Review Article

The Microbiome and the Entropy Paradox: An Evolutionary Perspective

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Abstract

The mucosal tissue microbiota, measured in millions, cause inflammation which contributes to the pathogenesis of a wide range of disease including neurodegeneration, atherosclerosis, cancer and psychiatric conditions. A broad range of pathological factors, both psychosocial and physical, interact with, amplify and otherwise modify the inflammatory process and thereby contribute to disease in general. In order to diagnose mucosal tissue dysbiosis and assess its severity in individual cases, it will be necessary to measure markers of inflammation and assess bacterial carriage of specific pathogens in faeces, using quantitative polymerase chain reaction (qPCR). Current methods of analysis of the gut microbiome, using 16S rRNA amplicon sequencing and DNA metagenomics, reveal the composition of the trillions of bacteria in the colonic lumen but not the millions in the wall. The relationship between the mucosal luminal microbiota, the mucosal tissue microbiota and the host; its evolutionary origin and importance in disease is analysed, in this paper, using concepts from information theory. The analysis explains the entropy paradox (increased entropy is usually a marker of disease but in the case of the faecal microbiome it is an indicator of health) and the affluence paradox (diseases which are a consequence of affluence disproportionately affect the least affluent members of the population). An increasingly sterile diet in affluent countries is leading to a sub-optimal mucosal luminal microbiota and as a consequence increased mucosal tissue microbiota induced inflammation. A rising tide of illness has followed and we need to give urgent attention to our diet. Increased consumption of milk and yoghurt will provide the diverse but safe supply of bacteria that we need.

Introduction

The possible role of the gut microflora in the pathogenesis of human disease has a long history. In the early years of the twentieth century the Nobel laureate, Metchnikoff, held the opinion that bacterial fermentation in the colon produced toxins which were absorbed systemically and accelerated aging [1]. He studied centenarians in Southern and Northern Europe, noting that there were more in the South than the North, even though the North was more prosperous. The Bulgarians, in particular, who ate a lot of yoghurt, seemed to live to a ripe old age. Metchnikoff suggested that yoghurt suppressed bacterial fermentation in the colon and thereby enhanced health in old age. Metchnikoff popularised yoghurt as a "health food" and that has lived on, even though we now know that yoghurt does not suppress bacterial fermentation in the colon. Indeed, many of the lactose fermenting bacteria in yoghurt are reduced by stomach acid and those that reach the colon have only a small effect on the overall microbial composition [2].

The concept that bacterial toxins produced in the colon have a role in disease gradually abated as the twentieth century progressed, but never disappeared. It lives on in the view that bacterial toxins could explain the increased incidence of carcinoma of the colon compared with carcinoma of the small intestine. The small intestine has more mitoses than the colon but fewer toxins.

The twentieth century saw the gradual conquest of specific viral and bacterial infections by a combination of immunisation and antibiotics. The chronic diseases that remained, such as atherosclerosis and carcinoma were classed as "non communicable", and causation was sought elsewhere. But interest in the microflora never died and received new impetus with the discovery of *Helicobacter pylori* [3]. This organism had evolved to occupy a niche between gastric mucus and the gastric epithelial cells. It causes gastritis and peptic ulceration. Its discovery revolutionised upper gastro-intestinal surgery. A hitherto "non-communicable disease" was directly caused by bacterial infection. But there was more to follow. *H. pylori* carriage was associated with increased risk of gastric adenocarcinoma, gastric lymphoma and ischaemic heart disease [3-6]. The usual argument that association does not mean causation followed, but it has gradually been accepted that *H. pylori* is part of the complex causative pathways leading to the conditions with which it is associated. The mechanisms are still in dispute but inflammation with secretion of pro-inflammatory cytokines is a recognised risk factor for the development of atherosclerosis [7].

The twenty first century has seen the development of new techniques for analysing bacterial DNA and has led to an explosion of interest in the gut microbiome and the gut microbiota. The main methods are 16s rRNA amplicon sequencing and DNA metagenomics [8]. And with the new methods of sequencing have come new methods of statistical analysis of the vast amount of data produced. There are hundreds of bacterial species in faeces, perhaps over one thousand strains, and each has between 3000 and 5000 genes. The genetic information of the gut microbiome greatly exceeds that of the host. The enormous information processing complexity of the microbiome presents both possible benefits and challenges to the host. It appears highly likely that this complex system is vitally important in both health and disease.

