Peertechz

Medical Group

Archives of Depression and Anxiety

DOI:http://dx.doi.org/10.17352/ada

ISSN: 2455-5460 CC By

James A Morris*

Consultant Pathologist, Education Centre, Royal Lancaster Infirmary, Lancaster, LA1 4RP, UK

Received: 12 October, 2018
Accepted: 22 October, 2018
Published: 23 October, 2018

*Corresponding author: Consultant Pathologist, Education Centre, Royal Lancaster Infirmary, Lancaster, LA1 4RP, UK,
E-mail: Jim.A.Morris@mbht.nhs.uk

Keywords: Inflammation; Cytokines; Atherosclerosis; Type 2 diabetes mellitus; Obesity; Depression; Anxiety; Sleep disorder; Pre-eclampsia; Stillbirth; Staphylococcus aureus; Yoghurt

https://www.peertechz.com

Case Study

A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease

Abstract

Social, psychological and biological factors interact to cause both mental and physical disease. Chronic low grade inflammation is a risk factor for many conditions including atherosclerosis and its complications, type 2 diabetes mellitus, obesity and depression. The inflammatory response is designed to protect against pathogenic micro-organisms but in the process some damage to our own tissues is inevitable. The process is complicated and is orchestrated by cytokines (intercellular messengers). Adaptive physiological responses to the many stresses of everyday life are also orchestrated by cytokines. The responses are nuanced and each variation involves a different specific tune. But if the response to stress runs at the same time as the inflammatory response there will be a cacophony. The inflammatory response will be sub-optimal increasing tissue damage and the physiological response to stress will be sub-optimal converting normal emotions into pathological mental states. Sleep, pregnancy and appetite control are also complex physiological states orchestrated by cytokines. They will be sub-optimal in the presence of chronic inflammation. Inflammation can be overt as in dental caries and periodontitis, or covert as in the carriage of bacterial pathogens such as *Staphylococcus aureus* within an epithelial surface. We must seek to modify the bacterial flora in order to prevent disease. It is suggested that the natural substance with most potential for achieving this aim is yoghurt.

Introduction

The argument advanced in this article is that biological and psychosocial factors interact to cause mental and physical disease. Furthermore a specific hypothesis is proposed to explain the nature of this interaction at a molecular level.

Sir Michael Marmot has shown, in a classic series of observations on British civil servants, that those at the top of the hierarchy are healthier and live longer than those at the bottom, and there is a clear gradient in between [1]. In his popular book "Status Syndrome" he argues that this is due to psychosocial factors associated with position in the hierarchy having a direct causative effect on physical health. Genetic factors, of course, influence intelligence and will have role in determining who ascends the hierarchy [2]. But our intelligence is a product of genes interacting with the environment from conception through to adult life. Thus psychosocial factors will play a role, be it direct or indirect. The observation that employees whose jobs are insecure, through no fault of their own, suffer worse health than colleagues at a comparable level whose jobs are secure, is more direct evidence of a causative role for psychosocial factors [3]. The economic downturn in Russia, following the collapse of communism, led to increased cardio-vascular mortality in the unemployed [4]. This is another example of a direct psychosocial effect on physical health. Those who are married and those with wide social contacts have better health than those who are unmarried and lack social support [5,6]. This involves both physical and mental health and psychosocial factors clearly play a part.

Wilkinson and Pickett in their book "The Spirit Level", review an extensive literature relating health to economic inequality [7]. Affluence brings health and increased longevity, but amongst the richest nations those with the least inequality enjoy the best health and have the longest life expectancy. These results provide further support for a direct role of psychosocial factors in disease.

Position in a social hierarchy and health inequality influence the risk of atherosclerosis and its complications, obesity, type 2 diabetes mellitus and depression [1,7]. These conditions also share another common risk factor which is chronic low grade inflammation [8-11]. The inflammatory response is designed to recognise and to destroy pathogenic viruses, bacteria and other parasites [12]. The response is extremely complex, it involves the co-ordination of many cells with the programmed secretion of intercellular messengers (cytokines). The aim

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

of the process is to cause maximum damage to the pathogen with minimum damage to the host. But if the inflammation becomes chronic the strategy is then to contain the pathogen even if more tissue damage must be accepted. The entire process is orchestrated by cytokines; they play a range of tunes depending on the precise organism, the precise dose and the tissue affected. Cytokines are also involved as intercellular messengers in acute stress reactions and in emotional states such as anxiety and depression. They also co-ordinate the phases of sleep and are involved in the stages of pregnancy, co-ordinating delivery and establishing lactation etc. Appetite control is another complex physiological process involving the co-ordinated activity of many cells throughout the body. In each case the cytokines must play a specific tune. But what happens if one of these complex physiological processes occurs in the presence of chronic inflammation? One cannot play two tunes at the same time; there will be a cacophony. The inflammatory response will be sub-optimal and more tissue damage will ensue. The physiological response will be sub-optimal leading to pathological mental conditions.

Thus the hypothesis is, as stated in the title, that a cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. I appreciate that the biopsychosocial model means different things to different people. I also accept that health is more than the absence of disease and there are sociological models of health that cover wider issues than discussed in this article [13]. But I am concerned with the mechanism, at a molecular level, by which psychosocial factors interact with biological factors to cause disease.

