

# Diabetes and C-Reactive Protein

Tom Elasy, MD, MPH, Editor-in-Chief

Since Celsus (~ 50 BC), who is credited with describing *rubor, calor, dolor, and tumor* as key attributes of inflammation, pathology has been a foundational study of physicians. The study of the structural and functional processes that underlie disease has always engaged physicians in much the same way that disturbances in economies would attract economists. And, like other professionals, our obser-

vations about processes beget inferences that occasionally beget predictions that occasionally beget recommendations.

In this issue, we see several attempts to understand or respond to the processes that underlie dysfunction. At a forest level, Robb Malone, PharmD, CDE, CPP; Betsy Bryant Shilliday, PharmD, CDE, CPP; Timothy J. Ives, PharmD, MPH; and Michael Pignone, MD, MPH (p. 31) describe an attempt to improve

care at a large hospital in North Carolina based on perceived dysfunctions in the system that delivers care. With this elegant and detailed description of an attempt to improve diabetes care, Malone et al. launch “Bridges to Excellence,” a new department within *Clinical Diabetes* that characterizes quality improvement initiatives aimed at improving the care delivered to individuals with diabetes. Michael J. Fowler,

MD (p. 25), after reviewing the burden of diabetes, gives a tree-level view of the mechanism underlying the four categories of diabetes as part of "Diabetes: A Foundation," another new department aimed at equipping physicians-in-training with core knowledge of diabetes. It is notable how simple our current diabetes classification system remains, despite significant advances in our understanding of the heterogeneous condition we call diabetes. Finally, David M. Capuzzi, MD, PhD, and Jeffrey S. Freeman, DO (p. 16), give leaf-level attention to a particular peptide that is sometimes elevated in diabetes: C-reactive protein (CRP). CRP is indiscriminately elevated in a variety of inflammatory conditions, and Capuzzi and Freeman make the case that inflammation is a key attribute of diabetes and that CRP has an important role in at least predicting future macrovascular events. An argument follows in support of recommendations for measuring CRP in certain populations.

It has been said that there are three common denominators of disease pathogenesis: inflammation, oxidation, and coagulation. Although such characterizations are simple if not simplistic, it is remarkable how many conditions appear to involve disturbances of these three "denominators" at some point along the continuum that characterizes their pathogenesis. Type 2 diabetes, unlike type 1, is perceived by some physicians to not involve these mecha-

nisms. This ought not be. From seminal work by Michael Brownlee<sup>1</sup> describing the key role of reactive oxygen species in the pathogenesis of microvascular complications to the vast body of work implicating inflammation in diabetes and atherogenesis, these broad mechanisms are quite relevant to diabetes. Inflammation, whose attributes Celsus purportedly described and Rudolf Virchow (~ 1858) refined, has become far better characterized with now legions of cytokines and cascades. So what role does CRP, one of many cytokines, have in helping us care for individuals with diabetes?

Capuzzi and Freeman implicate CRP in the atherogenic process, characterize its potential in predicting cardiovascular events, and review two large well-conducted studies that suggest CRP's association with the development of diabetes. These observations contribute to our understanding of the dysfunction associated with diabetes. Yet, one ought to be circumspect in transitioning from processes underlying disease to recommendations. This is especially relevant in diabetes, which is treated as the equivalent of having had a coronary event and thereby already necessitates intensive attention to known coronary risk factors. In addition, recommendations for monitoring are rarely associated with the same rigor as recommendations for treatment. Although the consequences of monitoring are unlikely to result in fulminant

hepatic failure, there are considerable efficacy and cost considerations that are often left untested at the time of monitoring recommendations. To be clear, the ease with which we issue recommendations for monitoring is not unique to CRP. Capuzzi and Freeman do hedge a bit regarding the added value of CRP beyond existing known risk factors for either the atherogenic process or the development of diabetes. It may be that many of these cytokine markers of inflammation represent more nibbling around the edges than core causal compounds related to meaningful outcomes. Even so, it is not surprising, given what appears to be a clear role of inflammation in atherogenesis and diabetes, that a variety of treatment options beyond aspirin are being developed in hopes of attenuating the impact of inflammation.

The contribution of inflammation will continue to be unraveled in both atherogenic processes and diabetes. Additional compounds, perhaps somewhat less promiscuous than CRP, will be identified, and the role of known peptides will be further clarified. Whether CRP is the pawn or the queen remains to be seen.<sup>2</sup>

## REFERENCE

<sup>1</sup>Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 414:813–820, 2001

<sup>2</sup>Yeh ETH, Palusinski RP: C-reactive protein: the pawn has been promoted to queen. *Curr Atheroscler Rep* 5:101–105, 2003