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Mucosal Tissue Dysbiosis Induced Inflammation Interacts with Psychosocial Factors and Genetic Factors to Cause Schizophrenia

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Abstract

Schizophrenia is a condition in which biopsychosocial factors interact with genetic pre-disposition to cause a disease of thought disorder. It is proposed that bacterial induced inflammation and toxemia, a consequence of mucosal tissue dysbiosis, is one of the key environmental factors in the pathogenesis of schizophrenia. Genetic polymorphisms identified in schizophrenia include genes involved in immunity. The age incidence and sex ratio seen in schizophrenia are consistent with previously published models of bacterial infection. Mucosal tissue dysbiosis induced inflammation can explain the key associated features of neuroinflammation, periodontitis, low levels of vitamin D, accelerated aging, and early life developmental changes. Mucosal tissue dysbiosis induced inflammation is orchestrated by cytokines as are emotional responses. This gives a plausible mechanism for biopsychosocial interaction in the genesis of thought disorder. Mucosal tissue dysbiosis induced inflammation can be investigated by using PCR (polymerase chain reaction) to assess the carriage of specific bacterial pathogens in cases and controls. Optimizing the microbial flora from early in life could reduce the severity of the disease. This could be achieved by simple measures, such as maintaining serum vitamin D levels and regular consumption of yoghurt.

Keywords: Schizophrenia; Mucosal tissue dysbiosis; Neuroinflammation; Periodontitis; Vitamin D; Yoghurt

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Key Messages

1. A distinction must be drawn between the mucosal luminal microbiota and the mucosal tissue microbiota. The former consists of a vast number of bacteria with many species, they are present on the luminal surface of epithelial cells, they derive their energy from surface secretions and restrict the entry of pathogenic bacteria into tissues. The mucosal tissue microbiota consists of pathogens which have genetic mechanisms which enable invasion and restrict immune elimination. It is these bacteria that cause systemic inflammation and contribute to a wide range of disease, both mental and physical.

2. The realization that human tissues are not sterile and that there is a mucosal tissue microbiota represents a paradigm change in understanding human disease.

3. Bacterial induced systemic inflammation and toxemia is a plausible explanation for neuroinflammation seen in schizophrenia.

4. Periodontitis is a clinical marker of mucosal tissue dysbiosis; it is commonly both a cause and a consequence of the conditions with which it is associated.

5. Low levels of vitamin D predispose to mucosal tissue dysbiosis and thereby contribute to the genesis of a wide range of disease, including schizophrenia.

6. Mucosal tissue dysbiosis induced inflammation interacts with other pathological and physiological processes to cause a wide range of disease. In the case of schizophrenia that could include psychosocial factors as well as germ line genetic mutations.

Introduction

In the last decade we have come to realize that the tissues of our bodies are not sterile [1-12].

There are pathogenic bacteria growing within the mucosal tissues that underly all epithelial surfaces. These bacteria have genetic mechanisms that enable them to survive within the body and avoid immune elimination [6,7,12]. The bacteria use glucose as their energy supply. They cause local and systemic inflammation which persists throughout life and gets gradually worse as our immune system ages. Many of these bacteria produce toxins, often within extracellular vesicles, and they can damage distant cells; including endothelial cells leading to atherosclerosis, and brain cells (neurons and microglia) leading to neuro inflammation.

Mucosal luminal dysbiosis is the condition in which the trillions of bacteria that survive on the surface of epithelia form a suboptimal mixture that allows pathogenic bacteria to become established within the tissues [1,2]. The resulting inflammation (mucosal tissue dysbiosis induced inflammation) then contributes to a wide range of disease [9-11]. This distinction between mucosal luminal dysbiosis and mucosal tissue dysbiosis is rarely made; but it is crucial to understanding how the micro biota causes disease (see appendix for definition of terms).

