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The inflammation paradigm: Towards a consensus to explain coronary heart disease mortality in the 20th century

Maria Inês Azambuja [a,*], Aloyzio Achutti [b], Richard Levins [c]

[a] *Department of Social Medicine, School of Medicine, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2600, 4/420, 90035-003 Porto Alegre, RS, Brazil*
[b] *Moinhos de Vento Hospital, Porto Alegre, Brazil*
[c] *Department of Population and International Health, Harvard School of Public Health, United States*

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Summary The etiology of coronary heart disease (CHD) has been debated over the last 60 years. There exists an alternative explanation to the rise in CHD mortality, consonant with knowledge about the role of inflammation. It is proposed that a cohort association existed between rates of vulnerability to influenza deaths in 1918 and CHD mortality among survivors from those vulnerable birth cohorts. According to this hypothesis, hypercholesterolemia may have been a marker of the 1918 immune-priming, with CHD deaths resulting from bursts of endothelial inflammation and thrombosis associated with influenza re-infections during the following decades. We propose a reconsideration of the way we model atherogenesis, from ''initiation'' and ''promotion'' to ''vulnerable substrate(s)'' and ''trigger(s)''. Also suggested, based on this hypothesis, is a possible shared condition between vulnerable substrates, which upon triggering, is associated with evolution to acute events, through an imbalance between COX and LOX products. This paradigm has implications for global prevention policies.

Introduction

The World Heart Federation is the co-publisher, along with the European Society of Cardiology, the American College of Cardiology and the American Heart Association, of a new universal definition of myocardial infarction [1]. It is extraordinary that the organizers made the decision to define this clinical entity without any mention of the etiology other than coronary obstruction or imbalance between demand and supply of oxygen to the myocardial muscle. The choice may be a reflection of a still

* Corresponding author. Tel.: +55 51 3342 8959.
E-mail addresses: miazambuja@terra.com.br (M.I. Azambuja), Aloyzio.achutti@terra.com.br (A. Achutti), humaneco@hsph.harvard.edu (R. Levins).

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incomplete understanding of the etiology and pathophysiology of coronary atherosclerosis, or of a lack of consensus.

This paper reviews the main hypotheses about the cause of coronary heart disease (CHD), debated over the last 60 years; proposes an alternative explanation for the rise in CHD mortality, consonant with knowledge about the role of inflammation in atherogenesis; and relates it to disease modeling, causality and global policies.

1940s—1970s (rise in CHD mortality): consensus: lipid-heart hypothesis and the degenerative paradigm

The epidemic of coronary heart disease emerged after World War I and attained public health significance, throughout the world, after World War II [2,3]. In the US, mortality attributed to CHD increased until the early 1960s, when it leveled off at rates of 35% of the total annual mortality [4,5]. Its decline began in 1968 and accelerated after 1972 [5]. By 1999, CHD death rates had fallen 60% [6], and the decline continues to this day. Similar trends have been documented in other countries [7].

During the height of the CHD epidemic, high serum cholesterol level was considered the hallmark of CHD cases. Along with hypertension and smoking, hypercholesterolemia and its purported determinant — high dietary fat intake — were believed to explain the rise in CHD cases and deaths associated with population aging, urbanization, economic development and concurrent lifestyle modifications [8]. In spite of a few discordant voices [2,9,10], until the late 1980s, the ideas of degeneration and clogging of coronary arteries by continuous deposition of cholesterol, supplied by high-fat diets prevailed, especially in the US [8].

1980s—1990s (beginning of the decline in mortality): Ross and the response-to-injury hypothesis

In the 1980s, the emergence of the AIDS epidemic forced a reassessment of the 1960s idea of ''the end of the infectious diseases era'' [11], and weakened the notion of degenerative changes. At the same time, impressive advances in the field of cellular biology contributed to sophisticated studies and a new understanding of pathophysiologic mechanisms underlying atherosclerosis.

In 1974, Russell Ross first described platelet derived growth factor (PDGF) and in 1976, Ross and Glomset [12,13] published the first version of the ''response-to-injury'' hypothesis to explain atherosclerosis. Their experiments suggested that an endothelial lesion initiated the atherosclerotic plaque. The adhesion of platelets to damaged endothelium, through a release of PDGF, then lead to migration of smooth muscle cells (SMC) to the vascular intima, followed by their transformation into foam cells.

