



## Seeing the wood for the trees: A new way to view the human intestinal microbiome and its connection with non-communicable disease

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### ABSTRACT

Our paper briefly reviews the connection of the intestinal microbiome to the rise in non-communicable conditions related to atopic disease, obesity and mental health. We consider that the microbiome is best treated as if it were a single entity and have borrowed the terms semiochemical, allomone and kairomone (5) to describe interspecies relationship between the microbiome and ourselves (Fig. 1). We use the term dysbiosis to describe the breakdown of these relationships leading to disease (Fig. 2). As a result of this analysis we tentatively suggest that components of the microbiome assess microbial antigens in our food and pass this information back to our immune system via as yet undescribed chemical messengers: kairomones. We call these hypothetical microbial agents Sentinel Cells. Our suggestion is that atopic disease arises partly as a result of consuming processed food that has insufficient antigens to activate this kairomone feedback mechanism, which atrophies as a result. We note that this is potentially similar to the Old Friends concept of Rook and his co-workers (16). We suggest that obesity is a consequence of dysbiosis-induced waning of the output of allomone-like psychotropic compounds (including the known microbial metabolites dopamine and serotonin) leading to the weakening of the gut-brain axis and a negative effect on mental health. Although dysbiosis can occur in other ways, including antibiotic use and sterile caesarian section, we believe that all these problems can be overcome to provide a future free of these non-communicable diseases.

### Introduction: The changing nature of disease

Life, liberty, and the pursuit of happiness, such are the dreams of men and women [1]. And the pursuit of health is not far behind, coming in at an official 6.5 trillion US dollars in 2012 – about a half of that in the USA itself [2]. Throughout most of history, it is probably fair to say that these endeavours were cut short mostly by infectious disease. Reliable information comes from the richer countries in the western hemisphere when, during the late 1800s and early 1900s, it seems that pneumonia, tuberculosis and enteric diseases such as cholera and typhoid wreaked the most havoc [3]. The progress of western medicine over the next century and a half is neatly encapsulated by a New England Journal of Medicine perspective published in 2012 [4]. In particular, the dramatic shift of deaths from infectious disease to non-infectious diseases such as cancer and atherosclerotic heart disease is emphasised. The rise of suicide as a cause of death was recorded but not commented upon, though it was comparable to pneumonia and

influenza in 2010 (12.2 v. 16.2 deaths per 100,000). The authors' note that a rise in obesity, predicted in 1912, has indeed come to pass while the previously steady rise in average life expectancy has stalled and was expected to reverse. The authors of the present work note that, while microbes are mentioned within this article, they are always considered to be malignant. Even at the late date of this review, there is no mention of the possibility that microbes may actually be helpful.

Indeed, the prevailing view of the 20th century seems to be that all disease was physical, while mental conditions were divided into those caused by “real” physical effects, treated by psychiatry, and behavioural conditions, relegated to psychology. Similarly, all microbes were treated as potential pathogens to be eliminated, or at least strictly monitored and kept under control. It remains to be seen how quickly these attitudes will change during the 21st century.

In this article, we use the word microbiota to indicate actual microbial species whereas the word microbiome is used to refer to sum total of genes relating to their collective beneficial properties. We

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consider that the microbiome is more important than individual microbes as useful genes may be shared between widely different species. We borrow interspecies communication concepts from plant/insect relationships (semiochemical, allomone, kairomone) [5], to describe compounds emitted by the microbiome so as to modify functions in the human host. We use the word dysbiosis [6] to describe the partial failure of either or both of these systems.

It is worth noting that, as far back as 1991, Margulis coined the term holobiont to describe a host and its microbiota as a single evolutionary unit [7]. Modern ideas of symbiogenesis have been reviewed more recently in the context of an effort to reformulate evolutionary theories applicable to multi-cellular organisms [8].

### Understanding the role of microbes: Denis Burkitt to Graham A.W. Rook

Burkitt was born in Enniskillen, Northern Ireland, in 1911 and trained as a surgeon [9]. After being based in Africa during the Second World War he returned and used his skills around the continent. He carefully noted the diet, lifestyle and disease of the inhabitants of the various regions of Africa and compared them with their western equivalents. He tracked the intake of dietary fibre and found a positive correlation with faecal volume – at least a three-fold increase on western norms – and a negative correlation with what he called western diseases, the latter being from heart disease to haemorrhoids [10]. In contrast to his theory about vegetable fibre, he failed to note that the Maasai, with their cattle-based economy, ate very little vegetable fibre and yet maintained excellent health [11,12]. They were not exceptional: steppe dwellers and peoples of the far north got on perfectly well without a steady supply of fresh fruit and vegetables. It seems that fibre is not the answer to the epidemic of modern non-communicable disease.