Inflammation

The cellular players in inflammation are the white blood cells (neutrophils, eosinophils, basophils, monocytes and lymphocytes). They are produced in the bone marrow, circulate in the blood and enter the tissues. Neutrophils phagocytose and kill bacteria, using destructive enzymes stored in intracellular granules. They clear bacteria from the blood and are involved in local tissue inflammation. Eosinophils also contain destructive enzymes and release them onto the surface of parasites. This kills or maims the parasite but inevitably does some tissue damage. When basophils enter tissues they are called mast cells. They have surface IgE molecules which recognise potential pathogenic bacteria. They are an early warning system for infection and release enzymes which switch on the inflammatory response. Macrophages are derived from blood monocytes. They phagocytose and destroy bacteria and viruses. The bacterial and viral proteins are then broken down into polypeptides approximately 8 to 12 amino acids long. These polypeptides are posted onto the surface of the macrophage in conjunction with the molecule MHC type 2. T helper lymphocytes have surface receptors and the ones that combine with the specific polypeptides undergo clonal proliferation. In this way the T helper cell is specifically recognising the bacteria or virus from which the polypeptide was cleaved. An antibody response to the bacteria or virus depends on the recruitment of B lymphocytes by the T helper cells. The B lymphocytes undergo clonal proliferation and some mature to plasma cells which secrete IgG, IgA, IgM, or IgE antibodies. T cytotoxic cells have surface receptors which recognise polypeptides in association with MHC type 1. These are found on the surface of virally infected epithelial cells. The T cytotoxic cells recognise the infected cell and kill it using perforins (which punch holes in the cell membrane) and injecting molecules which induce apoptosis. There are also T suppressor cells which are involved in the regulation of the other T cells.

The regulation of this response is co-ordinated by the secretion of intercellular messengers or cytokines. The main immune cytokines are the interferons and the interleukins. There are three major interferons but 35 interleukins. The cytokines have a number of key properties [12].

- Pleiotropy – they cause different effects on different cells
- Autocrine function – modulate the cell secreting the cytokine
- Paracrine function – modulate adjacent cells
- Endocrine effects – act at remote sites
- Synergistic action – interact with other cytokines by multiplication rather than addition.

The immune cytokines are secreted by lymphocytes and macrophages. They orchestrate the clonal proliferation of the various lymphocytes and with chemokines attract them into the appropriate positions. An effective response involves a rapid response to cause the maximum damage to the pathogen as quickly as possible, followed by an equally rapid close down to prevent the response running out of control. In this process lymphocytes are created but they are also destroyed. The cytokines are involved in both processes. We do not know the full details of this complex process but the principles are clear. The cytokines play a precise tune, and anything that interferes will cause a sub-optimal result. Tumour necrosis factor [TNF] and interleukin-6 [Il-6] are two of the cytokines which have been studied in some detail. Their properties illustrate the complexity of the system.

Tumour necrosis factor is a cytokine involved in systemic inflammation [14]. It is produced by macrophages, lymphocytes (T helper and natural killer), neutrophils, mast cells, eosinophils, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neurons. It acts on the hypothalamus to produce fever and malaise. It causes cell death by apoptosis and is responsible for cachexia seen in the later stages of disseminated carcinoma. It acts on the liver to stimulate acute phase reactants including the production of C-reactive protein. It induces insulin resistance and suppresses appetite. It induces local inflammation and in high doses systemic shock. Increased levels of TNF are found in the blood in Alzheimer's disease [15] and in depression [16].

Interleukin 6 is a pro-inflammatory cytokine and an anti-inflammatory myokine. Macrophages secrete Il-6 when

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

activated by specific microbial molecules as part of the innate immune system. Interleukin-6 in turn stimulates local and systemic inflammation. It acts with TNF on the hypothalamus to cause fever and malaise. It also stimulates acute phase protein synthesis and the production of neutrophils by the bone marrow. Adipocytes secrete Il-6, and this is one reason why obese individuals have increased circulating C-reactive protein [17]. Psychological stress causes the secretion of corticosteroids by the adrenal cortex, these in turn stimulate the production of Il-6 [18]. Interleukin-6 also has a role in the consolidation of memories during sleep [19]. During exercise myocytes secrete Il-6 which acts as an anti-inflammatory cytokine opposing the action of TNF [20]. This illustrates the sheer complexity of the cytokine cascade with different actions depending on the context in which it is produced. Interleukin-6 can potentiate or antagonise TNF depending on the setting. In Alzheimer's disease and in depression it appears that they act together as pro-inflammatory cytokines [15, 16].

Genes, complexity and redundancy

The human genome consists of approximately 20,000 protein coding genes in two sets; one inherited from our mother and one set from our father. Thus the diploid set has 20,000 loci with two genes at each locus. These genes code for over 250,000 proteins [21]. The proteins form complex networks which interact with our environment from conception through to adult life. Every human capability is a product of that interaction. For every skill we need many genes, many proteins and a great deal of practise. The genetic and protein networks for each skill are complex, highly redundant and robust. Complex systems which are redundant will still work even if there are one or two errors [2, 22-26]. Redundancy makes complex systems robust. But another key property of redundancy is that errors or insults interact synergistically to degrade performance. Genes act in complex networks to fight disease and preserve health. Thus disease, when it occurs, is likely to be due to several insults coming together at the same time. We should not be surprised, therefore, if several different factors interact to cause disease.