Schizophrenia is a disease of thought disorder with both positive and negative symptoms. The positive symptoms include the psychotic syndrome of delusions, hallucinations and formal thought disorder. The negative symptoms include lack of volition and flattening of affect. It occurs worldwide with a lifetime prevalence of the order of 1%. It is familial, with 60% concordance in monozygotic twins and closer to 10% concordance in dizygotic twins and other siblings [13]. The genetic component is well defined but there is also an environmental component since concordance in monozygotic twins is less than 100%. In this article we explore the evidence that mucosal tissue dysbiosis has a role in the pathogenesis of schizophrenia. The hypothesis proposed is that bacterial induced inflammation and toxemia interact with complex genetic systems impaired by germ line deleterious mutations; this leads to thought disorder and the other pathological features seen in patients with schizophrenia.

The concept that schizophrenia could arise as a consequence of bacterial toxins interacting with a complex genetic system in which deleterious mutations are present has been suggested previously [14]. The idea was plausible at the time of publication, but there is now much more evidence in support of this idea.

Genetic predisposition

Genome Wide Association Studies (GWAS) have shown that a large number of Single Nucleotide Polymorphisms (SNPs) are associated with schizophrenia [15]. SNPs are markers for neutral changes in nearby genes [16]. Each variant has a small effect on risk, usually less than a 50% increase. Each individual will have genetic variants which raise the risk and lower the risk by a small amount. Many of these variants are associated with inflammation and neuronal excitability. These variants include genes related to voltage gated calcium channels and to B cell lineages and components of complement [13].

GWAS can also identify small deletions in chromosomes, and these are more likely to be associated with deleterious mutations. Some of these deletions are associated with schizophrenia and they have larger effects [17,18].

Genes act in large complex networks to preserve health and prevent disease [19-24]. The networks are robust and therefore there needs to be a degree of redundancy so that if one or two genes are lost (deleterious mutations) the network will still function. A property of a complex, robust but highly redundant system is that deleterious mutations will act synergistically to impair performance. Thus, one or two deleterious mutations will have little effect on function but a third could lead to a large detrimental effect.

Schizophrenia is a disease in which there is thought disorder. There are obviously many genes involved in specifying the protein networks that control thought. It is therefore possible to construct a mathematical model in which M genes specify a system and a small number of deleterious mutations (n) lead to disorder in that system. If M is of the order of 10% of the human genome and n=3 then a reasonable model of schizophrenia is produced, with a lifetime prevalence of 1%, and approximately 10% concordance in siblings, but 60% concordance in monozygotic twins [15,24]. This model merely illustrates a principle that a small number of deleterious mutations acquired from parents (some present in the genome of parents, and some acquired *de novo* during spermatogenesis or oogenesis) can lead to the genetic predisposition to schizophrenia.

Mucosal luminal and tissue dysbiosis

There are of the order of ten trillion bacteria present on the epithelial surfaces of the human body [1,2]. These bacteria have co-evolved with our human ancestors. The vast majority of bacteria are present in the lumen of the colon. But bacteria are also present on all epithelial surfaces including the skin, the respiratory tract, the gastrointestinal tract from the oral cavity to the anus, and the vagina. There are bacteria in skin adnexal glands, and the ducts of salivary glands, the pancreas, the prostate, the breast etc.

Bacteria growing on epithelial surfaces derive their energy from epithelial secretions. These secretions include mucus in the gastrointestinal tract and respiratory tract, keratin on the skin, and glycogen secreted from the surface cells of non-keratinized stratified squamous epithelium in the oral cavity, esophagus, and vagina. The role of these bacteria is to out compete pathogenic bacteria and thereby prevent disease.

Pathogenic bacteria have also co-evolved with our human ancestors [5-8]. These bacteria have genetic mechanisms that enable them to invade tissues and grow near the epithelial surface but within the body. They grow in tissues, their energy supply is derived from the bloodstream and they cause inflammation [7,8]. These bacteria have a complex relationship with the immune system. The bacteria have mechanisms to survive an immune attack. But the immune system must contain them and prevent too much growth and too much inflammation. There is, however, a potential advantage to the host in growing the pathogens in low dose with minimal inflammation. It allows the host to generate and maintain an immune response to the bacteria throughout life.