In this article, we analyse this complex relationship between bacteria and host in evolutionary terms and the potential to benefit health and cause disease in information terms. This approach is useful in showing clearly how a simpler analysis of the microbiota is possible and could yield more direct clinical benefit.

Mucosal Luminal Microbiota

There are trillions of bacteria on the epithelial surfaces of the body [2,9]. These bacteria are present on the skin surface, but also in the lumina of the myriad internal ducts which are lined by epithelial cells. These bacteria are outside the body; their molecular secretions cannot passively diffuse into the body because tight junctions are present between epithelial cells. The tight junctions are water tight and therefore any bacterial secretions that enter the body must pass through the epithelial cells [10].

The colonic lumen is just one part of this vast array of internal ducts. But with 10^{11} bacteria per gm of faeces it contains a very large number of bacteria and the colonic microbiota is a major focus of research into the gut microbiome [2]. In common parlance the gut microbiome, the colonic microbiome and the faecal microbiome are synonymous. But the gut (gastro-intestinal tract) extends from the lips to the anus and involves the oral cavity, pharynx, oesophagus, stomach and small intestine as well as the colon and rectum [10]. Furthermore, secretions from the upper and lower respiratory tracts enter the oesophagus and pass through the stomach on the way to the small intestine. There are also secretions from the ducts of salivary glands, the pancreas and the biliary system. All these epithelial surfaces have a resident microbiota and therefore the colonic lumen contains bacteria from multiple different sites, as well as its own resident microbiota.

There are also bacteria in the ducts of the sebaceous, eccrine and apocrine glands of the skin. Bacteria are present in the ducts of the breast, and in the ducts of the genitourinary-system in males and females. These sites do not empty directly into the colon. However, they are part of the mucosal luminal microbiota, and in so far as the luminal microbiota is important in disease, they need to be considered and will form part of discussion in this paper.

The mucosal luminal microbiota has co-evolved with our human ancestors and the bacteria derive their energy from epithelial secretions. Specific mucosal sites have a specific microbial flora that has evolved to utilise epithelial secretions and to interact with the epithelial cells in order to maintain their integrity. The upper and lower respiratory tract and the colon produce mucus which supplies energy to their resident flora. The keratinised stratified squamous epithelium of the skin supplies desquamated keratin to surface bacteria. The sebaceous glands produce oily sebum. The non-keratinised stratified squamous epithelium of the oral cavity, pharynx, oesophagus and vagina has glycogen in the surface cells which feeds lactose fermenting bacteria. The glycogen is converted to lactic acid and this suppresses the growth of other bacteria.

Bacteria that have evolved to derive their energy from epithelial secretions and occupy a specific mucosal niche are present in large numbers. They are commensals. They out-compete pathogens and thereby protect the host against infection. They also have a role in maintaining epithelial integrity, some supply fuel to epithelial cells, some produce essential vitamins.

There are other bacteria that have evolved to occupy a niche towards the centre of the colonic lumen. They derive their

energy from bacterial secretions and in turn feed others. Some of these bacteria are potential pathogens but they mostly exist as commensals in the lumen. They are a substantial part of the faecal microbiota.

Mucosal Tissue Microbiota

There are a small number of bacteria that have evolved to occupy a niche within the body, growing in tissues just beneath the epithelial surface [11-13]. They have genetic mechanisms that enable them to survive in tissue and avoid immune elimination. These highly specialised bacteria derive their energy from the blood. They damage host cells and cause local low grade chronic inflammation. A key task of the mucosal luminal microbiota is to prevent or reduce the establishment of a tissue microbiota by out competing these bacteria in the lumen and inhibiting their growth.

The periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum* are examples of bacteria that form a tissue microbiota [14-15]. They are present in the lumen in low numbers but also invade the periodontal tissues and cause low grade periodontal inflammation. This damages the cementum around teeth and causes them to loosen. Periodontitis is the commonest cause of tooth loss. The bacteria have evolved a number of genetic mechanisms to evade immune elimination. They are phagocytosed by macrophages but resist intracellular killing mechanisms. They also citrullinate proteins which impairs the action of antibodies and complement.