Most of the pairs of genes at each genetic locus are identical but approximately one third have base changes leading to minor variations in the amino acid sequence of the protein, or to changes in regulatory control of transcription. These changes are neutral in evolutionary terms [21, 27]. There is no selection for or against the gene with the base change. All base changes are due to a point mutation that occurred in the remote past. It takes thousands of generations for a neutral variant to increase until it is present in over 1% of the human population. Advantageous variants, which are much less common, expand much more quickly. For instance a mutation in a regulatory element controlling expression of the lactase gene has spread rapidly in the last 200 to 400 generations as milk has become a stable part of our diet. Neutral mutations do not cause disease but they can influence disease. This is what is found in genome wide association studies (GWAS [21]. Each variant might cause a slight increase in one disease and a slight decrease in another, but neutral overall. Individuals are different because they have different neutral variants. In fact each individual is unique in their particular set of neutral variants, although they inherit the variants from their parents and will resemble them to some degree. Neutral variants in cytokine regulatory elements will influence the precise strength of reaction to infection and to emotional states and to stress. But they are only part of a complex genetic response to infection and to stress. The main genetic differences between races are also due to neutral variants. The races are different but equal; individuals are also different but equal in terms of the vast majority of genes which define us.

There are, however, also deleterious mutations in the genome. A deleterious mutation is one in which the protein product is lost (deletion) or doesn't function appropriately, or worst of all interferes with function. The number of deleterious mutations is a Poisson variable with a mean in single figures. The best estimate is a mean of approximately 5 to 7 in the advanced world at the present time [26]. We know that there are deleterious mutations in the genome because recessive disease is more common in the offspring of cousin unions than in the general population. But over 90% of the children of cousin marriages are healthy and free of recessive disease therefore there cannot be many deleterious mutations in most people. The mean is a Poisson variable because of the nature of meiosis; deleterious mutations are distributed at random to oocytes and spermatozoa. A further complication is that new deleterious mutations arise in each generation during spermatogenesis in particular. The best estimate is approximately one new deleterious mutation per generation [26]. Thus adults have a Poisson distribution with a mean of 5 to 7. Zygotes have a Poisson distribution of 5 to 7 plus one. There is, however, selection against the zygotes at the upper end of the distribution and approximately 30% do not develop. The zygotes that do survive have a Poisson distribution of 5 to 7 plus one minus one i.e. the population is in balance and the number of deleterious mutations does not rise from one generation to the next. This is a fundamental part of biology. Complex asexual organisms do not survive in nature because they accumulate deleterious mutations and die out [25]. Only sexual organisms survive long term because they can have progeny with fewer deleterious mutations than their parents. But sexual reproduction does create inequality. Deleterious mutations interact synergistically in complex genetic systems to impair performance. In general those with the least number of deleterious mutations will have enhanced life chances, because it is deleterious mutations which impair intelligence, impair the ability to fight disease and impair the development of body symmetry. The mean number of deleterious mutation in the genome is close to a genetic constant worldwide. Thus there is no meaningful genetic difference in intelligence, health or physical attractiveness between the races. But there are differences within a population as we can easily observe.

From the moment of conception when the zygote forms to our death, hopefully many years later, our body (soma) is asexual. Our cells divide by mitosis and accumulate mutations. Like all asexual beings our body will eventually die. The rate of somatic mutation therefore influences the rate at which we

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

grow old. But somatic mutation is not a universal constant and it is likely that improved living conditions in the Western World over the last 250 years will have caused a reduction compared with earlier times. That is probably one of the main reasons we are living longer. If the somatic mutation rate increases long term then the mean number of mutations in the genome increases slightly. Equally if the somatic mutation rate falls long term then the mean number of mutations in the genome falls slightly [22-26]. Thus the mean number of deleterious mutations will show minor variations between nations depending on their long term history. This steady rate of improvement however could change because the somatic mutation rate could rise with pollution, climate change, dietary changes etc.

Germs cause disease

In considering disease the following statement, in the form of a haiku, is a useful and practical rule:

Germs cause most disease

Genes act in complex networks

to prevent disease

This statement appears to put me firmly in the bio-medical camp, and this has become almost a term of abuse for those interested in psychosocial factors in disease. Furthermore it appears to contradict my assertion that several factors interact to cause disease. But read on.

There are very many diseases described in standard textbooks of medicine, but only a limited number of pathological processes that lead to disease. If there were 10 factors that cause disease but they only succeed when taken 3 at a time then there would be 720 different diseases. That is simplistic but it does illustrate the point that many diseases can arise from a limited number of causative factors if they interact to cause disease. There are a large number of bacterial, viral and parasitic pathogens. Thus it is likely that in practice there is at least one germ involved in the complex causative pathways leading to disease, and there is a considerable body of evidence pointing in that direction [28, 29].

Chronic inflammation caused by germs can be overt or covert. Dental caries and chronic periodontitis are examples of overt inflammation caused by pathogenic bacteria. The bacteria invade the dental pulp and the tissue immediately around the dentine and cementum. This causes local inflammation but the bacteria are also carried through the blood to distant sites and can cause covert inflammation elsewhere. We have come to realise in recent years just how important this process is in systemic disease. Culture free methods of bacterial identification using DNA sequencing have revealed dental pathogens at many sites and publications appear almost weekly from laboratories around the World linking dental infection to diseases such as atherosclerosis, Alzheimer's disease , type 2 diabetes and the complications of pregnancy amongst others [30-32].

