Connecting Global Priorities: Biodiversity and Human Health

A State of Knowledge Review
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8. Environmental microbial diversity and noncommunicable diseases

1. Introduction

Many countries worldwide, particularly in their urban centres, have undergone large increases in the incidences of chronic inflammatory disorders such as allergies, autoimmune diseases and inflammatory bowel diseases (Bach 2002), all of which are at least partly disorders of immunoregulation, where the immune system is attacking inappropriate targets (harmless allergens, self and gut contents respectively). Similar increases in these noncommunicable diseases (NCDs) are now occurring in emerging and urbanising economies.

There is also an increase in diseases associated with another consequence of disturbed immunoregulation: long-term background inflammation manifested as persistently raised C-reactive protein (CRP) in the absence of detectable medical cause. This is common in high-income countries, and is associated with cardiovascular disease, metabolic syndrome, insulin resistance, obesity (Goldberg 2009; Shoelson et al. 2007) and depression (Rook et al. 2014b; Valkanova et al. 2013). Finally, some cancers that are increasing in prevalence are also associated with poorly controlled inflammation (e.g. cancer of the colorectum, breast, prostate, classical Hodgkin’s lymphoma and acute lymphatic leukaemia of childhood) (Rook and Dalgleish 2011; von Hertzen et al. 2011b).

The purpose of this section is to explore the relationship between these worrying disease trends, and defective immunoregulation attributable to diminishing microbial biodiversity.

2. The ‘hygiene hypothesis’: the updated concept

The expression ‘hygiene hypothesis’ emerged in 1989 and since then has had wide, often misleading, media appeal (Strachan 1989). The problem has been that although based on a crucial underlying insight (that microbial experience modulates our immune systems) it was initially interpreted narrowly in the context of allergic disorders, and there was a tendency to assume that the relevant microbes were the common infections of childhood (Dunder et al. 2007; Strachan 1989). However, the concept has broadened so that it is now a fundamental component of Darwinian (or evolutionary) medicine, with implications for essentially all aspects of human health (Rook et al. 2014b). The allergic disorders are only a part of the story, and neither hygiene nor the common childhood infections necessarily play an important role. For this reason, more recent terminology now employs terms such as the biodiversity hypothesis (von Hertzen et al. 2011a) or the Old Friends mechanism (Rook et al. 2014b) to refer to situations where changing patterns of microbial exposure, in concert with changing diets, are
contributing to diminished immunoregulation, and to increased incidences of immunoregulatory disorders.

Earlier controversy surrounding this topic may be considerably reduced when the differing roles of major functional and evolutionary categories of organism are taken into account.

### 2.1 Categories of organisms

#### 1) The ‘Old’ infections

Co-evolved with humans (Comas et al. 2013; Linz et al. 2007; Wolfe et al. 2007). Modulate the immune system so they can persist for life in small hunter-gatherer groups without killing the host, or being eliminated by the immune system. Progressively eliminated by modern medicine (*Helicobacter pylori*, blood and gut helminths etc.). Known to regulate the immune system and to act as ‘Treg adjuvants’: they encourage development of the regulatory T lymphocytes (Treg) that regulate the immune system (Babu et al. 2006; Correale and Farez 2013).

#### 2) Symbiotic microorganisms

Co-evolved with humans. Loss of diversity in modern urban settings, due to caesarean delivery, lack of breast feeding, antibiotics (Rook et al. 2014b), and increasing uniformity of diet (Khoury et al. 2014; Thorburn et al. 2014). Known to drive development and regulation of the immune system (Round and Mazmanian 2010).

#### 3) Supplements to the symbiotic microorganisms from the natural environment

Major differences exist between hunter-gatherer, traditional rural and urban gut microorganisms (De Filippo et al. 2010; Yatsunenko et al. 2012). In an experimental model, exposure to the outdoor environment increased firmicutes, particularly lactobacilli (which produce short-chain fatty acids that have anti-inflammatory effects), whereas rearing in the indoor environment led to increased expression of inflammatory molecules in the gut epithelium (Lewis et al. 2012; Mulder et al. 2009).

Some soil spore-formers germinate and replicate in the human gut (Hong et al. 2009). Horizontal gene transfer from environmental microbiota to symbiotic microbiota has been documented, although transfer between microbiota where donor and recipient both inhabit the gut is more common (Smillie et al. 2011).

### 4) The ‘crowd’ infections; particularly common virus infections of childhood

Recently acquired (after Neolithic revolution) because they either kill or immunize, and so could not evolve or persist in small hunter-gatherer groups because a large enough population is required for susceptible individuals to persist (Wolfe et al. 2007). Therefore humans did not co-evolve with them as down-regulators of the immune system, and epidemiological studies have confirmed that the crowd infections do not protect children from allergic disorders (Benn et al. 2004; Bremner et al. 2008; Dunder et al. 2007) and in fact often trigger them (Yoo et al. 2007).

Therefore, using this simple functional classification it is possible to make a number of well-documented statements.

- i) The Old infections and the commensal microorganisms (as well as their supplements, as yet poorly defined, from animals and the environment) have potent immunoregulatory effects with well-studied and documented molecular pathways, summarized in the next section (reviewed in Rook et al. 2014b).

- ii) The Old infections are rapidly and progressively eliminated by modern medicine and lifestyles.

- iii) The biodiversity of the microorganisms is restricted by the modern lifestyle.