Staphylococcus aureus is another organism which has evolved to survive and grow within tissues [11]. All strains secrete alpha haemolysin, a perforin. And some strains secrete pyrogenic toxins which are superantigens. These pyrogenic toxins (Toxic Shock Syndrome Toxin (TSST) and enterotoxins A, B, C and D) cause non-specific T cell clonal proliferation leading to a non-directed inflammatory response mediated by the secretion of pro-inflammatory cytokines. In this way *S. aureus* has evolved the ability to avoid immune mediated elimination. An uneasy truce develops between the organism and the immune system. The latter must prevent growth and expansion of the pathogenic bacteria but avoid provoking a cytokine storm.

The majority of adults have measurable IgG antibodies to alpha haemolysin and the pyrogenic toxins [16-18]. This indicates that *S. aureus* carriage is common and probably occurs in most people throughout life. It is established early in life and the immune system is regularly exposed to the various pyrogenic toxins. These toxins are secreted at and above normal body temperature and they will not passively diffuse from the mucosal lumina. Further evidence that the bacteria are within tissues.

These pathogenic bacteria grow within the tissues but close to the mucosal surface. They spread by being shed into the lumen and then make their way to the external world by expectoration from the respiratory tract or carriage through the stomach and to the faeces. Thus, the measurement of these bacteria in faeces is a good way of assessing the total body load. *Staphylococcus aureus* carriage, for instance, increases following viral respiratory infection and carriage rates are of the order of 10^6 per gm of faeces [19]. But this compares with 10^11 commensal bacteria per gm of faeces. It means that current methods of assessment of the faecal microbiome will miss the key pathogens that cause disease.

The Blood Microbiota

The tissues of our body are not sterile. In addition to the tissue microbiota there are bacteria circulating in the blood. The best evidence for this comes from the study of the bacterial composition of milk [20]. In all mammals, milk contains bacteria that are transported from the mucosal luminal microbiota through the blood and lymphatics and secreted into breast epithelial cells. Milk contains lactose fermenting bacteria in moderate dose and bacterial pathogens in small dose. Milk has many functions, evolved over millions of years, one of which is to create an optimal microbial flora in the infant.

It is of considerable interest that milk contains both commensal organisms and pathogens. The lactose fermenters populate the mucosal lumina of the gut from the mouth to the anus and thereby protect against invasion by pathogens. But it is important that the infant meets a wide range of bacterial pathogens in low dose in the early months of life in order to build up immunity [21].

The concept advanced in this paper is that bacteria have evolved to occupy specific sites on the mucosal surface. To ensure that the specific bacteria in milk get to their specific site there must be some system for selection and transport through the blood to the designated site. For instance, the composition of saliva is important in preventing infection on mucosal surfaces. It cannot be left to chance which bacteria colonise the salivary ducts. There needs to be a transport system and it needs to start soon after birth and continue throughout life.

There also needs to be a system to transport pathogens around the body, again in low dose, so that local immunity to each organism can be established. The optimal tissue microbiota is not sterility, it is all pathogens in very low numbers at multiple sites, established early in life and maintained throughout life.

Thus, blood and tissues contain bacteria in transit between mucosal surfaces. The majority are probably commensals, but a few will be pathogens.

Mucosal Tissue Dysbiosis

The concept of disease that follows from this analysis is that

the mucosal tissue microbiota causes low grade diffuse mucosal inflammation [9,12,13,22-25]. This leads to loss of the tight junctions between epithelial cells and allows the passive diffusion of bacterial toxins from the mucosal luminal microbiota. In turn this causes systemic inflammation and can damage endothelial cells leading to atherosclerosis. The spread of pathogens from the mucosal tissue microbiota through the bloodstream can also lead to foci of inflammation at non-mucosal sites such as the brain. This contributes to neuroinflammation [13,23]. The inflammation is orchestrated by cytokines produced by lymphocytes and macrophages, these can also cause systemic damage. But they also interfere with normal physiological states, such as anxiety and depression, which are orchestrated by the same cytokines but in different relative dose and pattern. In this way inflammation can interfere with the normal physiological states of sleep, emotions, blood pressure, the complex events of pregnancy and childbirth etc. [22]. In responding to bacteria there is always the risk of the development of autoimmune processes, which seem to occur more commonly in women in the middle years of life [24]. Mucosal inflammation, by disrupting the orderly progression of the stem cell hierarchy, can also increase the risk of cancer [25].