Helicobacter pylori infection in the stomach causes gastritis, peptic ulceration and gastric adenocarcinoma. The bacteria are found on the surface of gastric epithelial cells but underneath the mucous layer therefore they are relatively protected from the stomach acid. They cause inflammation by damaging the cells in the gastric mucosa. *H. pylori* associated gastritis shows a social class gradient and is associated with atherosclerosis and its complications. Anybody who has suffered from indigestion will know that it affects mood and sense of well-being.

An example of covert infection is carriage of *Staphylococcus aureus* [33]. It is a skin commensal, but is also carried in the oropharynx and nasopharynx. *S. aureus* is a pathogen and invades between the squamous epithelial cells of the skin and oropharynx. All strains of *S. aureus* produce the exotoxin alpha haemolysin which is a perforin (these molecules punch holes in cell membranes and disturb the ionic balance leading to cell death). Some strains also produce pyrogenic exotoxins including toxic shock syndrome toxin (TSST) and a range of staphylococcal enterotoxins (SEs). The pyrogenic exotoxins are superantigens, they stimulate T cells to undergo clonal expansion. This leads to the secretion of cytokines including tumour necrosis factor (TNF) and produces an inflammatory response. At first sight it seems paradoxical that a bacterial pathogen should secrete a toxin to induce inflammation, as inflammation is designed to kill bacterial pathogens. But the superantigens stimulate a broad range of T cells non-specifically, so that the inflammatory response is not targeted at *S. aureus*. Thus the inflammation in this case causes maximal damage to host tissues and minimal damage to the bacteria. We all have circulating IgG antibodies to the staphylococcal exotoxins, indicating continual if not continuous exposure to this common organism throughout life [34,35]. Carriage increases following a viral upper respiratory tract infection [36,37].

Physiological stress reaction

The acute stress reaction is often termed "fight or flight" [38,39]. It is a complicated process, orchestrated by intercellular messengers. It involves the mobilisation of energy resources and is designed to prepare for intense physical activity [40]. Hypothalamic control centres release chemicals that stimulate hormone production by the anterior pituitary gland. These hormones in turn act on the adrenal gland which secretes a broad range of steroid hormones including glucocorticoids and mineralocorticoids. Hypothalamic centres also activate the sympathetic arm of the autonomic nervous system, leading to adrenalin release. The hormones interact to cause the release of glucose and fatty acids from storage. The enteric nervous system is involved and in turn hormones are released from the entero-endocrine cells in the gastro-intestinal tract. Many of the sensations we associate with acute stress are in fact visceral sensations mediated by the enteric nervous system. The acute stress reaction is a whole body reaction and depends on a flow of information between cells mediated by the intercellular messengers, the cytokines. There are so many cells, so many different molecules, so many different interactions that we will probably never know the full picture. But we can appreciate the general principles involved and realise that all other physiological processes must be closed down or the response will be less than optimal.

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

Lesser degrees of stress make us feel anxious. Consider a student preparing for an important examination. The student will feel anxious, and should do. Anxiety will encourage the student to work hard and forego other pleasures. But the student mustn't feel too anxious or it will interfere with thinking and prevent learning. The student will need a good night's sleep to prepare for work the next day. But sleep is also orchestrated by cytokines; therefore each day anxiety is switched on and each night it is switched off, or should be. But what will happen if this normal well balanced anxious response occurs in someone with chronic inflammation. Both processes cannot be optimal if they are using the same cytokines to play different tunes. If the chronic inflammation is sub-optimal there will be more tissue damage. If the anxiety response is sub-optimal there is a danger of it becoming pathological.

Bereavement is followed by a complex emotional response which can last weeks or months. It is characterised by extreme sadness but also other emotions such as guilt and anger. It is a whole body response with visceral sensations as well as cerebral changes. It is also a very complicated process as the individual gradually, over many days, comes to terms with the loss and slowly recovers and resumes their life. Divorce, unemployment, loss of one's house by flooding or fire can produce something similar. Complex, whole body responses organised by a flow of information between cells in which cytokines play their part. It is clear that these emotional states could become pathological if chronic inflammation occurs at the same time.

Sleep is a process which is essential for health, although for reasons which are not fully understood. The stages of sleep are co-ordinated by hypothalamic control centres and the secretion of cytokines plays a part [41]. Poor quality sleep is associated with a number of chronic disease states including atherosclerosis [42,43].

Pregnancy is another complex physiological state orchestrated by cytokines. There are a number of conditions in pregnancy which have never been fully understood. These include pre-eclampsia and stillbirth. They also include failure to progress in labour leading to Caesarean section, and other problems such as establishing lactation. Many women have chronic inflammation during pregnancy and it is interesting to speculate to what extent the normal physiological events of pregnancy are disturbed by a cacophony of cytokines.

Obesity

Gluttony and sloth are the cause of obesity. That, at least, is the impression one gets from comments and articles in the media and popular press. The scientific literature is more circumscribed, but the implication is clear that lifestyle choices involving too much food and too little exercise are the problem. Obesity is on the increase and therefore these moral failings must be more common. I doubt it.

Obesity is a failure of regulation; a failure to match calorie intake to calorie consumption over a long period of time. The difference between maintaining a healthy body weight and developing obesity is a very small daily excess of calorie intake over expenditure. The control of appetite is another complex physiological process in which cytokine secretion plays a part. There are anorexigenic and orexigenic control centres in the hypothalamus. Regulatory peptide hormones are secreted by entero-endocrine cells and circulate in the blood. Adipocytes secrete hormones which act as feedback systems to the hypothalamus. But if there is chronic inflammation, which is commonly found in obesity [44], then the process will be sub-optimal. Not gluttony and sloth; but an imperfect regulatory system.