By the late 20th century David Strachan noted the rapid increase in atopic diseases such as asthma and hayfever but he also observed that an early childhood spent in less hygienic surroundings was protective. His suggestion was that early microbial challenges allow the immune system to practise against microbes of lower pathogenicity and that such early training prevented inappropriate atopic responses [13]. Subsequent development led to the idea that modern society is too clean, if not for the development of disease in adults [14] then for early exposure to microbes in infancy [15]. Though not quite correct, Strachan's hygiene hypothesis was the first to recognise the concept that otherwise malignant disease-causing microbes could actually have a role in preventing disease [13].

Graham Rook and his team made the suggestion that only certain as yet unknown species are helpful in modulating an immune response. The expression used here is "Old Friends". Studies based around this concept have demonstrated the close connection between the microbiota, immunoregulation and mental health and their relationship to regulatory T cells and inflammation [16]. A large number of potential such old friends have so far been suggested. It is worth noting that attention is now shifting to the microbiota-gut-brain axis in obesity [17] and to the early establishment of the microbiome in the newborn infant [18,19]. The association with inflammation and cancer has been noted [20].

### The nature of the microbiome: The importance of diversity

As the connection between our microbiota and our health has slowly been uncovered there has been a parallel advance in the understanding of the overall relationship between animals and microorganisms, recently comprehensively reviewed in book form [21]. Typical microbial communities are constantly in a state of flux and can change between mutualistic and pathogenic states depending on challenges in the environment and the status of the host. Although rare, microbial species do disappear from time to time and that loss of

diversity is associated with decreased health, at least by correlation with metabolic markers [22]. There is a clear drop in diversity between people following a modern, western-derived lifestyle and those from the periphery of the modern world, reminiscent of the findings of Burkitt [10]. A striking example from ancient times is provided by Tito et al., who studied coprolites from a variety of sites around the world. Although their sample was small (the best result was from northern Mexico, dated to about 550 CE) their signal was clear enough so as to be able to identify a breast-fed child, for example. Their conclusion was that the ancient microbiome most closely resembled that of modern peoples peripheral to the western-style modern world [23]. Of course, in common with many observational human studies, it is hard to distinguish between correlation and causation, but we believe that the balance of probability is that degradation of the microbiome is primarily associated with non-communicable disease.

In this context, a study of coronary atherosclerosis in a relatively isolated Amazonian Bolivian population called the Tsimane has recently been reported [24]. These people have a mixed hunter-gatherer and farming lifestyle with high levels of activity and low levels of cigarette use. They have a high level of infectious inflammatory burden but the lowest reported levels of coronary artery disease of any population recorded to date. The investigators had established good relations with the Tsimane since 2002 and expanded their work from 2011, while the coronary study itself was carried out between 2014 and 2015. Medical assistance was provided but unfortunately there was no data reported on either their microbiome or recent antibiotic use.

### The function of the microbiome

The first hint that microbes were not just passive onlookers came when it became clear that they provided us with adequate levels of some of the B-vitamins [25]. We now know that the microbes in our intestine turn otherwise indigestible fibre into the metabolically useful short chain fatty acids acetate, propionate and butyrate, and that these help to enable the immune system [26]. In addition, microbes produce a variety of psychoactive substances such as dopamine and serotonin, which seem to strengthen the gut-brain axis, although the exact details can be hard to ascertain in humans [27].

As microbial communities generally consist of hundreds of different species drawn from all the microbial domains it seems to us to be impractical to gain much understanding from individual interactions, either within the communities themselves or between them and their host. The microbiome is best considered as a whole [7,8].

### The mutualistic microbiome: Dysbiosis (Figs. 1 and 2)

We suggest that the chemicals released by the microbiome act as semiochemicals [5], representing the mutualistic interaction of human organs with various microbial constituents. In this way chemicals that appear to help us to calibrate our immune system may be considered to be kairomones. By contrast, chemicals that appear to take nutrition from us, within the context of a mutualistic interaction, can be described as allomones. We suggest that the psychoactive components dopamine and serotonin act in the latter way to strengthen the gut-brain axis and improve gut motility. The microbiome thereby ensures that it receives adequate nutrition: hence the high faecal volumes noted by Burkitt (Fig. 1) [10]. The failure of these systems (dysbiosis) leads to the observed increase in body fat and a fall in the average volume of faeces (Fig. 2). In this interpretation, the lack of kairomones leads to atopic disease while the lack of allomones leads to problems with mental health and fat deposition: visceral and arterial fat deposits lead on to obesity, heart disease and diabetes.