- iv) Exposure to the Crowd infections should be avoided rather than promoted.

Therefore, depletion of categories 1), 2) and 3) is relevant to changes in regulation of the human immune system, whereas depletion of category 4) has not occurred in urban populations (except where an efficient vaccine has been deployed).
and is in any case not associated with changes in immunoregulatory circuits. Indeed, these infections often act as triggers of allergy or autoimmunity (Yoo et al. 2007). The original formulation of the hygiene hypothesis focused attention on the crowd infections, but this was an error, and the protection against allergic disorders attributed to the presence of older siblings (Strachan 1989), and assumed by many at that time to be a protective effect of the childhood virus infections, is now attributed to enhanced transmission of microbiota (Penders et al. 2013).

2.2 Lifestyle factors that reduce exposure to microbial biodiversity

While modern medicine tends to eliminate the Old infections, lifestyle factors in high-income urban settings reduce exposure both to maternal microbiota and to organisms from the natural environment (categories 2 and 3 above). Delivery by caesarean section, lack of breast feeding and excessive use of antibiotics in early childhood all delay, reduce or modify accumulation of essential microbiota (reviewed referenced in Rook et al. 2014a). The protective effect of cleaning a child’s dummy/pacifier by sucking it, and immediately replacing it in the baby’s mouth is an elegant illustration of the need for trans-generational transmission of microbiota (Hesselmar et al. 2013).

2.3 Links to socioeconomic status (SES)

The factors mentioned in the previous paragraph might be exacerbated in families of low SES, who tend to eat unvaried fast-food diets and more highly processed foods that lack any trace of soil and its microbes, whose homes are less likely to include gardens, and who lack access to travel, overseas holidays and rural second homes (Rook et al. 2013).

2.4 Immunoregulatory pathways driven by organisms of categories 1, 2 and 3

The immune system is potentially dangerous if it attacks inappropriate targets such as harmless allergens in air or food, the host’s own tissues, or essential gut microbiota. When these three types of inappropriate immune response occur they result in allergy, autoimmune disease or inflammatory bowel disease respectively. The immune system has a number of complex mechanisms, known collectively as immunoregulation, to suppress unwanted responses. While a full exploration of this topic falls outside the scope of this chapter, it is important to note that the immunoregulatory effects of categories 1, 2 and 3 are well documented. Old infections (such as helminths) have been shown to drive immunoregulation in humans (Babu et al. 2006; Correale and Farez 2013), and to block or treat animal models of numerous chronic inflammatory conditions (reviewed in Osada and Kanazawa 2010). Molecular structures responsible for immunoregulation are being identified (Grainger et al. 2010; Harnett et al. 2010; Kron et al. 2012). Regulatory T cells (Treg), provide one important immunoregulatory mechanism. When Argentinian multiple sclerosis (MS) patients become infected with helminths, the disease stops progressing and circulating myelin-recognising regulatory T cells (Treg) appear in the peripheral blood (Correale and Farez 2007), indicating that the helminths act as Treg adjuvants. Thus some helminths can be shown to specifically expand Treg populations (Grainger et al. 2010), or to cause dendritic cells (DC) to switch to regulatory phenotypes that preferentially drive immunoregulation (Hang et al. 2010; Smits et al. 2005).

Gut bacteria are also able to do this. A polysaccharide from Bacteroides fragilis, commonly present in the human gut, can expand Treg populations (Round and Mazmanian 2010), as can some members of clusters IV and XIVa of the genus Clostridium (Atarashi et al. 2011), some lactobacilli (Poutahidis et al. 2013), and very probably unidentified organisms from the natural environment, discussed later (Lewis et al. 2012). Some of these effects are mediated via short chain fatty acids (SCFA) that act on G-protein-coupled receptors (GPCR) (Thorburn et al. 2014). SCFA are generated by microbiota that ferment dietary fibre.

It seems unlikely that we will want to bring back all the Old infections, unless we create a ‘domesticated’, perhaps genetically modified...
helminth that could be administered to all children (Parker and Ollerton 2013). On the other hand we should be able to compensate for loss of the Old infections by optimizing exposure to categories 2) and 3) the microbiotas and their supplements from the natural environment. From a medical point of view the question is whether we can compensate for loss of the Old infections and depletion of our microbiotas by restoring those microbiotas and restoring inputs from a carefully maintained and biodiverse natural environment.

3. Commensal microbiotas and environmental biodiversity

From a biological perspective, humans are not individuals. We are ecosystems. Up to 90% of our cells are microbial, and the various microbiotas, particularly the gut microbiota, contain at least 100 times more genes than does our human genome (Wikoff et al. 2009). Consequently, approximately 30% of our metabolome (small molecules circulating in the blood) are products of enzymatic processes encoded in microbial DNA rather than in the human genome (Wikoff et al. 2009). We now know that the microbiotas play a role in virtually all aspects of our physiology, in addition to priming the immune system and its immunoregulatory pathways as described in the previous section. While there is no such thing as a germ-free human, work in experimental animals has revealed that the microbiota influence development of the brain, hypothalamo-pituitary-adrenal axis (HPA), gut, bones etc. (Gilbert et al. 2012; McFall-Ngai et al. 2013). The microbiota also influences energy retrieval from food sources and the likelihood of obesity, cardiovascular disease, metabolic syndrome and type 2 diabetes (Tremaroli and Backhed 2012). In animals, the microbiota modulate brain development and responses to psychosocial stressors (Bailey et al. 2011; Heijtz et al. 2011), and human experiments have shown that the gut microbiota influences aspects of cognition involved in human emotion and sensation (Tillisch et al. 2013). This finding may have significant implications for better understanding mental health, and attempts to treat psychiatric states by modulating the microbiota are beginning to be published (Messaoudi et al. 2011).

