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Iron, infection and the evolutionary ecology of heart disease

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Summary Levels of iron intake and stored iron have been implicated as risk factors for coronary heart disease. More recently, considerable interest has centered on the role of a variety of infectious pathogens, particulary bacterial pathogens, in the development of artherosclerosis and heart disease. The mechanism whereby elevated iron levels increase the risk of coronary heart disease is not well understood. Here it is proposed that the influence of iron levels on the persistence, pervasiveness and intensity of bacterial infections may play an important role in the development of coronary heart disease. © 2001 Harcourt Publishers Ltd

Recently there has been considerable interest in the relevance of evolutionary biology to disease and to medical practice (1,2). Williams and Nesse (3) stimulated this interest with a classic paper on the Dawn of Darwinian Medicine. They discussed several aspects of disease which they believed might benefit from an evolutionary perspective. One of these was the interaction between parasites and human hosts. Another was the effect of the evolutionary novelty of current environments on human health and disease. Recent developments in the medical literature suggest that a potential interaction between these two things may have contributed to the increased incidence of heart disease in the modern world.

Heart disease is the leading cause of mortality in the Western world (4). In particular, artherosclerosis is a major killer in the USA and Europe, especially among men. Risk factors for ischaemic heart disease are diverse (5). Recently, considerable attention has been focused on the hypothesis that elevated iron levels may play a role in the development of coronary heart disease (*6*). Sullivan (*7*) proposed that high levels of iron may contribute to heart disease, and that iron depletion could serve a protective function. He argued that differences in the incidence of heart disease between men and women might be explained by differences in the levels of stored iron between the sexes. Premenopausal women in affluent Western societies have a low rate of ischemic heart disease compared to men, but this difference ends with menopause (*8*). Sullivan (*7*) proposed that the lower incidence of coronary heart disease in premenopausal women is related to the periodic shedding of blood (and associated iron) during menstruation.

Since then, evidence has accumulated that high iron levels may be a significant risk factor in the development of heart disease and for the risk of mortality from heart attack. A variety of population studies have found associations between iron levels and heart disease. Salonen et al. (*9*) found that a high level of stored iron, assessed by elevated serum ferritin concentration, was a significant risk factor for myocardial infarction in a study of 1931 randomly selected Finnish men. Morrison et al. (10) found an association between serum iron levels and risk of fatal acute myocardial infarction in a large cohort of Canadian men and women. High iron levels have also been found to be a significant risk factor in large population studies in Austria (5) and the Netherlands (11).

Strong support for the relationship between iron levels and increased risk of death from coronary heart disease has been provided by studies of women who have a hereditary form of hemochromatosis (caused by a mutation of the HFE gene) which causes serum ferritin levels to be higher than normal. A significant association between this mutation and death from cardiovascular

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disease was found in a sample of 12 239 postmenopausal women (12). Studies on blood donors have indicated that blood donation (and the associated loss of iron) significantly reduces the risk of death from cardiovascular disease in US (13) and Finnish (14) men. Studies of animal models provide experimental evidence that high iron levels are associated with atherosclerosis (15). Not all studies have found a significant association between iron levels and coronary heart disease (16), but a significant amount of evidence in favor of the hypothesis has accumulated.

The mechanisms by which elevated iron levels might cause increased risk of heart disease are not well understood (17). One possibility is that iron participates as a catalyst in free-radical reactions that cause lipid peroxidation (6). However, the hypothesis that free-radical catalyzed oxidation causes atherosclerosis has come under criticism recently by Stebhens (18), who argued that it fails to explain several important aspects of coronary heart disease. Another possibility is that iron may influence the development of coronary heart disease through the interaction of iron levels in the body with levels of parasitic infection.

Recently the hypothesis that bacterial infections may be causative agents in the development of coronary heart disease has received considerable attention (19). A number of population studies have found an association between common bacterial pathogens, such as *Chlamydia pneumoniae* and *Helicobacter pylori*, and coronary heart disease. Saikku et al. (20) found a significant association between infection by *C. pneumoniae* and incidence of coronary heart disease and myocardial infarction. This same association has since been found in several different populations (21,22). Mattila et al. (23) found an association between periodontal disease (with its associated bacterial infections) and the incidence of myocardial infarctions. In a longterm study of 9760 dental patients, DeStefano et al. (24) found that patients with periodontal disease had a significantly higher risk of coronary heart disease relative to patients without such disease.

