Debate on the paper by Maria Inês Reinert Azambuja & Bruce B. Duncan

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The article by Azambuja & Duncan is a stimulus for rethinking cardiovascular disease (CVD) epidemiology. As the authors acknowledged, many individuals with atherosclerosis, a major component of the causal pathway for CVD, lack identifiable traditional risk factors. This is a reasonable argument for searching for other potential etiologies, and a potential infectious risk factor has recently gained strong support.

The authors presented ecological evidence of an association between coronary heart disease mortality and influenza infection. If true, prevention of CVD could be substantially changed. However, as the authors stated, ecological analysis may have many flaws and epidemiological data lack robustness due to the many possible confounding factors. Thus, socioeconomic level is an important risk factor for CVD and also a strong potential confounder for the association between coronary heart disease mortality and influenza infection. Interestingly, as mentioned by Azambuja & Duncan, the high mortality rate from influenza in whites as compared to blacks suggests that socioeconomic confounding factors are not the main explanation for the association. On the other hand, age-adjusted mortality rates from coronary heart disease (CHD) in Minnesota for the years 1960-1978 showed that influenza and pneumonia death rates were unrelated to CHD trends (Gillum et al., 1984).

Another important confounding factor is smoking. Cigarette smoking is associated with differences in the incidence and severity of a broad array of respiratory illnesses, ranging from the common cold to cancer. In addition, while the general effect of smoking on respiratory diseases is adverse, in the case of hypersensitivity pneumonitis, smoking may actually be associated with a decrease in the incidence. Therefore, smoking can modify the association between CHD and influenza infection in a complex way.

It should also be noted that CHD is not the first condition to be described by a multifactorial design that includes infection as one of the important factors. Other non-communicable chronic conditions such as hepatic cancer, dyspepsia, and gastric cancer have also been associated with specific microorganisms. In relation to cardiovascular diseases, several studies have shown *Chlamydia pneumoniae*, *Heliobacter pylori*, and herpes simplex virus infections as risk factors for the atherogenic process. Nevertheless, a role for microorganisms in the etiology of CHD has gained support by the understanding that the final occlusion of the vessel in atherosclerosis results from a combined effect of the plaque and inflammatory process, when infection of the endothelial cells may play a decisive role. According to these findings, new risk factors adding to the predictive value of old ones such as high body mass index, smoking, serum lipids, and sedentary life style, are markers of the inflammatory process. Thus, C-reactive protein, a non-specific inflammation marker, is an excellent predictor of CHD and stroke.

Infection can also be considered a potential effect modifier of traditional CVD risk. Azambuja & Duncan discuss that the risk of CVD associated with fat/cholesterol intake may depend on prior influenza infection. Other findings have supported this hypothesis, and it has been suggested that physical activity, smoking, and lipids can modulate immune status and thus susceptibility to infections that are potentially important in atherogenesis (O'Connor, 2001).

The importance of this nascent field associating chronic diseases with infections was recently highlighted in a symposium that critically examined the role of infectious agents in ulcer, cancer, obesity, atherosclerosis, and diabetes (Dhurandhar, 2001). However, to establish a causal link between infection and any chronic disease is a difficult task, because the presence of microorganisms may be undetectable by the time the disease is diagnosed, and the presence of antibodies does not establish a causal relationship. These methodological constraints were overcame in the case of the association between gastric cancer and *H. pylori*. The association was first suggested in the 1980s and is now well accepted, allowing the prevention of this chronic disease by antimicrobial agents. A similar therapeutic approach has been discussed for CVD prevention, but an inappropriate therapy for such highly prevalent diseases could lead to resistance in both targeted and non-targeted organisms (O'Connor et al., 2001). In conclusion, many new preventive strategies and treatment options could be developed if this infectious pathway proves to be true for CVD.