Why is obesity on the increase? Indeed the term "epidemic of obesity" is commonly used. I suspect the clue is in the phrase; epidemics are due to germs. Let us reconsider *S. aureus.* Improved living conditions over the last 50 years are associated with increased hygiene. Daily baths with bactericidal soap wash off surface *Staphylococcus epidermidis*, which grows on the skin surface. This gives a competitive advantage to *S. aureus* which grows between the epithelial cells. This could be the reason for the epidemic of eczema, asthma, and hay fever as well as type 1 diabetes mellitus seen at the end of the last century [45]. *S. aureus* grows within the surface and derives its nutrients from the blood. Prolonged elevation of blood glucose would therefore give the bacteria a selective advantage. Bacteria have a generation time of 20 minutes and therefore evolve quickly. Exotoxins which specifically damage insulin secreting beta cells in the pancreas or interfere in other ways with insulin action would raise blood glucose and give *S. aureus* a selective advantage. Insulin is part of appetite control and therefore the epidemic of insulin resistance, obesity and type 2 diabetes mellitus could all be linked and explained by the evolution of selfish genes in *S. aureus* or related organisms. This is why I consider *S. aureus* a prime suspect for the linked conditions discussed in this paper.

Sepsis

Bacterial invasion of the blood stream is common, and may well occur on a daily basis [46]. The bacteria are quickly cleared in most cases by neutrophils in the post capillary venules of the lung and in the sinusoids of the spleen. But if the bacteria grow faster than they are removed septicaemia ensues and the patient is gravely ill. Damage arises due to the direct effects of toxins and other excretory products produced by the bacteria together with the aggressive immune response mounted by the host. The term sepsis has now replaced septicaemia in this situation. It emphasises the damaging effects of the immune response and directs attention to managing the physiological response as well as using antibiotics to kill the bacteria. Cytokine secretion is involved resetting the thermostat in the hypothalamus and causing the patient to feel ill [14]. In fact the patient feels so awful that they want to go to bed, switch out the light and be left alone. This in effect switches off all other responses and allows an optimal immune response. We cannot allow a cacophony when life is threatened.

Psychosocial causation and blame

Sociologists, epidemiologists and public health medics who have amassed the impressive body of evidence linking

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

psychosocial factors to both mental and physical disease have had to overcome a great deal of prejudice [1-7]. They have had to work hard to show that the factors are causative and not merely associations. They have the best possible motives, envisaging a world in which socio-economic progress leads to more equal societies and better health for all. But there is a danger in downplaying the role of germs and genes.

Those who have argued the case that environmental stress can cause disease are inclined to blame society, or those who run society, for creating inequality and impairing health. But that can morph, quite easily, into blaming those who are the victims of the stress. In recent years there has been an increased incidence of mental disease in young people. If we put germs and genes to one side the cause must be either increased stress or decreased ability to cope with the stress. The proponents of increased stress blame changes in the educational system or the advent of social media, but the case is far from convincing. Others will accuse the young of being weaker and less able to deal with life's problems, hence the pejorative term "the snowflake generation". Women in the late teenage years are particularly at risk of mental health problems. Does this make them the weaker sex? No, bring in the germs and genes, consider the interactions and banish the blame. I do not think it is a coincidence that the so called "snowflake generation" have suffered an epidemic of eczema, asthma, hay fever, type 1 diabetes mellitus and obesity. This is surely a change in bacterial flora due to improved hygiene.

The concept of blame is never far from the surface, particularly when dealing with disease we do not understand. In fact the oldest idea in medicine is linked to blame:

Sin causes disease

Piety for prevention

Penance is the cure

Nobody would defend this idea today, not explicitly, but it surfaces by implication in both the popular and the medical press. I have discussed the role of gluttony and sloth in relation to obesity above. It is too easy to blame the poor for failing to heed sound medical advice on diet and exercise. It is even worse to suggest, in patronising tones, that it's not their fault because they are not clever enough to follow the messages, or that they lack the strength of character to act appropriately. The stress only model of disease causation is not kind.

It is not long since sections of the psychiatric profession downplayed the role of genes in the pathogenesis of schizophrenia. There was more emphasis on the quality of the child's early environment and this led to the pernicious concept of the "schizophrenogenic mother". The article in the Lancet entitled "The death of the schizophrenogenic mother" by Anne Harrington is worth careful study [47]. The idea of a cold mother causing the disease is no longer accepted but it was widely accepted by medical experts at the time. Harrington states "Today, memories of that whole era make many people wince". Harrington goes on to state "They (the parents) discovered and built alliances with the biological wing of psychiatry, who told them that schizophrenia was a disease like any other, and no one's fault, least of all theirs". But then she goes on to say in accepting the biological role we must not forget the psychosocial and cultural aspects of the condition.

