficult to reverse is because of the presence of a grossly abnormal gut microbiome that is not easily corrected and that fails to promote growth.[20] Sialylated milk oligosaccharides act via the infant microbiota to promote growth and mitigate effects of malnutrition.[36]

However, in large areas of the world, obesity rather than malnutrition is a growing problem and compelling evidence suggests that the gut microbiota is contibuting to energy harvest from our diet.[19] These points further emphasise the importance of the microbiota in life history plasticity and energy budgeting, which in turn affect the rate of ageing and susceptibility to chronic non-communicable diseases.[37]

Metabolism of macronutrients might require the coordination of processes encoded by the human genome and the microbiome.[19] For example, the gut microbiota

Panel 1: **Microorganisms, organ development, metabolism, and the immune system***

Microbial signals and organ development[3,16]

- Short-chain fatty acids, peptidoglycans, endotoxins, polysaccharide antigen from *Bacteroides fragilis*, tryptophan metabolites, and other neurochemicals (noradrenaline, dopamine, and acetylcholine), and unknown components of the microbial metabolome constitute signals that are involved in development of the gut and lymphoid system, testis, neuroendocrine system, skeleton, kidneys, cardiovascular system, and brain.

Microbiota, sex hormones, and life history plasticity[17]

- Transfer of microbiota from adult male mice to germ-free female mice causes an increase in testosterone concentrations.
- The composition of the microbiota changes at puberty, pregnancy, and the menopause.
- Antibiotic use changes concentrations of sex steroid metabolites because these are secreted into the gut conjugated to glucuronide or sulphate, and are lost in the faeces unless deconjugated by microbial enzymes, which also change the ratios of metabolites.
- Composition of microbiota in menopausal women correlates with levels of sex steroid metabolites relevant to breast cancer risk.

Lifestyle and diet in high-income countries[9,18,19]

- Lifestyle changes distort and limit diversity of the microbiota.
- These effects are compounded by the modern diet in high-income countries.
- Obese mothers might transfer inappropriate microbiota to the infant.
- Microbiota of obese individuals mediates increased energy harvest.
- Microbiota modulates insulin sensitivity and metabolism.
- Microbiota influences diurnal rhythms and cyclical variation in activity of metabolic pathways.
- Animal models suggest a critical window in early life for correctly setting up metabolic homoeostasis.

Malnutrition[20]

- Severe acute malnutrition in infants is associated with delay in the maturation of microbiota towards the adult pattern.
- In kwashiorkor, the microbiota is grossly abnormal and causes weight loss in recipient mice. This abnormal microbiota probably explains why infants with kwashiorkor are resistant to treatment by dietary supplements.

Burden of infection

- Vaccines and efficient treatment of infections reduce the need for and energy-intensive activity of the immune system. Thus a reduced burden of infections increases resources available for growth.

Immune system development

Microbiota[9,21–23]

- Caesarean deliveries, reduced breastfeeding, and inappropriate hygiene limit transmission of microbiota to baby.
- Abnormal microbiota, or microbiota of diminished biodiversity, is associated with increased risk of chronic inflammatory disorders, including allergies, autoimmunity, and inflammatory bowel disease.
- Intensive antibiotic use in pregnancy or infancy can also disturb the microbiota and is associated with chronic inflammatory conditions, obesity, and metabolic disorders.

Old infections.[24,25]

- Helminths, *Helicobacter pylori*, and *Mycobacterium tuberculosis* are examples of old infections with which human beings co-evolved.
- The old infections could persist in small hunter-gatherer groups by modulating the immune system
- These infections drive immunoregulatory pathways, including increased levels of regulatory dendritic cells and regulatory T cells, and act as regulatory T-cell adjuvants.
- They might protect against chronic inflammatory disorders, including allergies, autoimmunity, and inflammatory bowel disease.

Environmental organisms[26–28]

- Perinatal exposures to organisms from farms and dogs correlate with reduced risk of allergic disorders and inflammatory bowel disease.
- These exposures drive increased levels of regulatory T cells and accelerate maturation of neonatal type 1 T-helper cell response in animals and human beings.
- Environmental organisms do not necessarily colonise; they might also act as data input to the developing immune system of the gut and airways.
- These mechanisms might also be involved in the health benefits of exposure to green space, and to house dust rich in microbial biodiversity.