The classic lipid hypothesis was equally updated. According to Schwartz and Valente [14], while macrophages had been implicated in the pathogenesis of atherosclerosis, for the first time, in the 1950s, interest in their role grew only after the identification in 1979 of a receptor (later called ''scavenger''), which mediates the uptake of modified LDL and which could be implicated in the formation of foam cells [15].

The period between 1975 and 1990 was prolific in the identification of growth factors and cell hormones [16], and their roles in the cross-talk among different cell lineages involved in the maturation of the atherosclerotic plaque [17]. Those advances resulted in a new round of hypotheses actualization.

The 1986 version of the response-to-injury hypothesis [18] attributed the progression of atherosclerosis to cellular migration and proliferation, stimulated by cellular interactions which were mediated by adhesion molecules, cell hormones and growth factors. The latter were produced by macrophages, platelets, SMC, T lymphocytes, and endothelial cells, in response to the initial ''injury''. In this version, besides physical injury, endothelial dysfunction was also admitted as a CHD *initiator*, and the list of its potential triggers included infections and immune reactions. However, hyperlipemia was emphasized [18], ''*reconciling the response-to-injury hypothesis to the lipid infiltration hypothesis within a unified theory*'' [19]. Correspondingly, the 1990 Steinberg and Witzum review of the lipid infiltration hypothesis [19], known as the LDL oxidative modification hypothesis, acknowledged *progression* of the lesion as a response to injury, but attributed the initiation of atherosclerosis to LDL infiltration of the intima, followed by its oxidation and internalization by macrophages.

Thus, we could say that by the early 1990s, inflammation replaced degeneration as the mechanism responsible for the *progression* of atherosclerotic lesions. Its *initiation*, however, remained tied to the still very strong lipid hypothesis. It was as if Ross had to negotiate a prima donna role for the diet-heart hypothesis in exchange for advancing

his discussion on vascular inflammation. With the diet-heart hypothesis tied intrinsically to the notion of degeneration, the transition from the degenerative to the inflammatory paradigm remained incomplete.

1990s—2007 (continuing decline): moving towards a new consensus: the inflammation hypothesis

During the 1990s, with the continuing decline in CHD mortality, a modification in the metabolic profile of CHD cases emerged, so important as to be referred to as a ''second atherogenic phenotype'' [20]. Cases themselves became less fatal, progressively less associated with hypercholesterolemia and associated more with markers of insulin-resistance and inflammation [21,22]. A mirror image of this trend was observed during the rise in CHD mortality [23].

The changes observed in the attributes of cases during the rise and fall in CHD mortality are in accordance with Gould's interpretation of time-trends as expressing relative expansions and retractions of different sub-populations over time [24]. They suggest the existence of at least two different sub-populations of CHD cases, one characterized by insulin-resistance and inflammation, distributed over the entire 20th century, and the other characterized by hypercholesterolemia and sudden deaths, increasing from the late 1920s to the 1960s, and subsequently declining.

As cases associated with hypercholesterolemia decline, the explanation for vascular obstruction changes from lipid accumulation to plaque rupture and acute thrombosis, and inflammation becomes rapidly accepted as the pathway to coronary occlusion [21,22,25,26].

C-reactive protein was shown to predict not only outcomes of patients with acute vascular events, independently of the extent of damage, but also acute events themselves, such as myocardial infarction and ischemic stroke, in more than 20 diverse population cohorts [27]. Amazingly, markers of inflammation were also shown to predict type 2 diabetes [27,28] and hypertension [27], once considered antecedent causes of CHD. Their rise was also demonstrated in association with smoking [25]. In turn, the dietary benefits of $n-3$ and $n-6$ fatty acids seem to be related with their as yet not well understood effect on the arachidonic acid cascade and COX products, modulators of vascular inflammation and thrombosis [29]. Thus, with these findings over the last 10 years, an appeal to move the inflammatory hypothesis toward a consensus has finally been launched [27].