Therefore, in the context of this chapter, crucial questions are: 1) are the human microbiotas losing biodiversity? And, if so: 2) To what extent is reduced biodiversity of human microbiotas a consequence of changes in the biodiversity of the environment in which we live? 3) What are the implications for human health?

4. Loss of biodiversity: consequences for human health

Reduced gut microbial biodiversity is often found to associate with poor control of inflammation. Mice with lower microbial diversity have more biomarkers of inflammation (Hildebrand et al. 2013). Gut microbiota of limited diversity is also characteristic of human inflammation-associated conditions such as obesity and inflammatory bowel disease (Rehman et al. 2010; Turnbaugh et al. 2009). Similarly, diminished microbiota biodiversity in institutionalized elderly people correlates with diminished health and raised levels of peripheral inflammatory markers such as interleukin 6 (IL-6) (Claesson et al. 2012).

The same is probably true for skin disorders (Zeeuwen et al. 2013). There is an abnormal microbiota and reduced diversity on skin subject to eczema, with a tendency to return to greater diversity following effective treatment (Kong et al. 2012), and similar findings in psoriasis (Fahlen et al. 2012). It has been suggested that throughout human evolution the skin microbiota have included ammonia-oxidising bacteria (AOB) that would help to explain the presence of large quantities of ammonia and nitrate in human sweat (Whitlock and Feelisch 2009). The AOB convert this to rapidly absorbed nitrite and nitric oxide (NO) that regulates blood pressure and the immune system. AOB are very sensitive to triclosan and alkylbenzene sulfonate detergents, so they are absent from human skin in modern high-income settings.
Further information and references on some of the conditions listed in this paragraph are described below.

4.1 To what extent is reduced biodiversity of human microbiota a consequence of changes in the biodiversity of the environment in which we live?

Humans and other mammals obtain much of their microbiota from their mothers during delivery, and via breast milk (which is not sterile) and from family members. However many, probably all animal species (including humans), obtain components of their microbiota from soil (Mulder et al. 2011; Troyer 1984). It is an interesting possibility that geophagy (the eating of earth) by babies and infants is an evolved strategy for the uptake of soil organisms. This is manifested as the ‘oral’ phase, when all babies put whatever they can reach into their mouths. The quantities of soil and faecal matter that can be ingested by human babies with access to these materials (for example in an African village) are astonishing (Ngure et al. 2013). Circumstantial evidence that humans acquire important microbial biodiversity from the environment comes from studies of the effects of contact with farms, animals, and green spaces discussed below.

4.1.1 Health benefits of exposure to farms and farmland

Exposure of the pregnant mother or infant to the farming environment protects the child against allergic disorders and juvenile forms of inflammatory bowel disease (Radon et al. 2007; Riedler et al. 2001; Timm et al. 2014). This protection appears to be at least partly attributable to airborne microbial biodiversity assayed in children’s bedrooms (Ege et al. 2011). Similarly mere proximity to agricultural land rather than to urban agglomerations increased the biodiversity of skin microbiota, reduced atopic sensitization and increased release by blood cells of IL-10, an anti-inflammatory mediator (Hanski et al. 2012).

4.1.2 Farm animals and dogs

Some of the relevant microbiota come from animals. Contact with cows and pigs protects against allergic disorders (Riedler et al. 2001; Sozanska et al. 2013). Contact with dogs, with which humans have co-evolved for many millennia (Axelsson et al. 2013; Thalmann et al. 2013), also protects from allergic disorders (Aichbbaumik et al. 2008; Ownby et al. 2002), and people share their microbiota via dogs (Song et al. 2013), which also greatly increase the microbial biodiversity of the home (Dunn et al. 2013; Fujimura et al. 2010). Exposure to high levels of bacterial and fungal
components in house dust was associated with diminished risk of atopy (the tendency to develop allergic sensitisation to environmental allergens) and wheeze, though the origins of the organisms was not ascertained (Karvonen et al. 2014; Lynch et al. 2014). In a developing country, the presence of animal faeces in the home correlated with better ability to control background inflammation (CRP levels) in adulthood (McDade et al. 2012b), and in Russian Karelia (where the prevalence of childhood atopy is 4 times lower, and type 1 diabetes is 6 times lower than in Finnish Karelia), house dust contained a 7-fold higher number of clones of animal-associated species than was present in Finnish Karelian house dust (Pakarinen et al. 2008).