*An expanded, fully referenced version of this panel is available in the appendix

plays an essential role in disposal of cholesterol from the body by affecting host bile-acid metabolism. Cholesterol is oxidised in the liver to primary conjugated bile acids, which are released into the small intestine. The primary bile acids are metabolised by microbiota into more hydrophobic secondary bile acids, such as deoxycholic acid and lithocholoic acid, which can be secreted in the faeces.[38] Both primary and secondary bile acids are agonists for host receptors, including both GPCRs such as G-protein-coupled bile acid receptor 1 (TGR5), and nuclear hormone receptors such as farnesoid X receptor (FXR)-α, which are both important regulators of host metabolism. Gut microbiota could therefore contribute to host metabolism and physiology by modulating cell signalling through FXR and other receptors.[39]

The gut microbiota also contributes to the synthesis of trimethylamines generated from choline and carnitine, which are further oxidised to trimethylamine oxide by

flavin monooxygenases in the liver. High serum concentrations of trimethylamine oxide are strongly correlated with cardiovascular events and could provide a mechanism by which the gut microbiota contributes to the pathophysiology underlying cardiovascular disease.[39]

Through horizontal gene transfer, the gut microbiota can acquire new genes and functions to, for example, adapt to dietary components and thus contribute to human adaptability.[40] One such example is that enzymes accquired by horizontal gene transfer from marine bacteria enable Japanese gut microbiota to metabolise seaweed carbohydrates.[40] The natural environment thus constitutes a resource of genetic diversity for the microbiota, though the timescale of such changes is unclear. There is some controversial evidence that horizontal gene transfer from bacteria and protists to vertebrates might have also occurred, mainly involving genes encoding metabolic enzymes.[41]

Microbes and immune system function

Because studies of the adaptive immune system began as an outgrowth of pathogenic microbiology, its principal function had been thought to be for non-self-recognition, and its evolution driven by pathogenesis. With their recent awareness of the sustained interactions of the immune system with a co-evolved microbiota, immunologists are beginning to entertain the possibility that the principal evolutionary pressure on the adaptive vertebrate immune system has been the requirement to manage and maintain a stable microbiota (figure 2), while simultaneously protecting against infection. Thus the immune system co-evolved with the microbiota that provides crucial signals driving the development,[42,43] expansion, level of background activation,[44] and memory repertoire[45] of the lymphoid system. Crucially, in the context of this paper, the microbiota (and other organisms discussed below) needed to be tolerated (ie, integrated within the ecosystem) and so co-evolved to drive expansion of the regulatory pathways that control the immune system and prevent it from attacking inappropriate targets, and also to shut it down when inflammation is not required.

But human beings evolved as a grassland species in small hunter-gatherer groups and the various microbiotas were obviously not the only organisms with which they co-evolved (panel 1; appendix). Human beings were also exposed to microorganisms from animals and the natural environment, some of which were probably able to establish themselves within the microbiotas.[46,47] Moreover, approximately a third of the gut microbiota are spore-forming, so it can be hypothesised that wherever people have lived, the environment has been seeded with spores of human gut-adapted strains.[47]

Finally, there were certain so-called old infections that could regulate the immune system and establish long-term infections and so were able to survive within small hunter-gatherer groups.[48] Ancestral forms of *Mycobacterium tuberculosis*, *Helicobacter pylori*, gut helminths, and blood