An unsolved issue

If a great amount of evidence linking inflammation *to the whole process of atherogenesis* exists for current CHD cases, the same cannot be said for the hypercholesterolemic cases occurring at the height of the CHD epidemic. During the last years, Meade [30] has insisted on reaffirming Morris' observations regarding the contribution of thrombosis to the CHD deaths of the 1950s and 1960s. But no attempt has occurred in the mainstream literature to review the lipid (degenerative) hypothesis and reassess the diet-heart association. As we advance the inflammation hypothesis, we now need to decide whether to leave those cases outside the boundaries of this new pathophysiologic explanation, in a limbo between the degenerative and the inflammatory paradigm, or to readdress them.

Back from the present — inflammation, the 1918 influenza pandemic and a new hypothesis to account for the rise in CHD mortality

Since 1994, an alternative hypothesis (to the degenerative/diet-heart hypothesis) has been emerging. It proposes that an association existed between vulnerability to influenza deaths in 1918 and CHD mortality among survivors from those vulnerable birth cohorts [31—36]. The 1918 influenza pandemic was exceedingly severe among young adults, particularly among young white males. It is proposed that survivors belonging to those birth cohorts were left vulnerable to die from CHD upon influenza re-infections. According to this hypothesis, hypercholesterolemia, the hallmark of CHD cases in the 1950s and 1960s, may have been just a marker of the 1918 immune-priming, reinforced at each recurrent influenza infection. CHD deaths would have resulted from episodes of endothelial inflammation and thrombosis associated with influenza re-infections of those primed (hypercholesterolemic) individuals [31—36]. That would explain why, ''contrarily to the intuitive expectations [37, p. 616]'' at least two studies from the 1960s [37,38] found that the last or latest serum cholesterol measurement identified CHD risk, particularly the risk of a CHD death, better than a high average value of all measurements.

This hypothesis would be in complete conformity with the inflammation paradigm and it would do justice to Morris, who insisted that the higher rates of CHD mortality in England during the 1950s were related to an increase in acute coronary thrombosis and chronic coronary occlusion (secondary to the organization of previous thrombi), independently of the size of the mural atheroma [2,9,30].

Insights emerging from this hypothesis

The need to change our modeling of atherogenesis

As discussed in more detail in a previous paper [36], to unveil the association between the 1918 influenza pandemic and the CHD epidemic, it is necessary to look at old evidence with new (Darwinian) eyes. We need to change the way we model the process of atherogenesis. Instead of ''initiation'' and ''promotion'', it is more illuminating to think in terms of ''substrates'' (vulnerability) and ''triggers'' (''exposure'').[1] Until recently, individual vulnerability to chronic diseases would be instantaneously translated as genetic inheritance [10,40,41]. Now we have learned that, besides the genes, there are also *acquired* sources of variability, such as infections [42—44] and metabolic reprogramming associated with nongenomic mechanisms of inheritance [45,46]. It can be said that individuals' resistance/vulnerability (substrates) to tomorrow's challenges (triggers) is being actively built today, at the intersection between their current substrates (genomes X all previous experiences) and today's exposures [36]. Thus, in the process of getting sick, the individual's substrate is as decisive as the exposures that he might eventually experience. The suggestion of a movement *from vulnerable plaque to vulnerable patient* [47,48] possibly reflects some of the same issues discussed here.

CHD may represent several diseases [36], in the sense that there are several ways of acquiring vulnerability to it, and there are possibly different triggers capable of inducing a CHD event, this way unveiling the individual's hidden vulnerability to it. The question then arises: could different pathways to vulnerability lead to ''similar vulnerable substrates''? The following clues may help answer this question.

[1] This approach has already been applied effectively by Rosen [39], in a re-classification of cardiac arrhythmias.

Clues to a common vulnerable substrate

If the proposed association between the 1918 influenza pandemic and the 20th century CHD epidemic is real, and if hypercholesterolemia emerged as a secondary effect of an autoimmune priming, then the apoB-LDL receptor (LDLR) interface was the target in the auto-immune process [32—36].

