

Invited Commentary: Be Prepared to Change Your Mind

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Important lessons have been learned from the complex and controversial story surrounding the rise and fall of aprotinin. Although Brown et al. (1) rightly point out that one should see this as somewhat of a cautionary tale, drawing attention to the pitfalls of when marketing gets ahead of science, it is also a tale that was partly fueled by the co-dependence of the pharmaceutical industry and academia. In fairness, however, some of this criticism is clearly seen through the aid of the retrospectroscope. Despite the overall negative results of their meta-analysis aimed at evaluating the potential anti-inflammatory effect of aprotinin, at the time that many of the constituent trails were published, there was clear enthusiasm among manufacturers and academics alike for this pleiotropic drug. It was a drug that clearly possessed a primary antifibrinolytic effect, but also one that could plausibly be linked mechanistically to an anti-inflammatory action (through the role that kallikrein may have on inflammatory pathways). Furthermore, this paper also highlights the importance of integrating meaningful clinical endpoints with mechanisms of action. In the case of aprotinin, its multitude of actions on a complex series of serine proteases, any one of which could have a beneficial (or negative) effect, are at the heart of the issue. Even though small individual laboratory or clinical trials showed some relative beneficial effects on inflammation (such as a reduced cytokine profile), none of these studies attempted to meaningfully link this to discrete and important endpoints. Had they been designed to do so, perhaps the relatively poor effect on

clinical inflammation and outcomes could have been realized earlier.

The basic science researcher often chides the clinical outcomes researcher for not adequately focusing on mechanism, whereas the outcomes researcher criticizes the relevance of the minutiae of obscure, although potentially important, effects of a drug on various biochemical pathways. In reality, it is the rational melding of these two scientific worlds that perhaps is one of the other take-home messages.

What we are left with at the end of this aprotinin saga is a lesson that will, for any foreseeable time, be incomplete. We may never know which particular enzyme inhibition or interaction was responsible for its eventual adverse safety profile. Nonetheless, what we take away from this is to never lose sight of the important clinical endpoints but also to always attempt to integrate this with an understanding of the mechanisms related to these endpoints. This may help determine the difference between epiphenomena vs. true mechanistic effectors. There were clearly individual and distinct pieces of evidence suggesting an anti-inflammatory effect, and there is also an easy-to-link biological plausibility, but the overall weight of the evidence, that is, through this meta-analysis, does not support it.

One must clearly keep an open mind when examining the science surrounding the issue of this drug and others. Our scientific understanding is constantly evolving. Although many thought the drug once had benefit, we should never let this stop us from critically evaluating our understanding of it. Perhaps if these authors' critical analysis had been done earlier, we would have been further ahead in our understanding of the next steps forward with alternative therapies. Perhaps one of the final lessons to be learned is rather than circling the wagons around an issue, which arguably resulted in the polarization of clinicians around aprotinin, one needs to cautiously avoid putting blinders on.

John Maynard Keynes, noted economist of the Great Depression era (2) (whose writings have recently seen

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an upsurge in interest with the recent tumultuous economic times), once wrote about contradictions in his writing, stating that “When the facts change, I change my mind. What do you do sir?” Although many believed in the potential anti-inflammatory effects of aprotinin, it now seems that we need to be prepared to change our own minds.

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