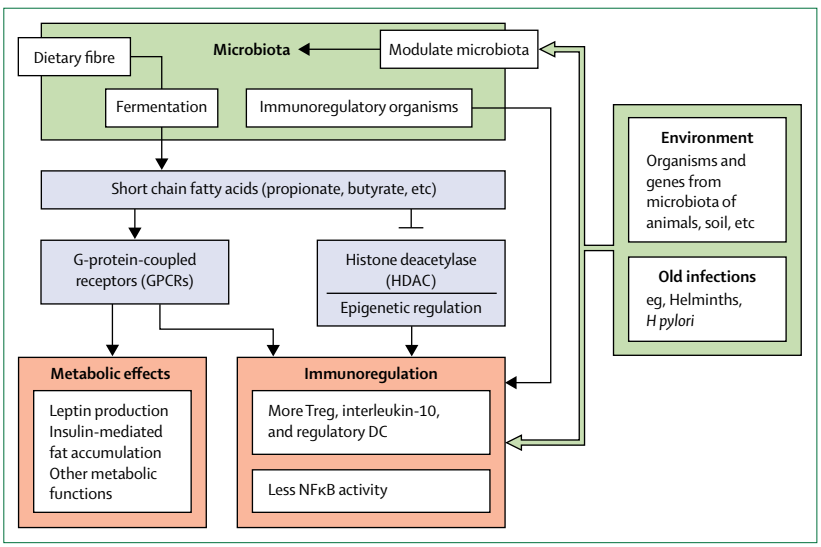

Figure 3: **Some major pathways involved in immune and metabolic regulation by organisms with which human beings co-evolved**

Various members of the gut microbiota drive expansion of effector and Treg populations. An example of an immunoregulatory organism defined in mouse models would be *Bacteroides fragilis*, which releases a polysaccharide antigen that expands regulatory Treg populations. Short-chain fatty acids have anti-inflammatory effects and drive epigenetic regulation of the immune system. Helminths can modify the microbiota, drive interleukin-10 release, alter dendritic cell function, and expand Treg populations. The contribution of organisms from the natural environment is largely unknown and undocumented, though strongly suggested by epidemiological associations. The old infections are largely eliminated by modern medicine, while trans-generational transfer and subsequent maintenance of the microbiota are compromised by modern lifestyles, diets, and antibiotics. DC=dendritic cells. NF-κB=nuclear factor-κB. Treg=regulatory T cell.

nematodes all fall into this category. Analysis of the phylogenetic trees of *M tuberculosis* and *H pylori*, and comparison with the human phylogenetic tree, reveal how these old infections co-evolved and spread with human populations.[48–50] *H pylori* is a notable example of a pathobiont that can contribute to immunoregulation, but under some circumstances triggers stomach ulcers and influences oesophageal cancer.[51] Some of the most studied mechanisms involved in immunoregulation by microbiota and old infections (helminths and *Helicobacter pylori* are used as an illustration of the latter) are described in figure 3.[16,24,52–54] The evolutionary history of human beings was therefore shaped by selective pressures acting on complex human–microbe dynamics, and these are continuing to change, in large part through the ways by which human beings shape their own living conditions.

Dearth of microbes and immune system dysfunction

Modern life, especially in urban settings, causes the human microbial experience to deviate from the co-evolved pattern (panel 1; appendix). Modern medicine eliminates the old infections, at least from the wealthy sections of society. Meanwhile, trans-generational transmission of the microbiota is compromised by caesarean deliveries,[55] absence of breastfeeding,[21] and inappropriate hygiene that diminishes transmission of maternal microbiota to the infant.[22] The microbiota is further disrupted by antibiotics,[23] and by dietary changes.[34,35] Finally, contact with the natural

world is diminished, particularly in people of low socioeconomic status living in modern cities.[26,27]

Since these microbial exposures have evolved crucial roles in setting up immunoregulatory circuits (figure 3),[16,24,52–54] diminished exposure to microbes is likely to be relevant to the sharp increase in chronic inflammatory disorders (allergies, autoimmunity, and inflammatory bowel disease) in high-income settings.[34,47,56] These are all at least partly disorders of immunoregulation, in which the immune system is attacking inappropriate targets. From a life history point of view, this can be seen as erroneous allocation of energy to the immune system. Disturbed immunoregulation also plays a role in long-term background inflammation manifested as persistently raised C-reactive protein concentrations in the absence of detectable medical cause. In terms of energy budgeting and life history strategy, the maintenance of unnecessary background inflammation is a misdirection of resources, but raised C-reactive protein concentrations is common in high-income countries,[57] and it is associated over time with increased risk of cardiovascular disease, metabolic syndrome, insulin resistance, obesity,[58] some inflammation-associated types of cancer,[59,60] and depression.[47,61]