Staphylococcus aureus is an example of a pathogen which has adapted to grow within the body [7]. Some strains produce superantigens. These are toxins which stimulate human T cells to undergo clonal proliferation and induce an inflammatory response. This does more damage to the host than to the bacteria. These toxins are produced at body temperature and above and induce the production of anti-toxin antibodies which are found in the blood of the majority of adults [7]. In effect the bacteria protect themselves and their niche against immune attack. *Porphyromonas gingivalis* is another example of a pathogen with genetic mechanisms to survive in tissues [12]. This is a Gram-negative anaerobe which grows in periodontal tissues, slowly destroys the cementum around teeth and

leads to tooth loss. The bacteria produce toxins which citrullinate proteins. The result is a change in the structure of antibodies and complement which reduce their anti-bacterial actions [12].

Features of schizophrenia

Age incidence: The age incidence of presentation or diagnosis rises through the teenage years to a peak in the early twenties and then slowly falls [25,26]. This age incidence curve is typical of a disease caused by exposure to common bacterial or viral pathogens [27-29]. Mucosal tissue dysbiosis increases with age as our immune system gradually deteriorates. But if in schizophrenia there is a specific inherited deficit in the immune response to a specific organism or a specific bacterial toxin then the risk of disease onset will peak at the time the organism is first well established in mucosal tissues. Furthermore, it is likely that the genetically determined immune deficit is not all or none, but instead an increased risk of a failure to develop the optimal response to contain the bacteria. Early in life the immune system is at its best in terms of developing appropriate immune responses, but as the thymus atrophies in the teenage years the risk of a less than optimal response rises [Appendix].

Sex ratio: Schizophrenia is more common in men than in women. The ratio quoted in one study is 1.7 [26]. A modest increase of this degree is, in fact, of considerable interest. This is because the ratio of approximately 1.5 to 1 is commonly found in diseases caused by bacterial or viral infection [30].

The X chromosome carries approximately 1,000 genes which is 5% of the human genome. This means that males have only 95% of the heterozygosity of females. Genetic variants which are conserved in the genome are neutral and lead to heterozygous loci. Consider a genetic variant concerned with cytokine regulation. If the variant increases cytokine production relative to the wild type, this might be advantageous against certain organisms but disadvantageous against others, thus neutral overall. The heterozygous individual with both the variant and the wild type will be at an advantage relative to the homozygous individual because both responses are available in the heterozygous state.

There are around three male deaths for every two female deaths throughout life. This fits with the idea that mucosal tissue dysbiosis contributes to a wide range of disease, including schizophrenia, and males are at increased risk because they have only one X chromosome [30].

Life time prevalence: The lifetime prevalence of schizophrenia is close to 1% in most countries and most cultures [31]. This is unusual for a disease with a strong genetic determinant. But there is strong selective pressure against the build-up of deleterious mutations in the human genome and the mean number is likely to be similar in different population groups. Thus, the chance of any three deleterious mutations in a large set of genes will also be similar world-wide. Mucosal tissue dysbiosis is also universal but it will vary between different cultural groups and over time.

More recent work, however, has shown that there is cultural variation [32]. There is, for instance, an increased prevalence in young male immigrants to the UK from the Caribbean. Complex social and cultural features will be involved but low vitamin D levels could also be a factor.

Neuro inflammation: Early autopsy studies revealed dilated ventricles with loss of neural tissue around the third ventricle [33]. Subsequent imaging has established that this is a feature of the disease and not merely a consequence of therapy [34-36]. Studies have established lateral ventricular enlargement of the order of 25% and brain volume loss of around 2%. The brain loss is mainly grey matter and involves frontal lobe, temporal lobe and the hippocampus [35,36]. The degree of brain loss increases with age, with disease severity and length of treatment.

It is only since the turn of the century that it has become established that human tissue is not sterile [1-12]. Bacteria and fungi are normal constituents of tissue and blood. They are present at very low levels compared with the epithelial surfaces, but the pathogens within can spread to the brain and cause neuroinflammation. The more marked the mucosal tissue dysbiosis, the more marked the systemic inflammation and the more likely it is that neuroinflammation will be present.