### Dysbiosis: Its causes and treatment:

1. Anti-infectives: The antibiotic age could be said to have begun when

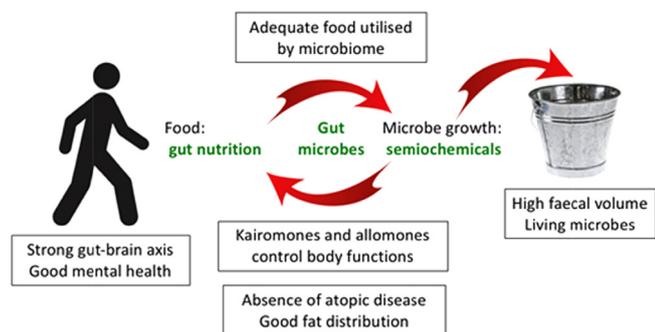


Fig. 1. Showing microbiome receiving adequate nutrition and high faecal volumes.

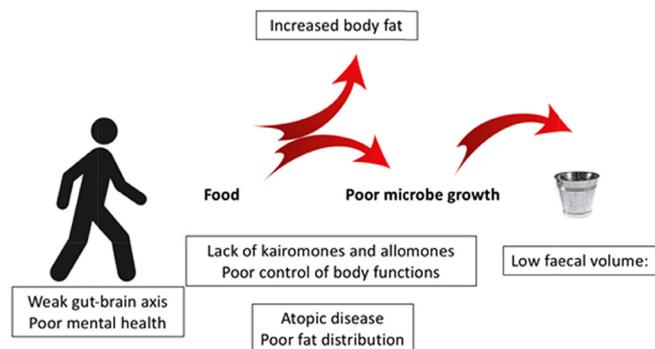


Fig. 2. Indicating dysbiosis results in increased body fat and a fall in the average volume of faeces.

Paul Ehrlich developed the notion of a magic bullet that would kill microbial cells but leave our own cells alone [28]. The first chemical agent, Salvarsan, was commercially introduced in 1910 [29]. As Salvarsan is an arsenical compound it seems probable that it drastically affected the microbiome. Throughout history well-off people had been attempting to beautify themselves with toxic heavy metals, which, even if it did not kill them, would most likely hamper their microbiome [30]. In contrast to the Tsimane, the mummies of ancient Egyptian have atherosclerotic deposits in their arteries [31], which we ascribe to their practice of using powdered galena around their eyes.

Antibiotics have been used as “growth promoters” to fatten farm animals, starting almost as soon as such agents became available [32]. The fact that the mechanism of this growth promotion was not understood did not hamper its use. Nor is it specific to mammals, as chicken farming benefits from the technique, suggesting a deeper evolutionary origin [21]. Unfortunately no one drew the connection between the growth-promoting effects of antibiotics in animals and their therapeutic use in humans. In the light of this connection, it may be that the current problems of obesity could have been anticipated.

Since the discovery and development of penicillin chemical antibiotics have been used to treat many complaints without prior confirmation that they are caused by susceptible bacteria and without any consideration of their effect on the microbiome [33]. *Clostridium difficile* is recognised as a pathogenic bacterium that proliferates when the native microbiome is severely disabled by sequential antibiotics. Fetal microbiota transplantation was not a medically recognized technique until doctors heard about it from their patients [34]. Instead of trying to add a single (patentable) probiotic, the whole microbiome is transferred in one go. As a treatment for people who are severely affected by this disease it is remarkably successful and well tolerated [35]. By contrast, commercial probiotics, though extensively studied, have little benefit to show for it. They can reduce the risk of diarrhoea induced by

antibiotics, including from the necrotising enterocolitis seen in premature infants [36]. Their greatest value probably lies in offsetting the problems noted in infants delivered by sterile caesarian section, especially in premature babies and in combination with prebiotics [37].