Mimicry between amino acid sequences involved in the cell attachment of viral hemagglutinin and those of apoB involved in the LDL binding to high affinity LDLR was described in some strains of the influenza virus [49]. Cross-reactive autoantibodies directed against the apoB-LDLR interface would be expected to lead to sub-endothelial co-accumulation of lipids and immune products, and result in lipid peroxidation. This sequence of events has been fully demonstrated in cases of Heymann nephritis, an autoimmune disease where the main autoantibody target (megalin/gp330) is also a member of the LDLR family [50]. But how would cross-reactive autoimmune interference at the apoB-LDLR lead to endothelial inflammation and thrombosis and result in the high CHD mortality observed during the influenza epidemics of the 1950s and 1960s?

The recent reports of untoward cardiovascular effects of selective anti-inflammatory drugs have enlightened us about an important group of inflammatory mediators associated with vascular homeostasis: the cyclooxygenase (COX) products [51]. COX is the rate-limiting enzyme in the synthesis of prostaglandins (PG) from free arachidonic acid (AA). It exists as two isoforms, COX-1 (mostly constitutive) and COX-2 (mostly inducible in pathologic situations) [51]. In 1991, Salbach et al. [52] proposed a new role for the LDLR: the regulation of cellular levels of free AA, and hence, of PG synthesis. The LDLR-AA pathway appears to couple directly with the PGH synthase (COX) reaction, but not with the 5-lipoxygenase (5-LOX) reaction [53]. Thus, upon re-infection, autoimmune interference on the LDLR-AA pathway could result in a LOX—COX reaction imbalance in favor of 5-LOX products. Interestingly, polymorphism studies of the gene ALOX5AP, which encodes the 5-LOX-activating protein, have shown that variants of this gene are associated with twice the risk of developing myocardial infarction and stroke [54]. These high-risk variants are associated with increased production of leukotriene B4, a key product of the 5-LOX pathway.

Thus, based on the site proposed as a target for the auto-immune response triggered by influenza re-infections of 1918-primed individuals (the

apoB-LDLR), a general hypothesis may be advanced to account for substrate vulnerability to CHD. It is possible that what defines a vulnerable substrate would be its predisposition, when challenged by a trigger, to respond with a LOX—COX imbalance in favor of 5-LOX products, independently of the determinant leading to it [55] — genetics, infection-autoimmunity, drugs, diet and, possibly, insulin-resistance.

Discussing the implications of these ideas is beyond the scope of this paper, but it is worth mentioning the growing recognition of atherosclerosis—diabetes—hypertension—obesity as a cluster of conditions association with low-grade chronic ''inflammation''. Evidence seems to be accumulating in favor of a review of our current nosology.

Influenza and other infections as possible triggers for acute vascular events and other complications of chronic diseases

The proportion of excess cardiac deaths during influenza epidemics grew from 1.6% in 1918—1919 to 18.4% in 1920—1929 and 51% in 1957—1960. From 1957 to 1966 there were seven influenza epidemics and a heat wave in the United States, associated with excess mortality. Besides pneumonia and influenza, arteriosclerotic heart disease was the only sub-classification which showed significant excess mortality during all the 8 periods, but excess deaths from diabetes were significant in six of the seven influenza epidemics [56]. Excess CHD deaths among persons aged 65 and older were also documented during the 1968—1969 and 1972—1973 influenza epidemics [57], and during the decline, influenza-associated CHD deaths became progressively concentrated among the oldest individuals of the population [58]. This evolution says more about the birth cohort pattern of substrate vulnerability to influenza than about the viral triggers themselves. But the fact that peak months of mortality for ischemic heart disease, cerebrovascular disease, and diabetes mellitus coincided with peaks in pneumonia and influenza, from 1959 until recently (1999) [59], suggests that, even now, influenza could remain an important trigger for heart, stroke and diabetes-related acute events.

Several other infectious agents could be as effective as influenza in triggering acute events in vulnerable individuals [60]. Additionally, other types of triggers, such as acute stress [61], warrant consideration.

Implications for global projections of mortality and cardiovascular diseases prevention policies

In spite of attempts to advance inflammation as underlying CHD to a consensus, current projections of global trends in CVD mortality remain, quite interestingly, strongly tied to concepts developed under the degenerative paradigm. Their proponents admit that they ''*depend on the assumption that future mortality trends in low-income and middle-income countries will generally have the same relation to economic and social development as has applied in high income countries* [62, p. 1578]''. Based on the experience of developed countries, the idea is that the 20th century CHD epidemic will be moving to middle and low-income countries, following the trail of urbanization and economic development, and that cardiovascular diseases are expected to become the greatest killers of population in less-developed countries by 2020 [63,64].