Neuroinflammation, due to direct bacterial invasion of the brain or secondary to bacterial toxemia, is a plausible explanation for thought disorder in this disease. Genetic predisposition could be secondary to immune deficits that allow the bacteria to spread, or failure to produce antibodies to neutralize toxins. Alternatively, neutral polymorphisms could have increased neuronal excitability or deleterious mutations could have impaired the blood-brain barrier. All these factors and more are likely to be present in some cases, if not all.

Accelerated aging: People with schizophrenia often have accelerated aging and die up to 15 years earlier than their peers. The commonest cause of death is one of the complications of atherosclerosis [37]. Once again this is one of the consequences of mucosal tissue dysbiosis. Mucosal tissue dysbiosis causes systemic inflammation and this is an independent risk factor for ischemic heart disease and stroke. Indeed, the mechanisms that cause neuroinflammation are the same mechanisms that damage endothelial cells and accelerate the development of atherosclerosis.

Periodontitis: Periodontitis is a clinical marker of mucosal tissue dysbiosis [38]. Periodontal pathogens grow in the tissues of the gum, they erode the cementum and lead to loss of teeth. The same organisms can spread *via* the blood stream to other sites, including the brain, and cause local inflammation [4,6,9]. They can also secrete toxins, often within extracellular vesicles, which can directly damage endothelial cells and neuronal cells. Furthermore, they lead to the secretion of cytokines which can also spread systemically and damage cells directly. The growth of periodontal pathogens in the gums is secondary to a sub-optimal flora on epithelial surfaces which has allowed the invasion in the first place (mucosal luminal dysbiosis). Thus, periodontitis is likely to be associated with mucosal tissue dysbiosis at other sites, including increased carriage of *S. aureus* in the pharynx.

Periodontitis is associated with a wide range of disease and that includes both schizophrenia and atherosclerosis [39-43]. Smoking is also strongly associated with schizophrenia and atherosclerosis. There can be neglect of oral hygiene in patients with schizophrenia. The pathways connecting these various features are complex, medication has a role and it is difficult to determine cause and effect [40]. But in general periodontitis seems to be causally related to the conditions with which it is associated even though in many cases the causal pathways are bi-directional.

Vitamin D: Low levels of serum vitamin D are, like periodontitis,

associated with a wide range of disease; and that includes both schizophrenia and atherosclerosis [44-47]. Sunlight stimulates the synthesis of vitamin D in skin epithelial cells. The vitamin D molecule is then hydroxylated in the liver and then the kidney to produce the most active form. The active vitamin D stimulates the production of anti-microbial compounds by epithelial cells and thereby aids in preventing or slowing down the development of mucosal tissue dysbiosis. In addition, vitamin D is a co-factor in immune responses. Thus, lack of the vitamin will impair the immune response that is involved in suppressing bacterial growth in tissues. Immigrants to the UK from tropical climates are at particular risk of low serum vitamin D levels as the production of vitamin D is reduced in melanin pigmented skin.

Low levels of vitamin D are associated with many conditions but there is no good evidence that oral supplements will, in the short term, have beneficial effects on specific conditions. For instance, low levels of vitamin D are associated with increased *S. aureus* carriage. But there is no evidence that oral supplements will reduce carriage [38]. Low levels of vitamin D are associated with increased markers of systemic inflammation, but supplements have only a small effect. The explanation is not, as some claim, that the association of low levels of vitamin D with disease is not causal [47]. But that low levels of vitamin D lead to increased mucosal tissue dysbiosis and oral supplements of vitamin D are unlikely to reverse the process in the short term. Supplements might slow the process by which mucosal dysbiosis gets worse but will not bring about a cure.

It is also worth reflecting that while there is a plausible mechanism by which vitamin D can limit the development of mucosal tissue dysbiosis there is no reason to believe that it will influence mucosal luminal dysbiosis.