Discussion

Genes code for proteomic networks which counteract environmental threats to keep us safe and free of disease. But no system is perfect and disease, both mental and physical, will occur from time to time. The genetic and proteomic networks are complex and highly redundant and therefore failure is most likely when several pathogenic factors operate at the same time [21-26]. Pathogenic bacteria pose an existential threat [12]. Inflammation is the body's reaction to the threat; the response is designed to cause maximum damage to the bacteria with minimal damage to host tissue. In most cases it succeeds. The response involves the co-ordinated action of many cells throughout the body. Cytokines play a key role. These intercellular messengers have autocrine, paracrine and endocrine functions and orchestrate the response. They also show pleiotropy and synergy, so that the precise pattern of secretion determines the precision of the response. There are neutral genetic variants in cytokine regulation and the precise response will vary between individuals. It could be that the variation is advantageous in fighting some organisms but disadvantageous in fighting others. If there are heterozygous deleterious mutations in the genetic networks then the response could be sub-optimal, this is another aspect of individual variation [21]. There are physiological adaptive processes that prepare us to deal with the stresses and strains of everyday life. These are complex whole body responses co-ordinated by cytokines, like the inflammatory response they will show a degree of individual variation. Two patterns of cytokine secretion cannot run at the same time without major interference. Thus in fighting sepsis other adaptive responses are closed down. But there is a problem in dealing with chronic inflammation; life must go on and the cytokine patterns will interfere. The physical disease caused by chronic inflammation will be made worse, and the emotional state created by the adaptive physiological response could be converted into mental disease.

Overt and covert chronic inflammation induced by pathogenic bacteria is a risk factor for a range of diseases such as atherosclerosis and its complications, Alzheimer's disease, type 2 diabetes mellitus, obesity and depression [8-11]. The same conditions are more common in countries with health inequality and in people within a nation who are at the lower end of the socio-economic hierarchy [1-7]. The data on health inequality and position in the hierarchy has been gathered over many years. It represents a major contribution to understanding health and disease. Those involved have been keen to establish that psychosocial factors have a direct causative role in both mental and physical disease. I find the evidence and their arguments convincing. But they do tend to downplay the role of genes. One thing we have learnt over the last 50 years is that everything in biology is a combination of

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

genes and the environment. Position in the social hierarchy will be determined in part by genes, and the response to the position will be determined in part by genes. Furthermore we cannot understand mental and physical disease at a molecular level without studying the properties of genes, genetic networks and proteomic networks. Sociologists are suspicious of arguments based on genetics because of the terrible history of the eugenics movement. But in fact they have nothing to fear. Most genetic variation is due to neutral mutations. Individuals and races are different but equal. Deleterious mutations do interact synergistically to impair the performance of genetic networks. There is a Poisson distribution in zygotes and this creates inequality. But there can only be very small differences in the mean of the distribution between races. However there are differences within races and this might cause some people concern. I don't think it should because it is common knowledge that within a population our skills and talents vary.

I have argued previously that conditions such as anorexia nervosa, irritable bowel syndrome and chronic fatigue syndrome, which are more common in young women, are probably autoimmune diseases [48]. The autoantibodies arise as a result of molecular mimicry with bacteria of the body flora. But the antibodies will only be maintained if there is continuous exposure and this indicates bacteria growing within the epithelial surface, once again organisms such as *S. aureus* are the prime suspects.

The arguments presented in this article have clinical implications. In all patients with disease, mental or physical, the following questions should be posed:

1. Is their evidence of chronic inflammation?
2. If so are we able to recognise the cause?
3. Is it possible to reduce the inflammation, or better still prevent it in the first place?

To answer the first question we need to measure bio-markers of inflammation in blood or urine. It will be necessary to widen the range of tests that are currently available. Mass spectrometry is the method with most potential as once the bio-marker is identified tandem mass spectrometry offers a cheap, quick and efficient method of assay [29].

Lancaster University students have produced some evidence, in recent years, relevant to the second question [49-51]. *S. aureus* toxins are secreted into the blood and combine with anti-toxin antibody to form immune complexes. These complexes are too large to be passively filtered by the glomerulus but they do appear in the urine. The toxins cannot be measured using ELISA techniques because there is no free toxin, other than in infancy when the anti-toxin antibodies are low [37]. But the toxins can be recognised using polyacrylamide gel electrophoresis with immunostaining. It appears that the complexes dissociate in the gel to some extent and toxin is released. It is possible to measure IgG with ELISA and using a reverse ELISA to measure specific anti-toxin IgG. Using these techniques staphylococcal exotoxins have been found in a small proportion of infants, and in a larger proportion of adults with myocardial infarction and rheumatoid arthritis [50,51]. Thus it is possible that the cause of covert bacterial infection can be diagnosed using this approach. For a quicker and more practical assay system mass spectrometric analysis of urine for bacterial toxins should be developed.

The third question was answered by Metchnikoff over 100 years ago [52]. He advocated yoghurt as a health food. He was right, but for the wrong reasons [32, 53]. In this enlightened age we seem to be following the wrong reasons not the right answer. Metchnikoff thought that aging and disease was due to the absorption of bacterial toxins from the gut. He suggested that yoghurt would reduce bacterial fermentation in the gut and therefore reduce toxin absorption. But yoghurt has very little effect on the gut flora [53], indeed many lactose fermenting organisms are destroyed by gastric acid. Today there is a great deal of interest in the gut flora and suggestions that the composition influences a wide range of disease. There is also interest in the leaky bowel syndrome, with large molecules entering the blood. Not far from Metchnikoff's ideas. There is also considerable interest in probiotics, which are essentially modified yoghurt. They contain selected lactose fermenting bacilli in massively increased doses in an attempt to modify the gut flora; but it does not work [53]. However probiotics do have beneficial effects. The answer to the conundrum depends on position. The majority of bacteria in the colon are present in the lumen, separated from the colonic epithelium by a mucous layer from which they derive their nutrients. These bacteria do not cause disease. The bacteria that do cause disease are between the mucus and the epithelial cells. They damage tissue and are in contact with the blood from which they derive their nutrients. There are similar pathogenic bacteria on all epithelial sites in the body. Furthermore these pathogens are transferred by the blood between epithelial surfaces [53]. Ultimately bacteria enter the body by the nasopharynx and by the oral cavity. They grow in the oropharynx and spread to colonise other epithelial surfaces. Yoghurt (live, natural, no added sugar) contains lactose fermenting organisms that suppress the growth of pathogens in the oropharynx and ultimately create an optimal bacterial flora elsewhere.

