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Guest Editorial

The Five Cardinal Signs of Inflammation: Calor, Dolor, Rubor, Tumor . . . and Penuria (Apologies to Aulus Cornelius Celsus, *De medicina*, c. A.D. 25)

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THE inflammation system may be considered, in some ways, a classic biological stimulation–response system. For example, in response to invading microorganisms, first the innate immune system and then the adaptive immune system engage the invaders and in most cases eliminate them. This type of stimulation–response activity generates some of the most dramatic aspects of inflammation, with large amounts of cytokine production, the activation of many cell types, and in fact the four cardinal signs of inflammation: heat, pain, redness, and swelling (1). In other settings, other aspects of this broad system of responses may become activated. For example, following physical trauma, the activation of the coagulation system is paramount, because blood loss is the greatest immediate challenge. Even in infections, such as sepsis, the activation of coagulation leads to some of the most serious clinical problems, for example, disseminated intravascular coagulation (DIC). Such examples also serve to illustrate the interconnectedness of the various pathways that compose inflammation, as the most effective new drug that has come to market in refractory sepsis in recent years isn't an antibacterial agent or an activator of the immune system, but rather an anticoagulant called activated protein C (APC, or Xygris) (2). Interestingly, APC is not only effective in treating septic DIC, but also appears to be anti-inflammatory. The exact biochemical and cellular pathways by which this occurs, although of great interest (3), have not been completely worked out.

However, the inflammation system may also be considered in some ways a classic homeostatic system, functioning on a moment-to-moment basis to maintain organ and organism function. For example, all organ systems engage in ongoing cellular removal and replacement. Some act on fast time scales (e.g., gut epithelium), whereas others are much slower (e.g., brain). As an example, humans remove and replace up to 10% of their bone structure each year (4). In early life this process nets an increase in bone mass, whereas in later life there is a decrease in bone. This ''removal–replacement'' process may also be considered part of ''inflammation,'' because at least the innate immune system is actively engaged. In the example of bone, specialized cells, osteoclasts, remove calcium phosphate, collagen, and other protein and cellular debris; the osteoclast is in many ways a highly modified macrophage, being derived from the same hematopoietic progenitor cell that gives rise to monocytes and macrophages (4), adapted to deal with an organ that is 65% mineral phase. Indeed, the epiphyseal growth plate activity has long been studied in animals through the rabbit femur fracture model, because the cell biology of bone repair has long been seen as very similar, if not identical, to growth plate function, albeit at a hugely accelerated rate. If one considers all such homeostatic activity that may occur across the human organ systems, it seems reasonable to conclude that this may represent a large fraction of the activity we consider ''inflammation.''

Given then the dual nature of inflammation (i.e., stimulation–response and homeostatic), we need to think carefully about the meaning of biomarkers that represent the underlying degree of activity. Two important questions arise. First, do biomarkers such as C-reactive protein (CRP; a member of the innate immune system), fibrinogen (a member of the coagulation system), or interleukin-6 (IL-6; a proinflammatory cytokine mediator) represent normal homeostatic function or a response to a pathological condition? The answer is most likely ''both,'' to varying degrees in different people, and in the same person at different times, under different conditions. In younger, healthier people, the biomarkers may likely represent the ongoing homeostatic activity of the various inflammation subsystem, for example, bone removal and replacement yielding growth and increase in function. With increasing age, there is increasing input from chronic pathological processes. For example, lipid deposition in arterial walls yields increasing innate and adaptive immune response activity as the body attempts to remove it. Finally, older people have developed significant amounts of disease burden, which now cause a stimulation–response type inflammation such as is seen in the activation of the coagulation system by large areas of atherosclerotic lesions in the arterial vasculature. Of course, there is always the possibility of acute perturbations being present (e.g., infections), adding another layer of complexity to the interpretation. Taken together, however, there is consensus that inflammation biomarkers are independent predictors of the future occurrence of cardiovascular events (5,6), as well as other chronic disease outcomes (7).

The second question is related to the first and is equally important: What aspects of an individual's genetic, physiological, and environmental makeup contribute to biomarker levels? The population correlates of inflammation biomarkers in healthy people are well known (8,9). Relatively strong correlates include the components of the metabolic system (insulin resistance, obesity) and measures

of the degree of activation of the coagulation system (fibrin fragment D-dimer). Weaker correlates include smoking status, age, gender, ethnicity, and measures of subclinical atherosclerotic disease. Also, biomarkers are generally higher in persons with clinically recognized diseases such as heart disease and diabetes.

The recent article by Koster and colleagues from the Health, Aging and Body Composition (ABC) Study (10) provides some important information related to these questions. First, this study demonstrates for the first time that relatively healthy older men and women of lower socioeconomic status (SES) have higher levels of inflammation biomarkers than do those of higher SES. This important observation has biological implications as it may help explain the known relationship of SES with health in older people (11), as well as societal implications because inflammation biomarkers continue to predict multiple adverse health outcomes in elderly persons (12–14).

Second, and interestingly, this finding in older people also complements the observation in younger people that low birth weight (which is associated with lower SES) is associated with higher inflammation biomarkers in later life (15). This latter observation may be linked to the ''thrifty phenotype'' hypothesis of Hales and Barker (16), who observed that low-birth-weight babies are more likely to be obese and have cardiovascular events in later life than are higher birth weight babies. In an argument analogous to the one proffered by Neel (17) in his article on ''thrifty genotype,'' Barker hypothesized that low birth weight is associated with caloric restriction in utero (in essence an estimate of low SES), which in turn established programming for aggressive caloric utilization. Because most low-birth-weight babies over the last century have found themselves in later life in improved conditions of caloric availability, they tended to store more calories as fat than did their higher birth weight contemporaries. This is a form of antagonistic pleiotropy played out at the level of the individual (in contrast to Neel's, which plays out at the species level), and may be expanded to include inflammation, as suggested in a recent review by Fernandez-Real and Ricart (18).

Third, and based on the argument given above, an important question that arises from the study of Koster and colleagues is whether the association of SES with inflammation in older people is a residual of Barker-like programming based on low SES in their earlier lives (which continued into older life), or a result of their current SES status. Data on birth weight and/or estimates of early-life SES might help to explore this. The observation that obesity explained some of this association doesn't help, because obesity itself is at least in part a residual of early life programming. The observation that behaviors such as smoking and drinking explained some of the association is somewhat helpful, but these behaviors are likely to be confounded by early-life SES, especially if lower early-life SES continued into later life; in addition, even the combination of existing diseases and poor health behaviors failed to explain all the contribution of lower SES to biomarker levels. The answer to this question has important implications for the most effective time for intervention. The finding of Koster and colleagues that a fraction of the association can be explained by bad health behaviors is important information in and of itself and suggests the need for surveillance of health behaviors and interventions to improve behaviors into later life. However, if most of the association were actually driven by residual effects of early life programming, the alternative strategy of weighting most of the effort into interventions designed to improve early-life SES would seem appropriate.

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