Neurodevelopment: The disease schizophrenia presents in adult life. But there is evidence of pre-existing pathological changes [48-50]. The condition is more common in those born in the winter months and in those whose mothers have suffered viral respiratory tract infections in pregnancy. Children who later present with schizophrenia are often more isolated in childhood. These features indicate a pathological process that starts early in life. Exposure to bacteria also starts early. There is some evidence that bacteria in mother's bloodstream can cross the placenta and enter amniotic fluid, but this is still a matter of dispute. Mother's milk, however, is not sterile and this is beyond dispute. It contains lactose fermenting organisms in moderate dose and pathogenic bacteria in low dose [5]. The infant's microbial flora is established shortly after birth, and this includes both bacteria on the surface and bacteria within tissues. *S. aureus*, for instance, is commonly carried in the nasopharynx of infants in the first few months of life [51].

Genetic defects in dealing with bacterial pathogens therefore will initiate pathological processes early in life.

Biopsychosocial interaction: The concept proposed in this article is that mucosal tissue dysbiosis contributes to a wide range of disease. It is not a single specific entity causing a specific disease, but a wide range of disparate entities interacting with other pathological processes. There are multiple different bacteria growing at multiple different sites, in varying dose, and interacting with other processes to cause disease. The other etiological factors will include pollution, which also causes inflammation, but also the less well defined, but no less important, psychological, sociological, economic and cultural factors that will influence the thought processes of young men and women as they enter adult life.

The interaction between physical, psychological and sociological factors, depends on chemical messengers (cytokine, endocrine and neurotransmitter molecules) which co-ordinate the action of cells throughout the body. The emotional states of depression and anxiety are orchestrated by these molecules, as are the cells of the immune system. The term orchestration is appropriate because the chemical messengers "play a complex tune" as they interact. Emotions are normal physiological states with a biological purpose, but that will be impaired in the presence of inflammation as different orchestrations interact (cacophony). Equally the immune response will be impaired in the presence of anxiety and depression. These ideas are developed more fully elsewhere [52].

Discussion

The key epidemiological features of schizophrenia can be explained by this concept of mucosal tissue dysbiosis interacting with genetic predisposition.

Schizophrenia is a genetic condition in which there is approximately 60% concordance in monozygotic twins and 10% concordance in siblings [13,15,17,25,26]. The lifetime prevalence is approximately 1%, but this is no longer considered to be constant worldwide [31,32]. Previously published models have shown that a small number of germ line deleterious mutations in a large genetic system can explain these features [19-24] (see Appendix). The models were conceived prior to the year 2000 when the human genome was first analyzed. Since then, a large number of polymorphisms have been identified which raise or lower the risk of schizophrenia [15]. These polymorphisms, identified in GWAS, have small effects. Many are close to genes involved in immunity. Others are close to genes which code for ion channels. GWAS can also identify small and medium sized deletions from chromosomes which are more common in schizophrenia. These are deleterious mutations and when identified they have large effects [17,18].

There are also published models of the age incidence and sex ratio in diseases in which common bacteria and viruses interact with genetic systems that deteriorate with age [27-29] [see Appendix]. In general, diseases cause by mucosal tissue dysbiosis increase in prevalence with the seventh power of age. But conditions which occur on first exposure to a pathogen have a different age incidence curve. They rise to a peak and then fall. The position of the peak depends on how common the organism is. Common organisms peak early, less common organisms peak in the late teens or early twenties. Furthermore, if the disease is more likely to occur in males than in females, the peak in males will be earlier. Diseases caused directly by bacteria are more common in males because they have only one X chromosome and therefore have less heterozygosity [30]. Diseases in which an autoimmune response to bacteria is responsible for damage are more likely to occur in females. Thus, in multiple sclerosis, an autoimmune disease which is more common in females, the age incidence curves are similar to those of schizophrenia but reversed so that the peak is higher in females than in males and occurs earlier in females than in males [28].

Periodontitis [6,9,10], low levels of vitamin D [44-47], accelerated atherosclerosis [37], neuro inflammation [33-36] and defects in neurodevelopment all fit with mucosal tissue dysbiosis [48-50]. Periodontitis is a clinical marker of mucosal tissue dysbiosis. If

periodontitis is present then there are bacteria growing within the gums, and there are likely to be the same and also different pathogenic bacteria at other mucosal sites. Smoking and neglect of dental hygiene can contribute to periodontitis thereby making the situation worse. Vitamin D is a co-factor for immune action and directly causes the production of anti-microbials from epithelial cells. Chronic low levels of vitamin D pre-disposes to mucosal tissue dysbiosis and to schizophrenia. Vitamin D supplements, however, have little short-term effect once mucosal tissue dysbiosis is established.