Major depressive disorder is rapidly becoming the major cause of human disability, so it deserves emphasis here.[62] Some studies[63] suggest that its prevalence is increasing though this is difficult to prove. It is clear, however, that some cases of depression (and some other psychiatric disorders) are associated with raised background levels of inflammation biomarkers (panel 2; appendix), and they are commonly associated with chronic inflammatory disorders.[67] Similarly, some cases of depression, especially those that are accompanied by raised biomarkers of inflammation, can benefit clinically from anti-inflammatory therapies.[64,65]

Data show that raised C-reactive protein or interleukin-6 can predict later depression in children,[68] and adults,[69] and can also predict susceptibility to post-traumatic stress disorder in army recruits.[71] New non-invasive techniques can show the presence of inflammation in the brains of depressed individuals.[72] Similarly, inflammation during pregnancy, from any cause, increases the risk of autism and schizophrenia in the child.[70] It is hypothesised that diminished immunoregulation can increase this risk further.[73] Panel 2 and the appendix list examples of the links between chronic inflammatory states and psychiatric disease, using, where possible, examples in which the role of infection or disturbed microbiota in the immunoregulatory dysfunction is apparent.

Crowd infections

Although the inhabitants of modern cities have distorted microbiota, encounter fewer of the old infections, and have reduced contact with the natural environment, they are increasingly exposed to the more recently evolved crowd infections. These infections affected human beings much later, as populations grew and settled into large communities. Crowd infections can only persist in populations larger than around 300 000 because people are infectious for only a short time before they recover (or die), and they are subsequently immune for a very long time. These infections tend to occur in epidemic waves with dramatic outbreaks, in which large numbers of susceptible people become infectious and ill. Then the number of cases falls, as dramatically as it once rose. In small populations, stochastic effects can cause fade-outs, in which one last infectious individual recovers before passing the infection to anyone else. Infection can be reintroduced to subsequent generations by the arrival of an infected person. Measles is the canonical example of a crowd infection, and the pattern outlined above was documented by Bartlett[74] and Black[75] in papers from the pre-vaccination era. Other infectious diseases (including those of childhood, such as diphtheria, mumps, and pertussis[76]) also have these behaviours.

When might these crowd infections have evolved? Phylogenetic analyses attempt to date the emergence of measles by studying the sequence divergence between measles and its two closest relatives, rinderpest and peste des petits ruminants, both of which affect animals. One such study[77] dates the emergence of measles to the 11th or 12th century. However, others[78] suggest that purifying selection can mask the more ancient origins of RNA viruses and suggest that measles emerged a few hundred years earlier. Either way, the increasing prevalence of crowd infections as populations increased will have diverted energy resources (particularly in childhood) towards the immune system, and away from growth, whereas more recently, measures such as vaccines enable the use of these resources for growth. These recently evolved crowd infections were clearly not major drivers of the evolution of the mechanisms that regulate the immune system, and epidemiological studies show that unlike microbiota and Old Infections, they do not protect against the chronic inflammatory disorders that are increasing in prevalence in developed, high-income countries.[79,80]

Managing microbial exposures

Which microbial exposures need to be restored, and how can it be done? Widespread misunderstanding of the current status of the hygiene hypothesis is leading to a worrying tendency for the media, and even the medical profession, to suggest the abandonment of hygiene and hand washing. However, a close examination of what is now known indicates that hygiene plays a minor role in the diminishing contact with beneficial microbes, and plays a crucial role in shielding people from the crowd infections.

Microbiota

Behaviours that inhibit transmission of microbiota from mother to child need to be limited where possible, particularly the excessive use of antibiotics in pregnancy or infancy.[9] But once the microbiota is established, maintaining it is largely a matter of diet.[34] A diverse diet

Panel 2: Microorganisms, immunoregulation, and psychiatric disorders

Microorganisms, immunoregulation, and psychiatric disorders*

Animal models[64-66]

Germ-free animals

- The brain, hypothalamo-pituitary-adrenal axis, and stress responses are all abnormal in germ-free animals. The abnormality is permanent if microbiota is not restored in the early weeks of life.

Effects on behaviour of altered microbiota

- Depleting microbiota with antibiotics or changing microbiota by transfer from a different mouse strain alters behaviour and expression of neurochemicals in the brain.