4.1.3 Green space

Living close to green spaces reduces overall mortality, cardiovascular disease, and depressive symptoms, and increases subjective feelings of well-being (Aspinall et al. 2013; Dadvand et al. 2012; Maas et al. 2006; Mitchell and Popham 2008). This health benefit has been attributed to multiple factors including exercise, exposure to sunlight and psychological effects. A detailed review and critique of these explanations has been published elsewhere (Rook 2013). Recent work suggests that the health benefits are not attributable to exercise alone (Lachowycz and Jones 2014; Maas et al. 2008), and in light of the clear-cut observations on exposure to farms and animals, exposure to diverse environmental microbiota is becoming the most likely explanation. For example, the gut microbiota of United States citizens is different from that of Amerindian hunter-gatherers and Malawian rural farmers, and strikingly less biodiverse (Yatsunenko et al. 2012). Particularly relevant experiments have been performed with piglets, showing that when maintained with the sow in a field they developed a characteristic gut microbiota rich in Firmicutes, particularly Lactobacilli. On the other hand similar piglets maintained with the sow on the same diet, but in a clean indoor environment developed a gut microbiota that was deficient in Firmicutes, and biopsies of the gut epithelium revealed increased expression of inflammatory genes such as Type 1 interferon and major histocompatibility complex class I (Mulder et al. 2009). Moreover, the piglets deprived of environmental exposure had reduced numbers of regulatory T cells and a predisposition to making antibody following introduction of a novel food (Lewis et al. 2012). This represents an elegant model of the way that human babies are reared in high-income settings with minimal contact with environmental biodiversity, and parallels the rising incidence of food allergies and other immunoregulatory abnormalities in such babies.

Thus the natural environment supplements and modulates the microbiota in a way that is relevant to regulation of the immune system. This area is currently under-investigated, particularly the role of spore-forming bacteria that are usually considered to be soil organisms, but which can germinate and replicate in the human gut (Hong et al. 2009; discussed and referenced in Rook et al. 2014b). It is important to note that we do not currently know how much of the human microbiota is derived from the microbial environment, though work on this point is in progress, and the overlaps between gut and root microbiotas have been discussed (Ramirez-Puebla et al. 2013). However it has been demonstrated that germ-free mice can develop a functioning gut microbiota following exposure to microbial communities from soil, and from other environmental sources, though these organisms get displaced by more mouse-adapted strains when co-housed with mice carrying normal mouse microbiota (Seedorf et al. 2014). A recent study, using novel computational strategies was able to assemble the complete genome of 238 intestinal bacteria, 76% of which were previously unknown (Nielsen et al. 2014). Similar methods have not, to our knowledge at the time of publication, been applied to the microbiota of the natural environment.

4.1.4 Fermented foods and beverages

Fermentation of vegetables (Breidt et al. 2013; Swain et al. 2014), meat (Leroy et al. 2013) and beverages (McGovern et al. 2004) was another source of human intake of microbiota from the natural environment.
environment. Chemical analyses of residues in pottery reveal that some of these methods were in use at least 9000 years ago (McGovern et al. 2004) and probably a great deal earlier (McGovern 2009). A mutation in alcohol dehydrogenase 4 that increased the efficiency of alcohol metabolism appears to have arisen in distant ancestors of mankind about 10 million years ago, perhaps triggered by consumption of fruit that had fermented after falling to the ground (Carrigan et al. 2014). Lactic fermentation of vegetables (e.g. sauerkraut, kimchi, gundruk, khalpi, sinki etc) or of meat (for example the Eskimo fermented fish, walrus, sea lion and whale flippers, beaver tails, animal oils and birds) adds nutritional and microbiological diversity to the diet (Leroy et al. 2013; Selhub et al. 2014; Swain et al. 2014). Fermentation increases the content of vitamins, lactoferrin, bioactive peptides and phytochemicals such as flavonoids which may in turn modulate our own intestinal microbiota (Lu et al. 2013). The increasing interest in modern fermented foods, and in sourcing new probiotics from fermentation processes and from the environment is exploiting the fact that human metabolism has evolved in the presence of such organisms and might have developed a need for their presence.

4.1.5 Horizontal gene transfer

In addition to exchange of whole organisms with animals and the natural environment, we need to consider horizontal gene transfer (HGT) (Smillie et al. 2011). This is common between bacteria and recent work has revealed the existence of a global network of HGT between members of the human microbiota, even between phylogenetically very divergent bacteria separated by billions of years of evolution. Exchange was related to similarity of ecology rather than phylogeny. Examples include the horizontal transfer of genes encoding the antibiotic resistome from soil microbes (Forsberg et al. 2012). This is worrying because huge increases in antibiotic resistance genes are being detected in the microbiota of farm waste as a result of antibiotic use in animal husbandry (Zhu et al. 2013). However HGT also plays essential beneficial roles. Consumption of seaweed by Japanese people induces horizontal transfer to their microbiota from environmental microbes of genes that enable the catabolism of novel seaweed-associated carbohydrates (Hehemann et al. 2012). Thus the adaptability of the human microbiota depends upon appropriate contact with potential sources of genetic innovation and diversity, and might therefore be threatened by loss of biodiversity in the gene reservoir of environmental microbes.