Thus, consideration of the interaction between pathogens, which have evolved to occupy a niche within the tissues, and potential pathogens, which have evolved to occupy niches within the ductal lumina of the body can explain a broad range of disease. Furthermore, because inflammation interacts with and interferes with all physiological states, mucosal dysbiosis will interact with psychosocial causes of disease thereby creating the biopsychosocial model of disease causation.

This analysis provides support for the considerable enthusiasm and optimism of the microbiome community in their efforts to understand disease. But it also provides a possible explanation for why the analyses to date of the microbiome in disease have been disappointing. Analysing the mucosal luminal microbiota is not sufficient. We must also make some quantitative assessment of the mucosal tissue microbiota and the degree of systemic inflammation.

The Shannon index

Analysis of faecal bacterial DNA reveals a number of phyla, a large number of genera and a very large number of species and strains. In comparing a group of patients with a specific disease and a group of controls who lack the disease there is always considerable diversity, both within and between groups. But one observation is that more diversity seems to be a feature of the controls and less diversity is a marker of disease. This has led to the use of the Shannon index as a marker of diversity and an indicator of health [26-30].

This is the age of information [31]. We are surrounded by devices which transmit and store information. It was Claude Shannon who devised a way to measure information. He measured it as the reduction of uncertainty on a log scale [32].

An observer is presented with 32 boxes and told that there is a red ball in one of the boxes. Two raised to the power 5 equals 32, and log (to base 2) of 32 equals 5. Thus, on the Shannon scale there are 5 bits of uncertainty about the position of the red ball. With respect to the specific task of determining the ball's position the observer has 0 bits of information. The observer is then told that the red ball is in one of the first 16 boxes. The amount of uncertainty is now 4 bits, and the observer has gained one bit of information. If the observer now looks into the boxes and sees the red ball in say box 11, then the observer has 5 bits of information and there are 0 bits of uncertainty.

In the above example each possible position for the red ball was equally likely. But if the **n** components are not equally likely then the information (**H**) equation is:

$$H(n) = -\sum p(i)\ log\ p(i)$$

The concepts of information, uncertainty and entropy are related. The equation for entropy is:

$$S = k\ log\ W$$

S is entropy, k is a constant (Boltzmann's constant) and W is the number of ways components in a system are arranged. S is a maximum when the distribution of the components is completely random. Entropy in a physical system increases with time.

Entropy and uncertainty are measures of disorder or randomness in a physical system. A reduction of entropy and uncertainty creates order and information. Thus, information is negative entropy (note the minus sign in the information equation above). If a beautiful vase on a table drops to the floor and breaks into pieces it loses order, it loses beauty, its entropy increases and disorder increases. Its energy is conserved but changes form. Evolution is a process in which order, information and even beauty increase with time. Systems become more complex. Information is stored in DNA and complex systems are required to repair DNA molecules when they are copied. The brain, our immune system, in fact the whole of physiology can be analysed in terms of information processing systems [33-37] The general principles are:

1. All information processing systems have a finite capacity.

2. Information is processed in noise and there is always a finite chance of error.

3. The components of an information processing system decay at random with time and the error rate will rise.

4. All complex robust information processing systems need a high level of redundancy to reduce the error rate and to slow down the rate of decay.

There is a very large amount of information stored in the microbiome. This has the potential to greatly enhance health but also presents an enormous challenge to health. Specific areas of the mucosal luminal microbiota have evolved to interact with each other and with the mucosal epithelial cells. This focal microbiota must be highly ordered, with a minimum of randomness and therefore a low level of entropy. This applies to every mucosal luminal focus ay every mucosal site. The composition of each niche will be subtly different and different epithelia will have quite markedly different microbiota. Since many of the sites shed into lumina which eventually empty into the colon, the lumen of the colon will contain a diverse mix of bacteria. Thus, while the mucosa associated microbiota at each specific site will have low entropy, the lumen of the colon will contain a random mix of bacteria from numerous sites and thus will have high entropy. If specific sites lack an optimal microbiota this could lead to reduced diversity of the faecal flora and be associated with poor health.