Stress and microbiota interact

- The microbiota participates in the stress response, which is diminished if microbiota are depleted.
- Early life or perinatal stress in monkeys and rodents causes long-term changes in the microbiota, and maternal prenatal stress does so in human beings.
- Maternal stress leads to altered microbiota in offspring, which releases metabolites causing autism-like CNS effects in mice.

Inflammation

- Induction of maternal inflammation during pregnancy causes abnormal brain development in the fetus, and behavioural changes reminiscent of autism and schizophrenia.
- Subthreshold prenatal inflammation and peripubertal stress synergise to cause behavioural and developmental abnormality.

Probiotics

- Results from numerous studies show behavioural modification by probiotics.

Human epidemiology[64,65,67-70]

Raised background inflammation (CRP or interleukin-6) and psychiatric disorders

- A subset of individuals with depression is known to have raised background CRP.
- Raised background CRP is predictive of depression in adults examined 12 years after assay of CRP.
- Raised interleukin-6 in children aged 9 years predicts psychiatric problems 9 years after assay.
- Raised resting CRP in army recruits was predictive of susceptibility to post-traumatic stress disorder when subsequently exposed to war zones.
- The incidence of autoimmune disorders is increased in veterans with post-traumatic stress disorder, implying an immunoregulatory disorder.
- In the Philippines, exposure to a microbially rich environment in early life correlates with lower background CRP and no rise in CRP in response to stressors.

Inflammation during pregnancy

- Any cause of inflammation (including infections) during pregnancy increases the risk of autism.
- Prevalence of chronic inflammatory disorders is increased in the families of autistic individuals.
- Raised maternal CRP is associated with an increased risk of autism in the infant.

Human interventions[64,65]

Inflammatory cytokines

- Therapeutic administration of interferon-α causes depression-like symptoms.
- A neutralising antibody to tumour necrosis factor had a therapeutic effect on the subset of individuals with depression with raised background CRP and markers of inflammation.

Probiotics

- Efficacious in irritable bowel syndrome, and can reduce psychological distress.
- A fermented milk product altered activity in brain regions that control central processing of emotion (assessed with functional MRI).

CRP=C-reactive protein. *An expanded, fully referenced version of this table is available as an online supplement.

helps to maintain the biodiversity of the gut microbiota, which decreases in institutionalised individuals.[81] Plant polyphenols such as flavonoids and resveratrol also help to maintain biodiversity.[82] In an animal model, a diet without fibre (polysaccharides that are fermented by microbiota rather than by the human host) leads to progressive loss of biodiversity of the microbiota, and over several generations, to irreversible extinctions of important species.[83] These findings generally support the results of studies indicating the health benefits of the Mediterranean diet.[84] However, the complex interactions between the gut microbiota and diet are only just beginning to be unravelled and it is clear that microbiota contribute to metabolic diseases such as obesity, diabetes, and cardiovascular disease,[85,86] and to inflammatory diseases and behavioural effects. It is still unknown whether studying the microbiota can also help predict who will develop disease. Nor is it known whether modulating the gut microbiota can provide novel treatments. Gastric bypass surgery can lead to rapid metabolic improvement and weight loss, accompanied by changes to the microbiota that might be mediating these effects.[87] Faecal transplantation can be used to treat *Clostridium difficile*-associated colitis and there are indications that such transplantation could also improve metabolic parameters.[88,89] These findings open up possibilities for therapeutically targeting the microbiota. We know that the microbiota influences development and life history plasticity, but we do not yet know what is optimal, or how this needs to accommodate differing diets and genetic backgrounds.[90] Much regulatory and clinical work remains to be done.