DHURANDHAR, N. V., 2001. Chronic nutritional diseases of infectious origin: An assessment of a

nascent field. *Journal of Nutrition*, 131:2787-2810.
GILLUM, R. F.; JACOBS Jr., D. R.; LUEPKER, R. V.; PRINEAS, R. J.; HANNAN, P.; BAXTER, J.; GOMEZ-MARIN, O.; KOTTKE, T. E. & BLACKBURN, H., 1984. Cardiovascular mortality trends in Minnesota, 1960-1978. The Minnesota Heart Survey. *Journal of Chronic Diseases*, 37:301-309.
O'CONNOR, S.; TAYLOR, C.; CAMPBELL, L. A.; EPSTEIN, S. & LIBBY, P., 2001. Potential infectious etiologies of atherosclerosis: A multifactorial perspective. *Emerging Infectious Disease*, 7:780-788.

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Association between influenza and coronary heart disease: how convincing is available evidence?

The first report of a temporal association between influenza epidemics and mortality from coronary heart disease (CHD) was published by British epidemiologists in 1978. However, the authors state that they "*could not hope to provide clear-cut evidence of a causal relationship, nor the sequence of the two conditions*" from their data (Bainton et al., 1978:238-239).

The old hypothesis that chronic inflammation and infection are involved in the pathogenesis of atherosclerosis and CHD has been revived in the 1980s and 1990s (Javier Nieto, 1998). Much of the current research has been stimulated by the finding that CHD patients more frequently present antibodies to pathogens such as *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori*, as well as serum markers of inflammation, than population controls (Muhlestein, 2001). Moreover, *Chlamydia* is frequently detected in atherosclerotic plaques of coronary arteries in CHD patients and induces atherosclerotic lesions in experimental models (Grayston, 2000). Evidence suggesting that this pathogen is involved in all stages of CHD is available. Chronic *Chlamydia* infections are associated with lymphoproliferative inflammatory responses characterizing the early stages of atherosclerosis, with changes in the lipid metabolism that may accelerate plaque formation, and with intra-plaque inflammation leading to plaque rupture and artery occlusion.

If a strong and plausible association between *Chlamydia* infection and CHD has been found, why should we look for other infections putatively associated with CHD? For at least two reasons: (a) when a careful adjustment for potential confounders (including socioeconomic factors) is made, the statistical association between the presence of anti-*Chlamydia* antibodies and CHD becomes rather weak (Danesh et al., 2000b), and (b) the positive association between low-grade chronic inflammation and CHD is unrelated to the presence of antibodies to *Chlamydia* or *H. pylori* (Danesh et al., 2000a). These findings suggest that other pathogens to which patients have been exposed, or their "pathogen burden", may be associated with chronic inflammation and CHD (Javier Nieto, 1998; Zhu et al., 2001). Here Azambuja & Duncan report an association between prior exposure to influenza and CHD mortality in the United States.

The ecological design represents a major limitation of the study by Azambuja & Duncan, since we cannot compare the exposure to several known risk factors for CHD and respiratory infections (including socioeconomic variables) in affected and non-affected subjects. The specificity (in the sense used by Bradford Hill) of a putative causal association between H1N1 influenza virus infection and CHD is disputable. We can hypothesize, for example, that a proportion of subjects infected with influenza virus during major epidemics are also more susceptible to other respiratory tract infections, including *Chlamydia*, perhaps because many of them are current or past smokers. In this example, therefore, *Chlamydia* infection and smoking represent major potential confounding factors that should be controlled for. Furthermore, the decline of CHD mortality over the last third of the twentieth century has alternatively been interpreted as a late consequence of the introduction of antibiotics, some of them active against *Chlamydia*, two to three decades earlier (Javier Nieto, 1998).

The biological plausibility of the etiologic association between influenza virus infection and CHD deserves further discussion. CHD pathogenesis has been associated with chronic inflammation caused by persistent *Chlamydia*, *H. pylori*, and cytomegalovirus infections (Muhlestein, 2001), but not by acute infections. Furthermore, in contrast with *Chlamydia* and cytomegalovirus, influenza A virus infection rarely involves the myocardium, the pericardium, or the vascular endothelium. The alternative hypothesis that a systemic, rather than local, inflammatory or autoimmune mechanism leads to plaque formation in influenza infection, proposed by Azambuja & Duncan, is insightful, but lacks further experimental support. On the other hand, the finding that influenza virus induces platelet aggregation, cit-