Mucosal tissue dysbiosis is not a single entity. Multiple different pathogenic bacteria, at multiple sites, in varying concentrations, interacting with other pathogenic agents can lead to many different pathological processes. In those with the genetic predisposition to schizophrenia bacterial action early in life can cause neuroinflammation and affect neurodevelopment. Late in life it can lead to accelerated atherosclerosis and death from ischemic heart disease or stroke. In the late teens, or early twenties, a new strain of a common bacterium could act directly on the brain to cause the symptoms that are diagnostic of the disease.

Stressing the role of mucosal tissue dysbiosis/genetic interaction in schizophrenia, does not exclude other pathogenetic factors. Indeed, one of the reasons why mucosal tissue dysbiosis is involved in so many different conditions is that it interacts with other causative agents. Bacterial induced inflammation is orchestrated by cytokines [52]. The same cytokines, in differing concentrations, orchestrate every physiological process in the body. Sociological and psychological factors leading to emotional states, such as depression and anxiety, are associated with specific patterns of cytokine secretion. A combination of inflammation and emotional response will lead to interference; the immune response is impaired as is the emotional response. This is a highly plausible setting for thought disorder.

There have been a number of studies of the fecal microbiome in patients with schizophrenia [53]. Analysis of bacterial DNA using 16S rRNA amplicon sequencing or DNA metagenomics reveals a large number of bacterial genera and bacterial species, although the analysis is expensive and the statistical computation extremely complex. It has proved difficult to establish the optimal fecal microbiome and thereby diagnosis mucosal luminal dysbiosis as deviation from that optimum. Studies reveal a great deal of diversity in both cases and controls with extensive overlap. Numerous statistical comparisons usually reveal some significant differences, but they are rarely consistent across different studies. Our approach is to define dysbiosis in terms of the pathogenic bacteria growing within the tissues rather than within the lumen. These pathogens are only a tiny fraction of the total and are not detected when bacterial DNA is analyzed as described above. They can be detected, however, with PCR. In addition, inflammatory markers, such as pro-inflammatory cytokines and endotoxin are elevated when bacterial pathogens are established within the body.

Studies of germ free and normal mice have also contributed to our understanding of dysbiosis and its consequences [54-58]. Laboratory mice live in clean conditions with sterilized food and filtered air. This induces a mild degree of mucosal tissue dysbiosis as revealed by studies in which the addition of yoghurt to the diet, or lactobacilli to drinking water, causes a marked improvement in health. Mice receiving the probiotic bacteria have lower levels of inflammatory markers, higher levels of anti-inflammatory markers, including increased oxytocin, show increasing grooming, and have faster and better healing [54,55]. Dysbiosis can also be induced by giving antibiotics to mice or by studies in which feces are transplanted from patients with suspected dysbiosis [56-58]. These studies have shown how dysbiosis can lead to systemic inflammation and to neuroinflammation. But it is not clear to what extent the changes induced are a consequence of mucosal luminal dysbiosis or mucosal tissue dysbiosis; perhaps both. The claims that animal models of schizophrenia can be produced in this way, however, are not universally accepted.

There is emphasis throughout this paper on a distinction between the mucosal luminal microbiota and the mucosal tissue microbiota. The key role of the former is to restrict the entry of pathogens into tissues; but it is the latter that are directly relevant to disease causation. But as always biology is more complex and the mucosal luminal microbiota does provide some essential molecules for the body and does influence the health of the nearby epithelial cells [59,60]. Furthermore, if pathogenic bacteria in tissues cause inflammation, then damage to epithelial cells can lead to leaky tight junctions, and endotoxin molecules from Gram-negative bacteria can diffuse passively into the tissues. This is an important contributor to systemic inflammation. But studies so far of the microbiota in disease invariably assess the luminal microbiota rather than the tissue microbiota and it is time to redress the balance.