4.2 Life history plasticity, and microbiota as epigenetic inheritance

Evolutionary biologists consider that life-history variables (such as litter size, birth weight, age at sexual maturity, adult weight and height) can be crucial developmental adaptations to a changing environment. However these life history variables can change stepwise over several generations even when the driving environmental change remains constant after it has first occurred (Price et al. 1999; Wells and Stock 2011). For example, improved nutrition in a colony of macaques led to progressive increases in female adult weight (and to increases in the birth weights of offspring) over 5 generations (Price et al. 1999). How is this mediated? Clearly a given genotype would be expected to yield a fixed phenotype under fixed conditions. Therefore epigenetic and developmental mechanisms are usually invoked to explain these generational effects. Such explanations are made more convincing when the microbiota are considered as part of the epigenetic inheritance of the infant. (Interestingly some products of the microbiota exert anti-inflammatory effects by inhibiting histone deacetylases (HDACs), so the microbiota is directly involved in epigenetic immunoregulation (Thorburn et al. 2014)). Dietary effects will alter the microbiota, which when passed on to the next generation will programme the immune system so that it is different from that of the mother, and that immune system will then interact with further environmentally-driven changes to the microbiota.
The previous paragraphs emphasise that humans evolved in a natural environment and in contact with animals. Until recently even our homes were constructed with timber, mud, animal hair, animal dung, thatch and other natural products, and ventilated by outside air. By contrast, modern buildings are constructed with synthetic materials, plastics and concrete, while the timber and cardboard are treated with adhesives and biocides, and ventilated by air conditioning systems. When these modern structures degrade, or become damp, or accumulate condensation in cavity walls, they do not become colonized with the bacterial strains with which we co-evolved. They harbour a low biodiversity, and become habitats for unusual strains that we did not encounter during our evolutionary history, some of which synthesise toxic molecules that we are unable to inactivate (Andersson et al. 1998; Sahlberg et al. 2010). Some examples of “sick building syndrome” have been tentatively attributed to prolonged exposure to these inappropriate airborne microbiota (Andersson et al. 1998; Sahlberg et al. 2010).

5. Commensal microbiota and noncommunicable diseases

As outlined above, as societies become westernized and urbanized, there are striking increases in chronic inflammatory disorders (autoimmunity, allergies and inflammatory bowel diseases (IBD)) that are at least partly attributable to defective immunoregulation, in which the gut microbiota plays a major role (reviewed in Rook et al. 2014b). Most of the epidemiological evidence applies to these three groups of conditions, covered in the previous paragraphs.

However other major health problems rise in parallel with the classic trio of chronic inflammatory disorders already mentioned (autoimmunity, allergies and IBD), and in these conditions also there are reasons for implicating the microbiota, the environment and immunoregulation.

The gut microbiota of lean and obese human individuals differ, and can transfer the tendency to leanness or adiposity to germ-free mice maintained on a standard diet (Turnbaugh et al. 2006). The mechanisms by which microbiota influence adiposity have been reviewed (Karlsson et al. 2013). They include effects on efficiency of energy harvest from ingested food, and complex effects on the function of the body fat-regulatory circuits that involve the central nervous system, leptin, neuropeptide Y, proglucagon and brain-derived neurotrophic factor (Schele et al. 2013a; Schele et al. 2013b). Some of these neuroendocrine phenomena may be secondary to central nervous system effects of inflammatory mediators such as IL-1 and IL-6 (Schele et al. 2013a), and indeed chronic inflammation contributes to insulin resistance and obesity via several pathways (Shoelson et al. 2007). Anti-inflammatory Foxp3+ regulatory T cells (Treg) in abdominal fat control the inflammatory state of adipose tissue, and the abundance of Treg in abdominal fat is inversely related to insulin resistance (Feuerer et al. 2009). A diet of western fast food aggravates the immunoregulatory deficit, promotes a low ratio of Treg to Th17 cells (pro-inflammatory), and drives abdominal adiposity in humans and mice (Poutahidis et al. 2013). This diet was shown epidemiologically to lead to obesity (Mozaffarian et al. 2011). Fatty diets and the accompanying dysbiosis can also increase gut leakiness and so increase uptake of pro-inflammatory products such as endotoxin (Cani et al. 2008).

The adipogenic and pro-inflammatory effects of the western fast food diet can be opposed by a probiotic (Lactobacillus reuteri) via a pathway that depends on the simultaneous presence of a normal gut microbiota, and is mediated by Treg (Poutahidis et al. 2013). (Interestingly, some strains of L. reuteri used in human food production might be derived from mouse gut microbiota (Su et al. 2012)). Thus the nature and diversity of the gut microbiota, together with the poorly documented inputs of microorganisms from the natural environment, may have multiple metabolic, neuroendocrine and immune-mediated effects on obesity, metabolic...
syndrome and insulin resistance, which are all major problems of our time.

5.1.2 Cancers associated with poorly regulated inflammation

The incidence of a number of cancers also increases in high-income urbanized settings in parallel with the chronic inflammatory disorders. These include cancer of the colorectum, breast and prostate, classical Hodgkin’s lymphoma and acute lymphatic leukaemia of childhood (Rook and Dalgleish 2011; von Hertzen et al. 2011b). Inflammation can enhance mutation (Colotta et al. 2009) and so play a role in carcinogenesis, but ‘smouldering’ inflammation that is not obviously related to any external inflammatory stimulus is common in tumours (Porta et al. 2009) and releases growth factors and angiogenic factors that enhance growth, vascularization and metastasis (Balkwill 2009; O’Byrne et al. 2000; Porta et al. 2009). Interestingly non-steroidal anti-inflammatory agents, such as cyclooxygenase-2 (COX-2) inhibitors, reduce the risk of developing colon and breast cancer and reduce the mortality caused by them (Cuzick et al. 2009).

The epidemiology of the cancers that increase in high-income settings is strikingly similar to that of the chronic inflammatory disorders. For instance, age-specific incidence rates for specific cancers in Asians correlate with the state of economic development of their country of residence. Incidences are much lower in Asians living in India compared to those living in the United Kingdom or United States (Rastogi et al. 2008). Another example is acute lymphatic leukaemia, which shows striking parallels with the epidemiological findings that gave rise to the original version of the hygiene hypothesis (Greaves 2006; Strachan 1989). A study in northern California provided preliminary evidence that protection from acute lymphatic leukaemia is proportional to the number and frequency of social contacts (Ma et al. 2002).