2. Caesarian section: In essence, the recent uptake of caesarian section can best be described as an epidemic [38,39]. When carried out under rigorously sterile conditions, this is the most direct way to lose microbial species, some of which could be vital. It is difficult to be completely sterile, however, and there are a number of ways in which contamination by helpful microbes can be magnified, especially with the agents in human milk [40,41]. Interestingly a recent study reported no discernable differences in community structure or function between infants delivered vaginally or by caesarean section over the first 6 weeks of life [19], perhaps suggesting that the seeds of future health problems are laid down even earlier than this.
3. Diet: It has been shown that there are profound effects of a western-style diet on obesogenic gut microbiota and that some effects may be reversed by changing the immune cell profile [42], however there was no indication that any components of the microbiota were actually lost in this process. In an attempt to replicate the long-term effects of a poor diet, a community of mice was fed on a low nutrient diet over several generations. Their microbiome became less diverse with each new generation [43]. It is more likely that dietary problems are associated with existing dysbiosis as such people are likely to have compromised gut motility, if not outright coeliac disease. Vegetable fibre presumably helps as its local irritant effect stimulates the gut; indeed this stimulation gives the impression of being a disease in its own right. People can be recommended gluten-free or FODMAP: diets low in fermentable oligo- di- and mono- saccharides and polyols [44,45]. We believe that this sensitivity is actually a sign of established dysbiosis.

## Recommendations

In the light of the above analysis, it is necessary for Western society to learn to tolerate non-pathogenic microbes. This does not necessarily involve significant disruption. Change is needed in three areas:

1. Antibiotics: A search was undertaken for increasingly specific antibiotics that avoid the side effect of microbiome depletion. A model of the distal colon was used to show that the antibiotic thuricin CD was effective against *Clostridium difficile* without any discernable effect on the resident microbes [46]. We anticipate that a similar model could be used more widely to assess the selectivity of novel antibiotics.
- Colostrum was exploited before the antibiotic age and should be revisited. Immunoglobulins specific to many human pathogens have been found in early mammalian milk expression, echoing their role in the establishment of the microbiome [47]. Other anti-infective agents preceding the advent of small molecule antibiotics are bacteriophage viruses. The opportunities and problems of this field have recently been reviewed [48]. They have been shown to spread bacterial genes, such as those for antibiotic resistance, by plasmid liberation upon lysis [49,50]. This mechanism could result in the rapid spread of valuable genes between different classes of microbes within the diverse microbiome.
2. Caesarian section: A recent innovation currently gaining ground is a procedure variously known as vaginal inoculation, vaginal seeding or microbirthing. Basically this consists of a swab designed to deliver faecal and/or vaginal microbes from the vicinity of the birth canal to the head of the baby, thus simulating natural birth, unless there is a pressing medical reason not to do so. Naturally this goes against the training of medical professionals who urge that this should not be undertaken without prior robust research findings

[51]. Presumably they feel that this procedure is sufficiently different from natural birth to merit such studies, however we urge that they should not neglect the potential protective effect of human breast milk and colostrum [40,41]. Such treatment cannot improve the microbiome by itself; only stop it from being further degraded. As future disease seems to depend on the state of the microbiome in infancy [18,19], then the child may eventually prove to be healthier than the mother if her own microbes had grown more diverse since her birth.

3. Diet: As the aim is to sustain a wide variety of microbes, logic suggests that our diet should be as diverse as possible, containing fibre and other substances that our own bodies cannot easily absorb. As the foregoing discussion makes clear, however, although low diversity modern diets have negative effects on our microbiome and on our health, it is not clear if these are a cause of dysbiosis in the first place.

We suggest that there is something particularly bad in the act of processing food – the removal of microbial antigens. We suggest that a function of our microbiome is to identify microbial antigens and pass this information back to our immune cells via kairomones. The continual absorption of antigen-free processed food allows this portion of our extended immune system to atrophy and thus lead on to dysbiosis. We tentatively name these microbes “Sentinel Cells” and expect that they will be discovered in the future. We suggest that these cells will correspond to the Old Friends being uncovered by Rook and co-workers [16]. This concept is a variant of David Strachan’s hygiene hypothesis in that the absence of microbial fragments makes processed food “too clean”.

## Conclusions

1. We have tried to summarise current literature in that the three branches of modern non-communicable disease (atopic, obesity and problems of the gut-brain axis) can be understood in terms of the partial degradation of the microbiome.
2. We argue that the microbiome can be usefully understood in terms of semiochemical-like interactions between microbes and our body while treating it as a single entity. These interactions come in two parts, one in which the microbiome helps us to calibrate our immune systems via as yet to be discovered kairomones and another in which psychoactive microbial metabolites act as allomones to strengthen our gut-brain axis.
3. We make a tentative suggestion that a component of the microbiome acts as an extension of our immune system by recognising microbial antigens and passing the information back via chemical kairomone signals. We suggest that these “Sentinel Cells” will eventually be found to correspond to the “Old Friends” of Rook and co-workers.

## Author declaration

The authors declare no conflict of interest.

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