Investigating the hypothesis proposed in this article will involve quantification of the pathogenic bacteria carried within tissues. Pathogenic bacteria growing in mucosal tissues will be shed into the lumina and most will make their way into the lumen of the colon. Thus PCR (polymerase chain reaction) for specific organisms is probably the best way to assess carriage. Other approaches are to measure specific bacterial toxins in body fluids or directly analyze extracellular vesicles in body fluids.

If this concept is confirmed, then there is a possibility of prevention based on optimizing the microbial flora from birth in those with the genetic pre-disposition to the disease. The argument for optimizing the microbial flora applies to many other conditions. The simplest way in the western world is to maintain vitamin D levels and to encourage the consumption of yoghurt, as argued elsewhere [61].

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Appendix

Age incidence of disease

All mathematical models of biological processes are wrong, but some are useful. They are wrong because the models involve simplification, therefore in the final analysis they will fail to allow for all eventualities. They are useful, however, if in the process of simplification, they preserve the essence of the biological process under investigation.

One way of producing a useful model is to assume complexity and work with the principles of complex systems which include redundancy, synergy and temporal decay [19-24].

Consider a complex system (specified by genes and composed of proteins) which is designed to preserve health by making a series of decisions in an uncertain world [27-29]. The probability of a correct response is **R**, and the probability of an incorrect response is 1–**R**. Over time the system will decay at random, and the probability of a correct response becomes $Re^{(-kt)}$. Now add in redundancy to make the system more robust. This involves creating **n** systems and a mistake will only occur if all the systems make the mistake at the same time. The risk of a mistake is now $[1–Re^{(-kt)}]^n$. If we consider death as the ultimate mistake then this function, with a value of n=7, produces a good fit to human mortality rates [29]. On a log scale the slope is **7**, and this fits with data for males, slightly less than 7 i.e., 6.8 and females slightly above 7 i.e., 7.04. (Note that 6.8 is 96% of 7.04).

The risk of death doubles every 6 or 7 years and the majority of diseases, such as atherosclerosis and cancer, show similar age prevalence. The prevalence of cancer, for instance, rises as the seventh power of age and the incidence (the first derivative) rises as the sixth power of age. But diseases caused by first exposure to common bacteria or viruses show a different age incidence. If a bacterium is common and the chance of exposure is constant with time then the probability of meeting the organism for the first time falls exponentially with age (if 50% meet it for the first time in year one, then 25% (50% of the remaining 50%) meet it for the first time in year two, and 12.5% for the first time in year 3, and so on). The appropriate function is $Ce^{(-kt)}$, where **C** and **k** are constants.

Now consider a common bacterium interacting with an aging system. The age incidence is now a combination of the two functions (but of course we need different decay constants now k1 and k2). The resulting age incidence curve rises to a peak and then falls. The position of the peak depends on how common the organism is. More common organisms lead to earlier and lower peaks, less common organisms lead to later and higher peaks. Furthermore, if the condition is more common in males (or females) then the peak is higher and earlier in males (or females). Bacterial infection, in general, is more common in males and therefore the peak is earlier and higher in males. Autoimmune disease, precipitated by exposure to bacteria, is more common in females, therefore the peak is earlier and higher in females [27-29].

The most likely explanation for the observation that males are more susceptible to bacterial and viral infection than females is that males have only one X chromosome [30]. The result is less heterozygosity and therefore less redundancy. The X chromosome carries approximately 5% of the human genome. It is therefore of interest that the slope of the male mortality curve is approximately 96% of the female mortality curve, at least it was in data analyzed in 1992 in the UK [29].

Thus, the observations that the age incidence of first diagnosis of schizophrenia peaks in the 20s in males, but the peak is lower and later in females fits with bacterial induced disease. Furthermore, the sex ratio of 1.7:1 is also consistent with bacterial induced disease [25,26].

Genetic models

Genes act in complex systems to preserve health and prevent diseases [19-24].