A large population-based case-control study (The UK Childhood Cancer Study (UKCCS)) revealed further evidence that social contacts in infancy can reduce the risk of childhood acute lymphatic leukaemia (Gilham et al. 2005).

Animal models have cast much light on the links between environmental organisms, immunoregulation, inflammation and cancer (Erdman et al. 2010). Inflammatory signals from bacteria in the gut can trigger mammary, colorectal and prostate cancers in mice (Erdman et al. 2010; Lakritz et al. 2014). Tumourigenesis can be attenuated by immunoregulatory pathways triggered by appropriate Treg-inducing organisms (Erdman et al. 2010). For example, in two different mouse models (one genetic, and one dietary) mammary carcinogenesis was inhibited by exposure to Lactobacillus reuteri. The mechanism was found to be the induction of CD25+Foxp3+ Treg (Lakritz et al. 2014).

Thus, although excessive immunoregulation might be permissive for some cancers by decreasing anti-tumour immunity, there is strong evidence that faulty immunoregulation leading to chronic background inflammation can provoke mutation and tumourigenesis, and contribute growth factors that favour tumour development, vascularization and spread. Since the microbiota plays a major role in immunoregulation and is supplemented by organisms from the natural environment, it is reasonable to postulate that changes to the pool of environmental microorganisms have consequences for the risk of such tumours.

5.2 Depression, reduced stress resilience and poorly regulated inflammation

It is estimated that depression will become the second major cause of human disability by 2030 (Mathers and Loncar 2006). Chronically raised levels of inflammatory mediators are routinely associated with risk of depression in high-income countries (Dowlati et al. 2010; Gimeno et al. 2009; Howren et al. 2009; Rook et al. 2014b; Valkanova et al. 2013), and the mechanisms have been reviewed elsewhere (Miller et al. 2013). It should be noted that clinical administration of interferon alpha (IFN-a) commonly causes depression as a side-effect (Raison et al. 2009).

Interestingly, one study failed to find a correlation between depression and raised CRP in a low-/middle-income country (McDade et al. 2012a).
In low-income settings, exposure to microbial biodiversity is greater and inflammation is shut off when episodes of infection are terminated, so that chronic elevated biomarkers of inflammation are not seen (McDade 2012). Thus decreasing exposure to microbial biodiversity, by reducing the efficiency of immunoregulatory circuits, is likely to be contributing to the increases in depression, and reduced stress resilience in high income settings (Rook et al. 2013).

**6. Ways forward: preliminary recommendations for global and sectoral policy**

What are the practical implications of these links between microbial exposures, microbial biodiversity, regulation of the immune system, and chronic inflammatory disorders?

**6.1 Better understanding the links between microbial diversity and health**

Practical recommendations are hampered by lack of precise information. Important areas for further research include:

a.1) **What are optimal compositions of the microbiota?** The physiological, metabolic and immunoregulatory roles of the microbiota are not in doubt, and constitute one of the most rapidly expanding and exciting branches of medical research. Nevertheless the techniques used, despite rapid progress, remain imprecise at the species level, and in most cases it is not yet possible to reliably link particular microbial species with health or illness. Even if we did have this knowledge, we do not yet know how to reliably bias the composition of the microbiota in the desired direction. **We also do not know whether humans with different genetics and...**

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**Box 1: Clostridium difficile; a practical example of modulating gut microbiota**

A gastrointestinal disorder characterized by diarrhoea and pain, caused by overgrowth of *Clostridium difficile* in the colon, provides a remarkable clinical example of the crucial importance of a correct balance of organisms within the gut microbiota, and illustrates practical ways of correcting such imbalance. Many people carry small numbers of *C. difficile* in their guts, but in some individuals antibiotic use can lead to overgrowth of this species, and to potentially life-threatening colitis aggravated by toxin production. (The same phenomenon is commonly seen in antibiotic-treated pet guinea-pigs (Rothman 1981)). Recently it has been observed that faecal microbiota transplantation (FMT) is an effective treatment in about 90% of patients (Cammarota et al. 2014). FMT involves administering faecal organisms from a normal donor (often a healthy family member). FMT suppresses growth of *C. difficile* and permits re-establishment of a normal microbiota. FMT is also undergoing trials in IBD, irritable bowel syndrome, and other chronic inflammatory conditions, though results remain variable (Borody et al. 2013).

Three important points need to be made here. First, as we learn more about the composition of a healthy microbiota and develop better ways of driving appropriate stable modifications of the microbiota, so our ability to treat diverse immunoregulatory and inflammatory disorders is likely to increase: this might also involve use of organisms from the natural environment. Secondly, we do not yet know whether people with different genetic backgrounds, or eating different diets, will require a different microbiota, though this is likely. Thirdly, as the number of conditions known to be modulated by the microbiota increases, so the selection of donors becomes more difficult. For example the material outlined in previous sections implies in addition to screening the donors for infections and load of *C. difficile*, we need to be sure that the donor is not obese, or at risk for cancer, cardiovascular disease, autoimmune disease, IBD, allergies or depression.
different diets require different microbiotas, although recent evidence suggests that this is likely.

a.2) The nature of beneficial organisms from the natural environment. The mother, family members and other people are major sources of microbiota, but the epidemiological data presented above provide powerful evidence to suggest that these microbiota are supplemented by organisms (and genes via horizontal gene transfer) from the natural environment and from animals. However, these organisms have not been formally identified. Experimental work with piglets strongly supports the view that the natural environment provides organisms that drive immunoregulation and suppress immune responses to novel foods, but again, the organisms involved have not been formally identified. This is a priority area for research.