Other studies have shown that a variety of bacterial pathogens can and do infect vascular tissue. Dorn et al. (4) found that three putative periodontal pathogens will readily invade human coronary artery cells in cell culture. Shor et al. (25) found that *C. pnuemoniae* DNA sequences are present in vascular artherosclerotic lesions, but not in normal vascular tissue. Maass et al. (26) found that viable *C. pneumoniae* are commonly associated with vascular tissue in patients with coronary heart disease.

Studies using animal models have also provided evidence for a connection between bacterial infections and coronary heart disease. Fong et al. (27) showed that innoculating the respiratory tract of rabbits with *C. pneumoniae* caused a significant proportion of the animals to develop artherosclerosis over a period of several months, relative to controls innoculated with the carrier only or with an alternative type of bacteria. Other forms of *Chlamydia* have also been found to produce artherosclerosis in animal models (28).

There is also considerable evidence that the use of antibiotics effective against bacterial parasites can ameliorate the risk of heart disease. In a population-based case-control analysis, Meier et al. (29) found that previous use of certain antibiotics active against bacteria is associated with a lower risk of myocardial infarction relative to individuals who did not use antibiotics. Intervention trials using randomized double blind administration of antibiotics have demonstrated a significant effect on the risk of myocardial infarction, and further support the hypothesis of an association between bacterial infection and heart disease (30,31).

In their overview of Darwinian Medicine, Williams and Nesse (3) argued that evolutionary explanations are particularly relevant to four aspects of disease: parasitic infections, mechanical damage, genetic diseases, and diseases that result from rapid environmental change due to technological and cultural change. In discussing the importance of distinguishing between symptoms that benefit the parasite and those that benefit the host, Williams and Nesse (3) noted that an important defense mechanism against bacterial infections is the sequestration of iron. This statement was made in reference to the work of Weinberg (32,33) who has elucidated the mechanisms of sequestration, and emphasized the importance of this process in depriving infectious agents of a nutrient that is critical to their growth and survival within the body of the host. A wide variety of infectious agents are stimulated to grow in the body fluids, cells, tissues and intact hosts in the presence of excess iron (34). Some bacterial pathogens even manipulate their hosts to induce the elevation of iron levels in host cells by causing the upregulation of the expression of transferrin receptor mRNA (35).

If iron is a critical element for bacterial parasites, and bacterial infections are potentially damaging to heart tissue, then elevated iron levels may contribute to the pervasiveness and population densities of potentially damaging parasitic infections. One of the main infectious agents implicated in heart disease is *C. pneumoniae*, and the growth and prevalence of this strain of bacteria is influenced by the presence of excess iron in host tissues (36).

The hypothesis that elevated levels of iron interact with the presence of bacterial pathogens to enhance the probability of coronary heart disease could also explain a puzzling feature of the relationship between infectious disease and heart disease. In poor countries with marginal industrial and technological infrastructures,

infectious diseases tend to be prevalent, but the incidence of coronary heart disease is typically low, relative to wealthier, more industrialized nations (37). If excess iron is a key element in the development of artherosclerosis, then the low incidence of heart disease in poor nations could be related to a relatively low intake of this element (38).

This hypothesis makes a connection between the association of elevated iron levels in the blood and the effect of parasitic infections on coronary heart disease. It also connects two of the factors discussed by Williams and Nesse (3): parasitic infections and environmental novelty. The evolutionarily novel availability of previously scarce resources such as fat and sugar may contribute to many of the diseases of civilization (3). Supplementation with various micronutrients, such as vitamins and minerals, has been promoted to replace nutrients that are removed from foods by processes involved in the large scale agricultural food production, transport and storage that characterizes the industrialized nations. It is ironic that the addition of excessive amounts of micronutrients, such as iron, may have unintended interactions with other causes of disease, such as bacterial infection. Humans, along with almost all other organisms in this planet, are participants in never-ending arms races with a plethora of coevolving parasites (39). There is a delicate balance between shoring up our own defenses and unwittingly providing ammunition for the enemy. In this view, the evolutionary ecology of heart disease may (in part) be seen as a delicate web of life-history tradeoffs, in which unilaterally increasing the supply of important nutrients to one side (i.e. the human body) may inadvertantly give an advantage to the enemy in the arms race (i.e. bacterial pathogens).

The hypothesis of an interaction between iron and infection in the development of coronary heart disease could be tested in animal models using a two-way crossed design with both iron supplementation and bacterial pathogen innoculation as experimental factors.

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