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Optimise the microbial flora with milk and yoghurt to prevent disease

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ABSTRACT

Pathogenic bacteria, which are temporary or permanent members of our microbial flora, cause or contribute to a wide range of human disease at all ages. Conditions include Alzheimer's disease, atherosclerosis, diabetes mellitus, obesity, cancer, autoimmunity and psychosis, amongst others. The mechanism of damage is inflammation which can be chronic or acute. An optimal microbial flora includes a wide range of pathogenic bacteria in low dose. This allows specific immunity to be developed and maintained with minimal inflammatory damage. Human milk has evolved to deliver an optimal microbial flora to the infant. Cow's milk has the potential, following appropriate fortification, to maintain an optimal human microbial flora throughout life. Yoghurt is a fermented milk product in which bacteria normally present in milk convert sugars to lactic acid. The acid suppresses the growth of pathogens in the oral cavity, oropharynx and oesophagus. Thus yoghurt can restore an optimal flora in these regions in the short term. Since bacteria are transported between epithelial surfaces, yoghurt will also optimise the flora elsewhere. The judicious use of milk and yogurt could prevent a high proportion of human disease.

Introduction

The hypothesis that low dose, early, mucosal exposure to pathogenic bacteria will reduce the frequency of microbial disease has been published previously [1]. The concept is based on the observation that the clinical severity of disease caused by bacteria and viruses is increased if first exposure is delayed beyond childhood, and if the infecting dose is high [2–4]. Furthermore the mucosal surfaces of the enteric tract, in particular, are richly endowed with lymphatic tissue early in life and the information processing capacity to generate an effective immune response is optimal at this time. The hypothesis also included the prediction that in the 21st century we will re-discover the germ theory of disease. That germs cause most disease and genes act in complex networks to prevent disease. The interaction between germs and genes leading to, not only the range of infections described in standard textbooks, but also atherosclerosis, Alzheimer's disease, carcinoma, diabetes mellitus, depression, psychosis, autoimmunity and many more. In fact the full range of human disease except trauma. This bold assertion was supported by evidence at the time of publication [4–10] and additional evidence has been gathered since publication [11,12].

In order to prevent disease we envisaged the development of an enteric coated pill containing a mixture of commensal and pathogenic bacteria [1]. The pill would be taken by mouth and the bacteria would be released in the small intestine and would eventually populate the colon. The total dose of bacteria would not be high, but the major component would be commensals and there would only be a small dose of pathogens. The pill would be precisely formulated and varied from day to day or week to week so that infants would meet all the common pathogens in the first year of life. The pill would then be continued throughout life and formulated to maintain an optimal commensal flora and a wide range of pathogens. The commensals would keep the pathogens in check and the presence of pathogens would maintain immunity. In addition to the enteric coated pill we envisaged that nasal sprays of low doses of epidemic viruses might be required from time to time. Furthermore it might be necessary to use lotions and creams containing commensal skin bacteria to establish and maintain an optimal skin flora. This is all very involved but worthwhile if it were to prevent disease and prolong active life.

A point we failed to make in the original publication is as follows: if low dose early mucosal exposure is an effective way of reducing disease then surely a mechanism to achieve this goal would have evolved naturally. It has and the medium is milk. Mammalian milk, including human milk, contains bacteria [13–18]. These are not contaminants. They are selected from other epithelial surfaces and carried through the blood to be actively secreted into milk. The composition of the bacterial flora of human milk varies between individuals, by geography and through lactation. It is also early days in the analysis and the methods are still in development but it appears that the majority of bacteria are commensals. They include the lactose fermenting bacteria which are used to make natural yoghurt (lactobacilli, bifidobacteria and lactose fermenting streptococci). But in addition to the commensals there are

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low doses of pathogens. Thus it appears that milk and yoghurt have the potential to achieve our aim of preventing disease by developing an optimal microbial flora.

The microbial flora

There are of the order of 10^{15} bacterial cells on or within the surface of the body [19]. The majority resides in the colon, but there are bacteria on every epithelial surface. The concept of on the surface is obvious and it applies to all commensal bacteria. But there are some bacteria which grow within the surface [12]. These include pathogens such as *Staphylocccus aureus,* which can grow on the keratin surface of the skin, but can also grow between the squamous epithelial cells of the skin. *S. aureus* also grows within the skin adnexal glands (eccrine, sebaceous and apocrine). Once again it can be on the surface or between the epithelial cells and therefore within the surface. Bacteria within the surface are in direct continuity with the systemic circulation and can induce inflammation. This is one way in which pathogens can cause chronic low grade damage over many years contributing to degenerative disease [12].

The vagina is lined by non keratinizing stratified squamous epithelium. The surface cells contain glycogen which is metabolized by surface lactobacilli to lactic acid. The acid pH inhibits the growth of pathogenic staphylococci and streptococci. Thus an optimal commensal flora protects the vagina from infection. This is the simplest and best characterized example of the interaction of commensal and pathogenic bacteria. In the colon the flora is much more complicated with up to 800 different species [19]. But the principle of a stable ecological system with commensal species dominating and inhibiting the growth of pathogens still applies. The pathogens maintain immunity but only if they are in direct contact with the systemic circulation and therefore growth within the surface might be more extensive than currently known. Pathogens can also invade the blood stream. In most cases they are rapidly cleared by neutrophils in the post capillary venules of the lung or by phagocytes in the sinusoids of the spleen [20]. These episodes of transient bacteraemia are clinically silent. But if the bacteria grow more quickly than they are removed, septicaemia occurs and provokes clinically overt sepsis.