If the alternative explanation to the rise in CHD mortality — an association with the 1918 influenza pandemic — is true, then their projections are wrong. That epidemic will be over and will not move anywhere. Actually, since at least 1980, Brazil has shown the same trend for stroke and CHD mortality as the US and other developed countries, namely a continuous decline [65]. Of course, this does not mean that heart diseases, stroke and other chronic diseases will not pose problems for Brazil. Globally, we still need to understand the cause of the current epidemic of obesity and appraise the size of its contribution to the pool of future cardiovascular diseases cases. Also, the ideas discussed in this paper suggest that *context* (translated as the population pattern of a historically built ''substrate vulnerability'') has been undervalued. The pattern of substrate vulnerability (given a trigger) would be what Rose [41] and Stallones [66] called ''*the cause of the disease occurrence*'', different, as they recognized, from ''*the cause of the cases*'': the trigger (given a vulnerable substrate).

During the last 60 years, Brazil has gone through a process of rapid urbanization with population growth. The urban population increased from 19 million people in 1950 to 138 million in 2000 [67], a large proportion concentrated in metropolitan areas. Accompanying this urbanization, a decline in fertility and a consequent relative aging of the population have occurred [67]. These processes happened in one of the most socially unequal countries in the world. According to the 2006 World Development Report, in Brazil, 47% of total income

is appropriated by the 10% richest group, which leaves 0.7% to be shared by the 10% poorest stratum [68]. Contrary to what happens in first world countries, where programs to improve health among disadvantaged populations target a clearly defined, fairly small segment of the population, allowing for relative ease in monitoring and assessing results, in less-developed countries there is ''*a jungle of exclusion with some isolated ''campi'' of inclusion* [69]''. A comparison of income distribution curves among the G-20 countries [70] gives a very good idea of what inequality means in less-developed countries.

Taking all the above information into account, during the coming years we may expect relative and absolute increases in poor middle-aged adults living mostly in the peripheries of huge metropolitan areas, with low quality jobs and poor access to quality services. These populations can be expected to concentrate both vulnerable substrates (due to poverty, low birth weight, smoking, poor quality diets and chronic stress) and environmental triggers (infection, acute stress), along with low quality access to acute care. Together these will make them preferential candidates for early CVD deaths.

Porto Alegre, the capital of the southernmost state of Brazil, has 1,350,000 inhabitants and has the highest quality of life among Brazilian state capitals, as measured by the Human Development Index. In this city, age and sex standardized mortality from cardiovascular diseases for those between ages 45 and 64 years is 2.6 times higher among city dwellers living in districts classified within the lowest quartile of social development, as compared to those living in the highest quartile [71]. A regression analysis using social and CVD data stratified by district and weighted by their respectives population sizes (RIDIT), estimated a 3.3 relative-risk of dying early from CVD between districts classified at the extremes of social development [71].

Like tuberculosis in Britain in the 1800s [72], cardiovascular and cerebrovascular diseases, and particularly early deaths related to them, may become increasingly associated with poverty during the upcoming years.

As stated by Leeder et al. [73], health is not a sectoral policy. It is a component of a macroeconomic agenda to development. This same idea was behind Chadwick's strong defense of the 1848 ''Public Health Act'' in England. Edwin Chadwick, the father of English public health argued that poor health caused destitution and that the maintenance of the working population was an economic benefit needed to fuel the growth of Britain's new industries [74]. Sanitary reform was the way envisaged to reduce poor health while investing in engineering to improve economic grow, which, in turn, would increase food supply and further ammeliorate the workers' health and the economic productivity of the country.

Perhaps chronic disease prevention policies in low and middle-income countries would benefit from Chadwick's ideas. Instead of circumventing poverty and social inequality, health promotion and disease prevention policies could be redesigned to reduce destitution and improve economic growth. To reduce the amount of substrate vulnerability in populations should be a goal as important as to treat supposed causes of individual cases.

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