6.2 Mainstreaming across health- and biodiversity-related sectors

It is difficult to make clear recommendations until the questions addressed in the previous sub-section are better defined. As such knowledge increases we will be able to offer more precise guidance on some of the relevant issues listed below.

b.1) Agricultural methods: Extensive monoculture and chemical use will reduce environmental biodiversity, and so reduce the adaptability of the human microbiota, which depends upon supplementation with organisms from the environment, and contact with potential sources of genetic innovation and diversity. However the evidence that organic farming increases biodiversity at the floral, faunal (Schneider et al. 2014) and microbial level is suggestive but incomplete and inconsistent (Sugiyama et al. 2010). The use of antibiotics in animal husbandry results in large increases in the abundance of antibiotic resistance genes (Zhu et al. 2013). Not only is this inherently undesirable, but is also likely to cause changes in the composition of the microbiota.

b.2) Human behaviour; targeted hygiene: The public should be taught the concept of ‘targeted’ hygiene. The sound bites generated by the ‘hygiene hypothesis’ has led to erroneous media backing for the notion that “we are too clean for our own good”, despite the massive health benefits of hygiene. The public needs to understand, for example, the difference between the dangers of the gut microbiota of an uncooked chicken, and the benefits of contact with maternal microbiota, green spaces, animals and the natural environment.

b.3) Antibiotics: There is strong evidence that antibiotic use in childhood increases the risk of a wide range of chronic inflammatory and metabolic disorders in childhood and later life.

b.4) Health benefits of fermented foods/traditional diets: Fermentation of vegetables, meat, oils and beverages can be traced back many millennia, as discussed in section 4.1.4. The fermentation process adds nutrients and microbiological diversity (Selhub et al. 2014). It is likely that humans have evolved a requirement for the fermenting organisms and their products, and it is widely believed that these foods provide health benefits. Although the science is strongly suggestive and most workers in the field are confident that fermented foods, probiotics and prebiotics will one day play a role in treatment and prevention of NCDs and inflammation-dependent psychiatric diseases, clinical trial data with the existing preparations have been inconsistent as revealed in recent rigorous reviews (Frei et al. 2015; West et al. 2015). More effort should be made to ‘mine’ traditional fermentation processes for novel probiotics before the diversity of strains is lost (Swain et al. 2014), and clinical trials should be more specifically targeted.

b.5) Food supplements: Food companies potentially have a major role to play in this endeavour. Too much testing of probiotics (and prebiotics) has been conducted with unsuitable organisms (and oligosaccharides) simply because the company concerned has the relevant intellectual property rights, or access to a bulk manufacturer of the strain in question. Probiotics
have multiple modes of action. For example, when immunoregulation is required, it is obviously essential to test a probiotic that has that particular property (Frei et al. 2015), rather than a strain that acts by blocking an ecological niche in the gut and reducing pathogen access, however useful this property might be in other contexts. Some probiotics based on the spores of environmental Bacillus species are also marketed for human and animal use, but we are not aware of any systematic attempt to identify other relevant environmental organisms (as pointed out in a.2 above), though such work is in progress.

b.6) Design of cities: The realization that much of the health benefit of green spaces is not attributable to exercise alone and is likely to be due to exposure to microbial biodiversity leads to the possibility that not all green spaces need to be large parks appropriate for team sports. Multiple, small, high quality green spaces, designed to harbour the optimal fauna, flora and accompanying microbiota, might provide a major health benefit. These could include roof gardens, vegetated walls, grass verges etc. In London, environmental engineers have created “edible bus stops”, which are small community gardens often located at bus stops where people congregate (http://www.theediblebusstop.org/). These projects are mostly driven by aesthetic considerations, whereas we now have medical reasons for supporting and amplifying such movements. This concept will again be facilitated when we have clear answers to question a.2) outlined above; what is the optimal flora to plant? How do we encourage the organisms that we want? It is worrying that use of water supplies contaminated with antibiotics on city parkland is changing the pattern of antibiotic resistance genes in the local soil, and so inevitably distorting the natural microbiota of these urban green spaces (Wang et al. 2014).

b.7) Interdisciplinary publications and media attention: The health world concentrates its reading, research and publications in medically-orientated journals while ecologists, environmental engineers, soil scientists and city planners disseminate their information in quite different ways. We need to encourage cross-disciplinary media attention and review publications.
6.3 Giving policy-makers an idea of tools available

An important consideration for policy-makers is that our knowledge of the microbiome is changing extremely rapidly, but the tools to perform these analyses and their limitations are also changing very rapidly. It is therefore a substantial risk that technologies or findings will be adopted before they are robust, leading to unstable conclusions, but at the same time a risk that powerful technologies of findings that could have large impact on people’s lives will not be deployed in a timely fashion. This section describes some of these considerations.

