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Biological (anti)terrorism by mother nature?

Numerous attempts have been made to explain the time-trend patterns in coronary heart disease (CHD) mortality in America and Europe over the last century. The question as to why CHD mortality rose steadily until approximately mid-century and then began to decline has been intriguing investigators for a long time, and a series of possible explanations for such a pattern have been described. In their article, Azambuja & Duncan introduce another interesting hypothesis seeking to explain the rise and fall in CHD.

Focusing on events in the United States, the authors argue that the time-trend pattern in CHD mortality can be explained by the influenza epidemic striking that country during the first half of the 20th century. The infection, they explain, could have changed individual susceptibility to other known risk factors for CHD, leading to increased mortality among the exposed. Since the flu epidemic was restricted to certain time periods, new generations of unexposed individuals were then responsible for the later decline in CHD mortality.

It is interesting to note the growing interest in infectious disease theories for many of the most common degenerative diseases of our times. For some specific cancers, for example, established mechanisms have already linked the diseases to various infectious agents. Some even claim that every disease has an infectious "cause", an argument that has been disputed by others that affirm that most "causes" are "environmental".

Without going into each theory's pros and cons, which is beyond the scope of this article, it is interesting to note that some infectious agents such as *Chlamydia pneumoniae* and cytomegalovirus have already been associated with coronary and peripheral arterial diseases. In addition, it is known that influenza epidemics are associated with excess morbidity and mortality, not only from respiratory diseases but also from other causes.

Nevertheless, the contribution of influenza to clinical events, including clinical cardiovascular diseases, is frequently not recognized (Siscovick et al., 2000). We identified some articles in this respect showing associations between influenza vaccination and both reduced risk of primary cardiac arrest (Siscovick et al., 2000) and reduced mortality from influenza among older persons (Reichert et al., 2001).

However, the main argument of Azambuja's & Duncan's theory is built upon data from influenza and pneumonia mortality (a marker for

influenza activity). It is conceived that about 99% of mortality classified as due to pneumonia and influenza are in fact due to pneumonia, clearly not all associated with primary influenza virus infection. The sources of the data they used are from death certificates and hospital discharge diagnoses. Both probably underestimate the impact of influenza, but using pneumonia and influenza can overestimate the impact of influenza as well.

Moreover, they state that the epidemic affected whites and males most heavily, which were also the main groups hit by the rise in CHD mortality in the US. However, one can argue that if the pandemic had hit these groups the hardest, survivors of the pandemic, that is, the ones "primed" by the infection to predispose them to future development of CHD, would more likely be blacks and women.

In addition, influenza A (H1N1) circulated in human populations from 1918 (the great pandemic) to 1956, and reemerged about 1976-1977. The authors do not discuss, at least not very clearly, what happened to CHD in the period from 1956 to 1976, when H1N1 was not circulating in humans. Also, they do not propose any association between coronary cardiac diseases since H3N2 emerged in 1968 until the present.

Borrowing Hill's criteria for assessing "causality" to illustrate this commentary, we observed that the Authors provided a series of clinical-pathological and biomolecular clues to reinforce their argument, thus presenting *biological credibility* or *plausibility* for their findings. However, this is one of the most criticized criteria in the epidemiological literature, given that biological mechanisms can easily be elaborated linking an exposure to an outcome. If the epidemiological evidence pointed exactly in the opposite direction it would not be difficult to find another biological explanation.

As far as the *strength* of the association is concerned, the authors consider a Spearman correlation = -0.68 with a descriptive level of significance = 0.042 as being a NOTABLE (our capitals) negative correlation. It should be noted that with nine observations, they had only seven observations to contribute to the calculation of the residual in the estimated linear equation, and particularly that taking into account an $R^2 = 0.46$ (-0.68²), which means low precision, they do lacked sufficient evidence to consider correlation notable.

The essential *temporal relation* criterion is clear in their analysis of birth cohorts, but another important criterion that could be investigated is the *consistency* of findings. During 1918-1919, influenza was pandemic, since it affected most countries in the world. In Brazil,

there are reports of more than 300,000 excess deaths attributed to the flu epidemic. The same occurred in European countries, where historical data are usually available. Thus, it would be interesting to replicate similar analysis to data from other countries to learn whether a similar pattern of CHD mortality across birth cohorts, in accordance with mortality from influenza in the same cohorts, corroborate their study's findings.

Finally, as the authors made clear, the study presented here is a correlational one with the clear purpose of raising new hypotheses to be further evaluated using different epidemiological designs. According to Hennekens & Buring (1987), the chief limitation of such studies is their inability to link exposure to diseases in particular individuals, in other words, correlation data represent average exposure levels rather than individual values. Thus, it could be that individuals unexposed to the influenza virus were the ones who later died of CHD, that is, the so-called *ecological fallacy*. A second major limitation of correlational studies, as recognized by the Authors, is the inability to control for the effects of potential confounding factors.

Notwithstanding such considerable limitations, Azambuja & Duncan were brave in facing the challenge of introducing a new pioneering theory.

As such, it is worth quoting Andrew J. Hall (2001:1197-1198), commenting on another pioneering article: "*the study illustrates another saying of Geoffrey Rose: an epidemiologist needs dirty hands and a clean mind*". Dirty hands from collecting all of the confounding variables, influenza, and CHD data, and clean minds with which to judge the evidence.

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The authors reply

Os autores respondem

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Capturing determinants of vulnerability from modifications in disease occurrence

"In science, just as in art and in life, only that which is true to culture is true to nature" (Luwidick Fleck, 1979:35).

"Once we recognize that state of the art is a social product, we are freer to look critically at the agenda of our science, its conceptual framework, and accepted methodologies, and to make conscious research choices" (Richard Levins & Richard Lewontin, 1987, *apud* Krieger, 2001:668).

First of all, we wish to thank *Cadernos de Saúde Pública/Reports in Public Health (CSP)* for the opportunity to publish this paper. It presents a nearly 10-year-old hypothesis (Reinert-Azambuja, 1994) of an association between the 1918 influenza pandemic and the rise and fall in CHD mortality registered in the 20th century, which, prior to its submission to the CSP, had found no room in scientific journals.

During this period, we witnessed the emergence of inflammation as the best synthesis of accumulated knowledge about the morphological and biochemical characteristics of atherosclerotic plaques (Ross, 1993) and a substitution of inflammation for degeneration as the main pathogenic process leading to several additional common chronic diseases (Lorber, 1996).

Transitions in paradigms have implications for epidemiology (Pearce, 1996; Silva, 1990). As we know, the degenerative paradigm did more than target lifestyle-related exposures as potential risk factors for CHD. It also coherently targeted the individual as the most adequate observation unit for studying those exposures and their effects. For epidemiological research, this meant a huge investment in individual-centered epidemiological studies and a proportional abandonment of traditional, more society-oriented approaches to the understanding of causes of disease occurrence in populations (Pearce, 1996; Silva, 1990; Susser & Bresnahan, 2001). This trend now appears to be changing: "*epidemiology is in transition from a science that identifies risk factors for disease to one that analyzes the systems that generate patterns of disease in populations*" (Koopman, 1996:630).