Thus, although in general terms a low Shannon index, low entropy, is associated with health, in the specific context of the gut microbiome a low index is associated with disease. It indicates a deficit at some specific epithelial site. In contrast the microbiome at a specific site, such as the vagina, would show low diversity in a healthy state.

This is the entropy paradox. In general, low entropy is associated with health but in the specific case of the faecal microbiome low entropy indicates disease. This also applies to the microbiome of colonic mucosal tissue biopsies. These do contain the microbiota close to the mucosal surface but there are still many layers of bacteria and they have considerable diversity. Furthermore, a mucosal tissue biopsy will not reveal the mucosal tissue microbiome as there are close to 100,000 bacteria on the mucosal surface for every bacterium in the wall.

The Shannon index is used extensively in gut microbiome research, but its use is limited. It is the equivalent of placing a dozen vases on a table, smashing them all to floor, mixing the multiple pieces into an enormous mess and then trying to work out if the original vases were leaky or not. We must do better.

Disease Causation

In recent years we have come to realise, that although there are literally thousands of different distinct diseases documented in medical textbooks and research publications, there are relatively few pathological processes that cause disease. Biopsychosocial factors interact in complex causative pathways with these pathological processes and a number of factors are common to most disease. The factors that cause disease are much more common than the diseases they cause.

Smoking increases the risk of most disease. Pollution increases the risk of most causes of death [38]. Low levels of vitamin D are associated with many chronic conditions [39]. Periodontitis is also a condition which is associated with many degenerative, so called "non communicable" diseases [40]. Inflammation is a factor in the metabolic syndrome (obesity, ischaemic heart disease, hypertension, type 2 diabetes mellitus and depression) cancer and neurodegeneration [41]. Dietary fibre protects against a wide range of cancers, not just colorectal cancer [42].

Smoking causes chronic inflammation. Pollution also causes inflammation. Vitamin D restricts the entry of pathogenic bacteria into tissues and therefore deficiency will lead to mucosal tissue dysbiosis induced inflammation. Periodontitis is a clinical marker of mucosal tissue dysbiosis. And dietary fibre augments the mucosal luminal microbiome and thereby reduces inflammation.

There are a number of lifestyle factors that are negatively correlated with depression and anxiety. These are a good night's sleep, regular physical exercise, a reduction in time spent sedentary, moderate alcohol consumption, social contact, a healthy diet and never smoked. The same factors are negatively correlated with physical disease including neurodegeneration, atherosclerosis and cancer. These factors are also negatively correlated with inflammation, as measured by C reactive protein [43].

The concept that emerges is that all pathogenic factors, both physical and psychosocial, interact with the mucosal tissue microbiota induced inflammatory response. This response is complex and only partly understood. But there are multiple different bacteria at multiple different sites causing cell damage in multiple different ways. The result is that the mucosal tissue microbiota is capable of causing a wide range of disease. Pathogenic factors, by modifying, and often amplifying inflammation can then raise the risk of most disease.

Changing Patterns of Disease

The age standardised mortality rate has been falling in the affluent western World for the last 100 years [44]. This is a good measure of the overall health of a population and has led to some complacency. At first sight it would appear that our modern hygienic lifestyle, together with modern medical care is fostering a healthy population. But the current age standardised mortality rate reflects the health of those born between 1920 and 1950. It is not a good measure of the health of the population born since 1960, and there is disturbing evidence concerning the overall health of successive cohorts born since 1960.

Asthma, eczema and hay fever were uncommon in children prior to 1960 but are now very common [45]. There has been a marked increase in the prevalence of type 1 diabetes mellitus in children [46]. Depression and anxiety have increased in adolescents and young adults in the last 20 years [47]. The disorders anorexia

nervosa, irritable bowel syndrome, chronic fatigue syndrome and anxiety neurosis are increasing [48-50]. The sperm count is falling [51-53]. Autoimmune diseases in women in the middle years are on the increase [54]. There is even an increase in the incidence of cancer in the under 50s [55]. There has also been a marked increase in obesity and type 2 diabetes mellitus, which is well documented. Autism has also increased, but some of the increase is due to changes in diagnostic criteria.

There appears to be increased inflammation in people in the UK born since the 1960s and it seems to be increasing in successive cohorts.