Bacteria enter the body through the oral cavity in food and drink. They also enter the upper respiratory tract in inhaled air, and these bacteria are then carried into the oropharynx by nasociliary action. The lining of the oral cavity, oropharynx and oesophagus is non keratinized squamous epithelium, as in the vagina. Bacteria can grow on and within this epithelium. There are also deep crypts within the tonsils within which bacteria can grow. Many bacteria are destroyed by stomach acid, but the upper small intestine contains bacteria and they increase in numbers as they transit to the colon. Bacteria can also alight on the external skin surface and extend into the skin adnexal glands. There is also transit of bacteria through the blood from one epithelial lined surface to another. This certainly occurs in the case of breast milk. But the extent to which the ducts of the non lactating breast, the pancreas and prostate are colonized by direct extension from the surface or from the blood is unclear.

Probiotics and yoghurt

Metchnikoff, the Nobel laureate who discovered phagocytosis, first popularized the consumption of yoghurt as a health food [21]. He studied the distribution of centenarians in Europe and noted there were more in Greece and the Balkans than in Northern Europe. Bulgaria in particular was noted for a long lived healthy population of peasants whose diet included yoghurt. He postulated that natural fermentation of milk, producing an acid product, would suppress fermentation by bacteria in the colon. The absorption of toxic products from the colon would, therefore, be reduced and their harmful effects in causing disease and aging would be ameliorated. But in many ways yoghurt, as a health food, has been a disappointment. Yoghurt consumption has a minimal effect on the composition of the bacterial flora in the colon [22]. Furthermore, the idea, that absorption of toxic products from the colon is a major cause of disease, is no longer accepted. The bacteria used to produce yoghurt, however, are the basis of probiotic therapies and these have been extensively investigated [22,23]. It is difficult to summarise the results because the trials use different combinations of bacteria and varying doses in a wide range of conditions. In general there are small positive effects in most trials.

I believe it is time to re-evaluate the role of natural yoghurt [12]. It contains far fewer bacteria than the therapeutic probiotic preparations but it generates an acid environment which is essential for suppressing the growth of pathogenic bacteria. This is certainly the situation in the vagina and probably will apply to the oral cavity, oropharynx and oesophagus which have a similar lining. Daily consumption of yoghurt is likely to change the flora around the teeth and in the tonsillar crypts in the short term. It will also determine the flora in the small intestine and perhaps influence the resident bacteria at other sites by blood borne transfer from the oral cavity. It won't affect the colonic flora in the short term but it could in the longer term.

Hypotheses and predictions

Chronic inflammation is a risk factor for a range of diseases of middle and later life, such as atherosclerosis [6], Alzheimer's disease [5], type 2 diabetes mellitus [24], endogenous depression [25,26] and obesity [27]. Dental caries and chronic periodontitis are amongst the commonest inflammatory conditions and they are associated with the aforementioned diseases [28]. Dental infections are caused by a wide range of pathogenic bacteria, including pathogenic streptococci such as *Streptococcus mutans.* Pathogenic staphylococci and streptococci also grow in the tonsillar crypts and within the squamous epithelium of the oropharynx. The inflammatory response is designed to specifically destroy pathogenic bacteria with as little damage to the host as possible. But the cytokine molecules released during inflammation are designed to damage all biological material and therefore some damage to host tissues is inevitable [12]. Systemic release of cytokines will therefore damage endothelial cells, hence atherosclerosis, and perhaps directly damage neurons, hence Alzheimer's disease.

Staphylococcus aureus grows within the surface epithelium and is therefore in direct contact with the immune system. Many strains of this organism secrete pyrogenic toxins which act as superantigens. They directly stimulate T cells and lead to a non-targeted inflammatory response. This means maximal damage to the host with minimal damage to the bacteria [12]. We all have antibodies to these superantigens and therefore we all must be frequently exposed [29–31]. This makes *S. aureus* carriage a prime candidate for a pathogenic role in the above conditions. The secretion of pyrogenic toxins into the blood leads to the formation of immune complexes with their specific anti-toxin IgG antibody. These complexes are secreted in the urine [32,33] . This is an active process as the complexes are far too large to be passively filtered by the glomeruli. Thus measurement of urinary IgG and identification of the toxins is theoretically possible.

The experimental approach envisaged is an observational study of patients in the early stages of the above conditions. The patients would consume yoghurt daily for several months and the effects on the microbial flora of the oral cavity, inflammatory markers, urinary IgG and the progression of the disease would be assessed. It is likely that yoghurt will take time to have an effect on the flora, particularly around the teeth and in the tonsillar crypts. Furthermore success in the case of Alzheimer's disease and atherosclerosis would be slowing progression of the condition rather then any marked improvement. The response in endogenous depression might be more gratifying and perhaps should be tried first.

The winter months in the UK bring an increased number of viral respiratory tract infections followed by an increase in the number of