Organisms from the natural environment

Contact with microbial diversity from animals and the environment appears to explain the fact that exposure to farms, dogs in the home, green space, livestock, or animal faeces in early childhood (panel 1) provides some protection against chronic inflammatory disorders.[26,28,56,57] New evidence indicates that exposure to such organisms via the airways is a crucial factor, at least where protection from asthma and hayfever are concerned. Plant and microbial components interact with a range of receptor systems in the airways, including the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin pathway,[91] the aryl hydrocarbon receptor,[92] Toll-like receptors,[93] and pulmonary neuroendocrine cells.[94] The overall effects of these sensors are likely to be immunoregulatory.[91] For example, exposure to bacterial components causes increased expression of tumour necrosis factor α-induced protein 3 (*TNFAIP3*) in the airways.[95] This protein inhibits the inflammatory pathway that attracts dendritic cells to the sites of allergen deposition in the airways, and so limits the initiation of the type 2 T-helper-cell response.[95] These considerations all lead to the view that homes and cities need to be designed to optimise contact with the natural environment, but they do not suggest the abandonment of hygiene.

Helminths

It is suggested that human beings need to restore the exposure to helminths that will have been normal during human evolution. This is controversial. To persist in small hunter-gatherer groups, these organisms needed to minimise potentially fatal host immunopathology by downregulating the host's immune system. Some authors suggest that, like the microbiota, this helminth-mediated immunoregulation might have evolved to become a physiological necessity.[96] However, greatly varying prevalence of infection[97] and the diverse range of immunoregulatory mechanisms exerted by the helminths[98] render the argument for helminth driven evolution of human immune regulation less convincing. There is some clinical and laboratory evidence that natural exposure to helminths,[25] by driving immunoregulation,[53] is effective in patients with multiple sclerosis in Argentina, where helminth infections are common, but so far, no convincing efficacy has been shown using *Trichuris suis* in a high-income setting where the participants might have been helminth-free for several generations.[99] This might simply mean that *T suis* is inappropriate. But it is equally possible that immune systems developing in the babies of helminth-infected mothers are epigenetically programmed to require the continuing presence of the relevant helminths, but that this requirement is lost in subsequent generations. We hope that ongoing clinical trials will resolve this dilemma.

Pathogens, antibiotics, and vaccines

While human beings maintain our exposures to our microbial partners, we will need to continue to combat pathogens, and to understand and conserve the tools we have to control them. Many microbial pathogens have a remarkable capacity for rapid evolution because they have large population sizes, short generation times, and high mutation rates. This capacity, combined with large dense human populations and rapid air travel, are leading to greatly increased risk of the evolution of novel pathogens, as modelled in detail elsewhere.[100] Meanwhile, we might be compromising our reliance on antibiotics and vaccines. Detailed discussion of the evolution of antibiotic resistance and prospects for circumventing it are found in the appendix, as is an account of vaccine efficacy, and the factors that determine the evolution of vaccine-escape mutants. We pay a penalty for losing microbes that our regulatory systems expect, and we pay another penalty when we meet microbes that cost us energy, but we pay a third penalty if our medical strategies inadvertently make the pathogens more virulent.

Conclusions

Vertebrates are ecosystems (or holobionts) that include the microbiota, and they also receive poorly understood inputs from microbial biodiversity in the natural environment. The flexibility of the microbiota contributes to life history plasticity. The adaptive immune system probably evolved to handle the complex task of farming the microbiota, while stopping other organisms (ie, pathogens) from disturbing any component of the ecosystem. Inevitably, infections, whether in the gut or even in the lungs, have profound effects on the composition of the microbiota,[101] and the microbiota have profound effects on the regulation of the immune system (figure 3). The immune system, metabolism, energy harvest, growth, and the gut–brain axis are tightly linked via the microbiota.

The microbiota therefore plays a key role mediating the association between the organisation of society and human health outcomes, giving them unique relevance to public health programmes in the era of globalisation and rapid economic transition. Perhaps as the understanding of the human ecosystem and its evolved requirements increases, and targeted hygiene is developed that does not exclude essential organisms, human beings will learn to modulate our microbial exposures in ways that reduce developmental, inflammatory, and infectious disorders with less reliance on anti-inflammatory treatments, antibiotics, and vaccines.

Contributors

All authors wrote sections of this report, provided feedback on drafts, and approved the final version.

Declaration of interests

GR, BRL, ARM, and MM-N declare no competing interests. FB is a founder and shareholder of Metabogen AB. The authors are responsible for the views expressed in this paper, and they do not necessarily represent the views or policies of the institutions with which they are affiliated.

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