Mice and Men

Experimental mice are kept in clean conditions. Their food is sterilised and the air intake is filtered. But the result is that they are less healthy. If yoghurt is added to the diet or lactobacilli are added to drinking water their health improves [56,57]. They groom more, their fur shines, even the testes of the male mice become larger. Experimental wounds heal more quickly. The production of oxytocin is increased. The mice are healthier and probably happier. Lactose fermenting bacteria from milk optimise the mucosal luminal microbiota and reduce the production of pro-inflammatory cytokines.

Mice tend to eat the faeces of other mice, particularly young mice. This process, coprophagy, helps to maintain an optimal mucosal luminal microbiota and reduces inflammation [58].

Analysis of The Faecal Microbiota

There are 10^{11} bacteria per gm of faeces. The vast majority are bacteria that have evolved to occupy niches on the mucosal surfaces and in the lumina. These bacteria derive their energy from epithelial secretions. The majority are commensals. A few are potentially pathogenic but in so far as they have evolved to occupy a niche within the colon then harming the host has no evolutionary advantage. They exist as commensals for most of the time.

Bacteria that form 1% or 0.1% of the faecal microbiota (10^9 or 10^8 per gm) are also commensals. In the case of *S. aureus,* colonies only reach 10^6 per gm following viral respiratory tract infections [19]. Thus, most analyses will not assess the mucosal tissue microbiota.

Mucosal tissue microbiota induced inflammation is present in everybody. But it is the degree of inflammation that will best define dysbiosis. Inflammation has two parts. One is a direct consequence of the mucosal tissue microbiota and the second is due to the passive diffusion of large molecules from the lumen into the tissues through leaky tight junctions.

A direct assessment of the carriage of specific pathogens will depend on specific quantitative PCR analysis. This should include

S. aureus and the periodontal pathogens initially. But there are also streptococcal pathogens and fungi such as *Candida albicans* to consider. The race to determine combinations of bacteria that cause the neurodegenerative conditions of Alzheimer's disease, Parkinson's disease and motor neuron disease should begin.

Pathogenic bacteria secrete toxin laden extracellular vesicles locally and into the bloodstream. This is another potential way to assess, albeit indirectly, the mucosal tissue microbiota.

DNA metagenomics and 16S rRNA amplicon sequencing can analyse up to 99.99% of the faecal microbiome, but that omits the 0.01% that contains most of the mucosal tissue microbiota. It is for this reason that the analyses, although providing a wealth of information, rarely lead to information that is directly clinically useful. What we require is the ability to measure the degree of mucosal tissue dysbiosis in individual cases and then monitor dysbiosis in response to specific interventions.

Discussion

Human physiology, psychology and pathology can be analysed in terms of information theory [33-37]. We are extremely complicated organisms with information coded in the genome and expressed in our proteome. Extreme complexity necessitates a high level of redundancy, because information is processed in an uncertain world and in the absence of redundancy errors will inevitably lead to breakdown. A highly redundant system has multiple components in parallel and the failure of one component will not lead to breakdown. Equally errors can be corrected if there are checks in the system. System failure or breakdown or uncorrected errors are only likely if several pathogenic factors operate at the same time, often acting in synergy. All complex systems are subject to the laws of entropy and the probability of error and breakdown will rise with age. These ideas have been developed at length in previous publications [33-37].

Humans are composed of trillions of cells and can only be considered a unit in so far as information flows between the cells to keep them in the same phase. Small chemical messengers (cytokines, endocrines and neurotransmitter molecules) fulfil this function. The various physiological, psychological and pathological functions are orchestrated by these molecules. The result is that each process influences the others and it is not possible to consider any one process in isolation from the others. Thus, we should not be surprised that the complex relationship between the mucosal tissue microbiota and the immune system is in turn influenced by whatever else is happening in the body [22].

Most pathological factors that increase the risk of any one disease also increase the risk of most disease. Such factors include, smoking, pollution, chronically low levels of vitamin D, periodontitis, lack of exercise, poor quality sleep, lack of social

contact, low position in a social hierarchy, loneliness, being sedentary and eating a poor diet [38-43]. The diseases that arise include neurodegeneration, atherosclerosis, cancer and psychiatric disease. Although, at first sight surprising, these observations are an inevitable consequence of a highly complex, highly interconnected, chemically co-ordinated information processing system. Cellular damage is caused by the action of bacterial pathogens and the immune response to those pathogens. Thus, connecting the pathological factors to the diseases they bring about is mucosal tissue dysbiosis induced inflammation. The latter is therefore a factor in most disease, both physical and mental.