6.3.1 Assessment

There is need for interdisciplinary studies, where epidemiologists work closely with microbiologists studying the microbiota of the environment (plants and soil), transport systems, homes, offices and public buildings. We already know that microbial biodiversity in a child’s bedroom correlates with reduced risk of asthma and atopy (Ege et al. 2011). It will be important to extend such studies to other situations. For example, how does the microbial biodiversity of an underground train line (subway) that never runs above ground, compare with that of a line that is sometimes above ground (e.g. respectively, the Victoria and Piccadilly lines in London)? Are there detectable differences in the proportion of organisms from the natural environment? Are there detectable influences on the health of the passengers? Unfortunately transport companies and organisations are extremely unwilling to allow such investigations. Can we make the technology cheap enough and develop a robust enough database that individual families are willing and able to perform microbial tests of their homes, as they may already be doing when concerned about fungi? Can relevant governmental entities play an important role by facilitating rather than obstructing the study of public buildings and the effects of features of their microbiology on the health of their inhabitants or visitors?

Methods available

Skin microbiota can be sampled by lightly pressing a sterile swab on the skin. Faecal samples are also easy to collect. Questionnaires suitable for assessing health, disease prevalence and mental state are well validated. The progress in developing DNA sequencing and bioinformatic techniques has been rapid, and the microbial composition of any sample can be determined. Thus it is possible to couple disease epidemiology with biodiversity measurements. Similarly high-sensitivity C-reactive protein (CRP) assays are easy to perform and give a good measure of background inflammation levels. At present, most studies have focused on bacteria, although the viruses, fungi and microbial eukaryotes in general are also important components of the microbiota and are becoming increasingly feasible to assay. Similarly, most studies have focused on marker genes such as the 16S ribosomal RNA gene, which provide very efficient readouts of who is present in an environment, but assays such as shotgun metagenomics (which identifies all genes present in a given sample) or metabolomics (which identifies chemicals including those produced by microbial metabolism) are increasingly approachable and may provide a much richer picture. However, techniques that carry a risk of sequencing human DNA found in a given environment must be used with more caution in relation to human research ethics.

Appropriate environmental measurements to correlate with the human microbiota and health data include:

1) Assessment of airborne microbial biodiversity, perhaps including fungal and viral diversity. In general, outdoor air and indoor air differ substantially from each other (Kembel et al. 2012), and land use can also have a large effect on microbial sources in outdoor air (Bowers et al. 2011), with dog faeces being a substantial input in cities under some circumstances (Bowers et al. 2011).

2) Assessment of microbial biodiversity of homes and public places. Crowdsourcing can be an effective method for obtaining such samples, especially given the high public interest in such studies (Dunn et al. 2013).
a) Traditional versus microbiota-damaging building materials. Studies of the effects of building materials on environmental microbes, rather than on individual species of interest, are still very much in their infancy but are urgently needed.

b) Open windows versus air conditioning, and propagation of microbes from open windows through the rest of a building. Given increased automation of window shades and/or tinting for energy efficiency reasons, it may also be feasible to automate window opening at temperature-appropriate times to facilitate microbial exchange with the outdoors. It is also unknown whether exposure to beneficial microbes from the outdoors, or lack of ongoing exposure to largely human-derived microbes trapped indoors, explains more of the links between building microbes and human health.

c) City zones with and without green spaces. If green spaces have an effect, the effects of large parks versus small high quality green spaces, and the composition of trees, flowers and grass should also be assessed.

d) Dog parks, urban farms/petting zoos, and other sources of human–animal contact.

Compare farming methods:

a) Mono- versus poly-culture: Is the diversity of crops more or less important than which crop species are present? Does diversity within a species, e.g. growing multiple varieties of apples together rather than a monoculture, important?

b) Organic versus intensive chemical use. The effects of agricultural chemicals, including herbicides and pesticides, on leaf microbes or on soil microbes that are known to be immunomodulatory in humans are largely unknown.

c) Food in traditional farmers’ markets versus modern supermarkets. These foods tend to vary along several dimensions including production methods, chemical inputs, amount of washing and remaining soil, and duration of storage, all of which likely affect the microbes.

### 6.3.2 Ways forward

Several remedies are also available from a policy perspective. Most urgently needed are global policies to preserve the biodiversity of the natural environment. These would include major restrictions on antibiotic misuse both in human and agricultural settings and possibly including antibiotic remediation of wastewater; assessing the effects of agricultural and building practices on microbes, perhaps including microbial biodiversity reserves in our houses, schools and offices, and identifying and preserving reservoirs of human-associated microbes in hunter-gatherer communities in Africa, Pacific Islands and South America, and ancestral reservoirs of microbes in the Great Rift Valley that represent the microbial heritage with which our species coevolved. City planning and architectural designs that optimize biodiversity of microbial exposure in urban settings are also needed, including green spaces, opportunities for contact with microbes from wildlife and farm animals, and modified air conditioning strategies that spread beneficial microbial diversity rather than *Legionella*. Finally, a broad-scale education initiative, including citizen-science efforts parallel to those employed by American Gut (where members of the public can both act as subjects and participate in an open data analysis effort) and MOOCs (massive open online courses), as well as more traditional classroom and online resources aimed at children, educators, physicians, politicians, the press, advocacy organizations, and members of the general public will be needed both to communicate the results obtained to date in this exciting field and to lay the groundwork for appropriate assimilation and deployment of new findings in this rapidly evolving field.
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Chapter 8


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