My final haiku:

Keep fit and health

Drink a pint of milk a day

Eat lots of yoghurt.

References

1. Marmot MG (2004) Status Syndrome: how your social standing directly affects your health and life expectancy. Bloomsbury Publishing Plc, Soho, London, UK.
2. Morris JA (1999) Information and redundancy: key concepts in understanding the genetic control of health and intelligence. Medical Hypotheses 53: 118–123. Link: https://goo.gl/kDU1r9
3. Ferrie JE, Shipley M, Stansfield S, Marmot MG (2002) Effects of chronic job insecurity and change in job security on self-reported health, minor psychiatric morbidity, physiological measures and health related behaviours in British civil servants in: The Whitehall II study. Journal of Epidemiology and Community Health 56: 450–454. Link: https://goo.gl/4V3kGt

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

4. Marmot MG, Bobak M (2000) International comparators and poverty and health in Europe. British Medical Journal 321: 1124–28. Link: https://goo.gl/1xPYQS

5. Van Poppel F, Joung I (2001) Long term trends in marital status mortality differences in the Netherlands, 1850 – 1970. Journal of Biosocial Science 33: 279–303. Link: https://goo.gl/25FwUy

6. Berkman LF, Glass T (2000) Social integration, social networks, social support and health. In Social Epidemiology, editors L F Berkman and I Kawachi, Oxford University Press, Oxford, UK. Link: https://goo.gl/u7eHp7

7. Wilkinson RG, Pickett KE (2009) The Spirit Level: why equality is better for everyone. Penguin Books, London, UK.

8. Libby P (2002) Inflammation in atherosclerosis. Nature 420: 868 – 874.

9. Almond M (2013) Depression and inflammation: examining the link. Current Psychiatry 12: 24–32. Link: https://goo.gl/oqZHC6

10. Zunszain P, Hepgul N, Pariante CM (2013) Inflammation and Depression. Curr Topics Behav Neurosci 14: 135–151.

11. Monteiro R, Azevedo I (2010) Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm. Link: https://goo.gl/fdjLMb

12. Kumar P, Clark M (2012) Clinical Medicine. 8th Edition, Saunders Elsevier, London, UK.

13. Nettleton S (2006) The Sociology of Health and Illness. 2nd Edition, Polity Press, Cambridge, UK.

14. Locksley RM, Killeen M, Lenardo MJ (2001) The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell 104: 487–501. Link: https://goo.gl/yejg2W

15. Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, Hermann N (2010) A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 68: 930–941. Link: https://goo.gl/8Ph8bj

16. Dowlati Y, Hermann N, Swardfager W, Liu H, Sham L, Reim EK et al. (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67: 446–457. Link: https://goo.gl/UaYVGb

17. Bastard J, Jardel C, Delattre J, Hainque B (1999) Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentration in obese subjects. Circulation 99: 2219–2222.

18. Cohen S, Doyle WJ, Skoner DP (1999) Psychological stress, cytokine production and severity of upper respiratory illness. Psychosomatic medicine 61: 175–180. Link: https://goo.gl/9oW3oD

19. Benedict C, Scheller J, Rose-John S, Born J, Marshall L (2009) Enhancing influence of intranasal interkeukin-6 on slow-wave activity and memory consolidation during sleep. FASEB Journal 23: 3629–3636. Link: https://goo.gl/NwnPe9

20. Petersen AM, Pederson BK (2005) The anti-inflammatory effect of exercise. Journal of Applied Physiology 98: 1154–1162.

21. Morris JA (2015) The genomic load of deleterious mutations: relevance to death in infancy and childhood. Frontiers in Immunology 6: 1–8. Link: https://goo.gl/T9HkoR

22. Morris JA (1997) Genetic control of redundant systems. Medical Hypotheses 49: 159–164.

23. Morris JA (2001) Information theory: a guide in the investigation of disease. J. Biosci 26: 15–23. Link: https://goo.gl/KCmCHZ

24. Morris RD, Morris KL, Morris JA (2002) The mathematical basis of sexual attraction. Medical Hypotheses 59: 475–481. Link: https://goo.gl/WY5TgR

25. Morris JA, Morris RD (2003) The conservation of redundancy in genetic systems: effects of sexual and asexual reproduction. J. Biosci 28: 671–681. Link: https://goo.gl/5u9jBk

26. Morris JA (2005) Synergistic interaction of heterozygous deletions impairs performance and confers susceptibility to disease at all ages. Medical Hypotheses 65: 483–493. Link: https://goo.gl/v1Xzvg