There are approximately 20,000 genes in the human genome (haploid set) [16]. But when cells divide in mitosis and meiosis there is a finite chance of a deleterious mutation occurring. The result is that deleterious mutations accumulate in the genome as parents pass germ line mutations and *de novo* mutations to their offspring. The frequency of deleterious mutations in the genome can be estimated from the frequency of recessive disease in the offspring of cousin unions compared with the frequency of the same disease in the general population. The best estimate is that the mean number of deleterious mutations is close to seven with a mean of one new mutation per generation. The deleterious mutations are distributed at random in meiosis and therefore the number of deleterious mutations will form a Poisson distribution with a mean of seven in the germ line of adults but eight in the zygotes of the next generation. In complex

systems the deleterious mutations will interact synergistically to impair performance. Thus, some of the zygotes at the upper end of the Poisson distribution will not survive and those that do will have a mean of seven; and the population comes into balance.

If we consider the disease schizophrenia. There are many genes concerned with thought and more than one deleterious mutation to cause thought disorder. Consider the following model, published in 2005 when it was thought there were 30,000 genes (haploid set) in the human genome and that the mean number of deleterious mutations in the genome of adults was 10 [24]. Assume that 3600 genes (diploid set) form a complex system concerned with thought. Then 1.9% of the population will have three deleterious mutations in the 3600 set and will be at risk of schizophrenia (calculated using the Poisson distribution). If the concordance rate in monozygotic twins is 60%, then 60% of 1.9% is 1.14%. This is the lifetime risk of schizophrenia in the population. If one child has three deleterious mutations and develops schizophrenia, the chance of a sibling having three relevant deleterious mutations was calculated as 0.19 (This is a more complex calculation; the chance of the same three is 0.125 but the parents might have more than three relevant mutations between them and there is also the possibility of *de novo* mutations). A sibling with the three deleterious mutations has a 60% chance of developing schizophrenia so the risk in siblings is 11.4% (60% of 19%).

These calculations merely establish the principle that more than one deleterious mutation in a large complex highly redundant system can explain the occurrence of schizophrenia in family members. Each family, however, will have a different set of deleterious mutations and therefore at risk of a different set of bacteria. But still there is sufficient in common between the genetic and bacterial sets to allow a specific disease to be defined.

Definition of terms

Mucosal tissue microbiota: The mucosal tissue microbiota consists of pathogenic bacteria which have evolved genetic mechanisms that enable them to survive and grow within mucosal tissue. They derive their energy from the bloodstream and cause low grade local inflammation. They grow close to the mucosal surface as this allows them to shed bacterial progeny into the mucosal lumen and thereby spread to infect other people. Examples of these bacteria include *S. aureus* and the periodontal pathogens, *P. gingivalis* and *Fusobacterium nucleatum*.

Mucosal luminal microbiota: These are bacteria that have evolved to occupy niches close to the mucosal luminal surface but not within the tissues. They are resident external to the apical surface of epithelial cells. These bacteria derive their energy from epithelial secretions. In general, these bacteria are commensals. They act to protect the host by out-competing pathogens and by supporting the integrity of epithelial cells. These bacteria vastly outnumber the mucosal tissue microbiota.

Fecal microbiota

The mucosal luminal microbiota shed progeny into the center of ductal lumina and many of these bacteria are carried into the gut lumen. The mucosal tissue microbiota also shed progeny into ductal lumina and they too arrive in the gut lumen. Thus, the fecal microbiota is made up of bacteria from every mucosal surface including the colonic mucosa. Bacteria that have evolved to occupy a specific mucosal niche will form an ordered community (a low entropy state). But the feces contain bacteria from multiple different mucosal niches and thereby form a diverse state (high entropy). In general, a healthy system is one that is highly ordered, non-random and with low entropy. By comparison, disease is associated with disorder, increased randomness and high entropy. But an increased Shannon index (a measure of entropy) is accepted as an indicator of a healthy fecal microbiota. This appears paradoxical but the answer is that increased diversity reflects the large number of possible mucosal niches. Less diversity in feces would indicate unfilled niches.

The vast majority of the DNA of the fecal microbiome is of the mucosal luminal microbiota. Thus, methods developed to assess the fecal microbiome will not be suitable for assessing the mucosal tissue microbiota.