The mucosal luminal microbiome, which for this discussion includes all the bacteria on epithelial surfaces and in ductal lumina, has more genomic information than the human genome. This vast information store must be of considerable importance in health and disease. Indeed, some have suggested that the gut microbiome should be regarded as another organism. But this concept falls foul of the entropy paradox. High diversity indicates high entropy and this is not a feature of a complex organism but of a sump containing a random mix of bacteria from multiple other sites. It is better to regard the entire microbiome situated close to the multiple epithelial surfaces as another organism. Each specific niche of *epithelial cell/ surface bacteria* forms a high information complex with extensive cross talk contributing to human health. This interaction would then define an optimal microbiota and any deviation would indicate dysbiosis. But it will be a long time before we can diagnose dysbiosis in this way in an individual patient.

The recent Covid-19 pandemic illustrates many of the points made in this paper [12]. A small virus, SARS-CoV-2, with just a few genes, causes a mild respiratory tract infection in the majority of young, otherwise healthy adults. But in some people, it causes a severe systemic disease. All viral respiratory tract infections interact with the respiratory mucosal tissue microbiota. If there is significant mucosal tissue dysbiosis induced inflammation it can be amplified or otherwise modified to cause a wide range of disease. Furthermore, the mucosal tissue dysbiosis induced inflammation can persist after the virus is eliminated leading to post viral disease. It is a mistake to try to explain these protean disease manifestations purely in term of the properties of the virus; it does not contain enough information.

Increasing prosperity, since the industrial revolution in developed countries, has led to improved health. But since the 1960s in the UK there has been a pernicious process which is leading to increasing ill health in younger people. A range of diseases are on the increase and this includes increased cancer incidence in the under 50s [45-55]. However, this process is only just starting to affect age standardised mortality rates. An important factor is an increasingly sterile diet leading to mucosal tissue dysbiosis induced inflammation. Studies in mice indicate that clean living conditions and a sterile diet can cause increased inflammation and ill health which is reversed by simple measures such as putting yoghurt in food or lactobacilli in drinking water [56-58]. But if we are to tackle this problem in humans, we need to provide evidence; that will need tests to diagnose mucosal tissue dysbiosis in individual patients and then monitor the effects of any intervention.

There is an interesting paradox when we examine the data on the harmful effects of prosperity. Those who are most affected by the diseases of affluence are the least affluent in society [59,60]. We see this most clearly with the metabolic syndrome (obesity, atherosclerosis, hypertension, type 2 diabetes mellitus and depression). Only affluent societies enjoy an excess of food, but it is the least prosperous that suffer the most from this excess. It is tempting to blame the obese for eating too much high calorie food or not taking enough exercise (the sins of gluttony and sloth, but only by implication); or food manufacturers for producing the wrong type of food. A sterile diet leads to mucosal tissue dysbiosis induced inflammation in every member of society. But those at the bottom of the socio-economic scale also have other pathogenic factors to contend with. They are more likely to be exposed to pollution, are less likely to have access to open spaces for exercise, more likely to smoke, to live in poor quality housing, are less able to purchase certain healthy food options, more likely to have low levels of vitamin D etc. These pathogenic factors will interact with mucosal tissue dysbiosis, amplifying and modifying the inflammation, and leading to a greater incidence of disease. There is, however, an interesting caveat to the affluence paradox. Pathogenic factors acting on complex systems with high levels of redundancy will show synergistic interaction. It is a mathematical property of the system. Thus, any single factor, such as the regular consumption of yoghurt, which reduces mucosal tissue dysbiosis will disproportionately benefit those at the bottom of the socio-economic scale. We could level up health with yoghurt [9].

We all have a degree of mucosal tissue dysbiosis induced inflammation, but some will have more than others. This inflammation, depending on degree, raises the risk of almost all disease. But the current methods of analysing the microbiome are not suitable for diagnosing dysbiosis in individual cases. We need to assess the tissue load of specific bacterial pathogens and measure the degree of systemic inflammation in individual patients and then see to what extent changes in lifestyle can mitigate the damage caused by inflammation.

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