27. Nei M (1987) Molecular Evolutionary Genetics. Columbia University Press, New York.

28. Morris JA, Harrison LM, Lauder RM, Telford DR, Neary R (2012) Low dose, early microbial exposure will minimize the risk of microbial disease. Medical Hypotheses 79: 630–634. Link: https://goo.gl/n6nrhT

29. Morris JA (2016) Re-discovering the germ theory of disease: a major role for proteomics. Journal of Proteomics & Bioinformatics 9: 84–86. Link: https://goo.gl/4HHqvi

30. Li X, Koltveit KM, Olsen I (2000) Systemic disease caused by oral infection. Clin Microbiol Rev 13: 547–558. Link: https://goo.gl/JF89VL

31. Babu NC, Gomes AJ (2011) Systemic manifestations of oral diseases. J Oral Maxillofac Pathol 15: 144–147.

32. Gao L, Xu T, Huang G, Jiang S, Gu Y, et al. (2018) Oral microbiomes: more and more importance in oral cavity and whole body. Protein & Cell 9: 488–500. Link: https://goo.gl/eD4BS6

33. Morris JA (2017) Staphylococcus aureus bacteraemia: a hidden factor in the pathogenesis of human disease. JSM Microbiology 5: 1037–1039.

34. Harrison LM, Morris JA, Bishop LA, Lauder RM, Taylor CAM, et al. (2004) Telford DR. Detection of specific antibodies in cord blood, infant and maternal saliva and breast milk to staphylococcal toxins implicated in sudden infant death syndrome (SIDS). FEMS Immunology and Medical Microbiology 42: 94–104. Link: https://goo.gl/xki8YE

35. Harrison LM, Morris JA, Lauder RM, Telford DR (2008) The effects of Staphylococcus aureus carriage in late pregnancy on antibody levels to staphylococcal toxins in cord blood and breast milk. FEMS Immunology and Medical Microbiology 54: 137–143. Link: https://goo.gl/csLzV8

36. Harrison LM, Morris JA, Telford DR, Brown SM, Jones K (1999) The nasopharyngeal bacterial flora in infancy: effects of age, gender, season, viral upper respiratory infection and sleeping position. FEMS Immunology and Medical Microbiology 25: 19–28. Link: https://goo.gl/J4oNVJ

37. Harrison LM, Morris JA, Lauder RM, Telford DR (2009) Staphylococcal pyrogenic toxins in infant urine samples: a possible marker of transient bacteraemia. Journal of Clinical Pathology 62: 735–738. Link: https://goo.gl/UJ7BCe

38. Selye H (1956) The Stress of Life. McGraw-Hill, New York, USA.

39. Sapolsky RM, Romero M, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory and preparative actions. Endocrine Reviews 21: 55–89. Link: https://goo.gl/LEYZAm

40. Elenkov IJ, Chrousos GP (2002) Stress hormones, pro-inflammatory and anti-inflammatory cytokines and autoimmunity. Ann N Y Acad Sci 966: 290–303. Link: https://goo.gl/f9W8yN

41. Krueger JM (2008) The role of cytokines in sleep regulation. Current Pharm Des 14: 3408–3416. Link: https://goo.gl/p3KfWP

42. Nagai M, Hoshide S, Kario K (2010) Sleep duration as a risk factor for cardiovascular disease –a review of the recent literature. Current Cardiology Reviews 6: 54–61. Link: https://goo.gl/iXj45h

43. Kapsimalis F, Basta M, Varouchakis G, Gourgoulianis K, Vgontzas A, et al. (2008) Cytokines and pathological sleep. Sleep Medicine 9: 603–614.

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034

44. Zeyda M, Stulnig TM (2009) Obesity, inflammation and insulin resistance. Gerontology 55: 379–386.

45. Marshall AL, Chetwynd A, Morris JA, Placzek M, Smith C, et al. (2004) Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria. Diabetic Medicine 21: 1035–1040. Link: https://goo.gl/qvrVa6

46. Morris JA, Harrison LM, Biswas J, Telford DR (2007) Transient bacteraemia: a possible cause of sudden life threatening events. Medical Hypotheses 69: 1032–1039. Link: https://goo.gl/RfRpZK

47. Harrington A (2012) The fall of the schizophrenogenic mother. Lancet 379: 1292–1293.

48. Morris JA, Broughton SJ, Wessels Q (2016) Microbes, molecular mimicry and molecules of mood and motivation. Medical Hypotheses 87: 40–43. Link: https://goo.gl/Su9Rs1

49. Price FS (2013) Analysis of urine as a marker of Staphylococcus aureus bacteraemia during intensive care. MSc thesis, Lancaster University.

50. Bull KL (2014) Analysis of urine for Staphylococcus aureus toxin alpha haemolysin immunoglobulin as markers of infection. MSc thesis, Lancaster University.

51. Grace L (2016) Detection of staphylococcal enterotoxins in patients with rheumatoid arthritis. PhD thesis, Lancaster University. Link: http://eprints.lancs.ac.uk/83030/

52. Metchnikoff E (1908) The prolongation of life. New York; Putnam & Sons.

53. Morris JA (2018) Optimise the microbial flora with milk and yoghurt to prevent disease. Medical Hypotheses 114: 13–17. Link: https://goo.gl/a8Ahjn

Citation: Morris JA (2018) A cacophony of cytokines explains the biopsychosocial interaction model of mental and physical disease. Arch Depress Anxiety 4(2): 056-064. DOI: http://doi.org/10.17352/2455-5460.000034