

## How do we solve the puzzle of unintended consequences of inflammation? Systematically

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THE ODDS ARE HIGH that the inflammatory process will play a key role not only in protecting us from harm over the course of our lives, but also in triggering our deaths. The benefits of the inflammatory process lie in its ability to respond to a variety of stresses and to promote adaptation. The detrimental side of the inflammatory process has several facets, many of which fall into the category of unintended consequences. In the case of the systemic inflammatory response syndrome (SIRS) that accelerates to severe sepsis and/or multiple organ dysfunction syndrome, the consequence may be rapid death (7, 9). In the case of persistent, low-level inflammation, the consequences include the promotion of chronic diseases such as Type 2 diabetes mellitus and atherosclerosis (4, 5).

Ideally, the magnitude of the inflammatory response matches the level of stress, e.g., there is enough inflammation to eliminate an infection but not so much that SIRS accelerates to a lethal stage. Numerous factors with the potential to enhance or attenuate the process may push the response to over- or undershoot the target. SIRS is induced by a wide variety of stresses, such as major acute trauma, systemic infection, or surgery. Several clinical factors influencing the likelihood of accelerating from SIRS to severe sepsis have been identified, but the ability to predict, act early, and prevent this occurrence from escalating to lethal levels remains a substantial challenge (7, 9). Similarly, some of the factors influencing persistent, low-level inflammation have been identified. Strategies to reduce this type of inflammation have had limited success, and more work is needed to identify effective interventions (4). These challenges may exist because the complexity of the underlying mechanisms has not been unraveled, but also because there are many gaps in the research base.

A recent research study by Steiner et al. (11) in the *Journal of Applied Physiology* titled “Nicotine administration and with-

drawal affect survival in systemic inflammation models” is an eloquent demonstration of the complexity of the picture surrounding a single factor influencing the inflammatory response. The study also provides a framework for a systematic approach to investigating other factors influencing inflammation. The study was performed using both septic and aseptic inflammatory stimuli. The influence of acute exposure, chronic exposure, and withdrawal from nicotine was compared for both the time course of SIRS and survival rates in mice. How does nicotine affect the outcome of SIRS? The answer is more complex than a description of the known anti-inflammatory effects of the compound. For example, acute nicotine administration increased survival threefold in aseptic inflammation and decreased survival twofold in the septic inflammation. The facilitation of microorganism proliferation by the inhibition of inflammation (1) was identified as a likely factor differentiating the outcomes between septic and aseptic inflammation. In contrast to acute exposure, chronic nicotine exposure did not influence survival rates relative to the saline control; however, withdrawal from nicotine increased survival rate twofold for the septic inflammation (opposite the effect of acute administration). As pointed out by the authors, the complexity of the influence of nicotine is increased by the fact that their findings of the constant-rate infusion differ from studies in which there are surges in the nicotine dose and also in which nicotine is injected into a different compartment. Individuals entering the hospital are likely to be in a withdrawal from any number of factors, including cigarette smoking, alcohol, physical activity, and others. The inclusion of withdrawal is an important but frequently missing element in the characterization of factors influencing inflammation. Furthermore, research regarding low-level inflammation and disease risk typically does not address whether the underlying source is septic or aseptic.

While the work of Steiner et al. (11) demonstrated the effects of constant-rate nicotine infusion on the outcome of SIRS in an animal model, it is important to consider the

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### MODULATION OF THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

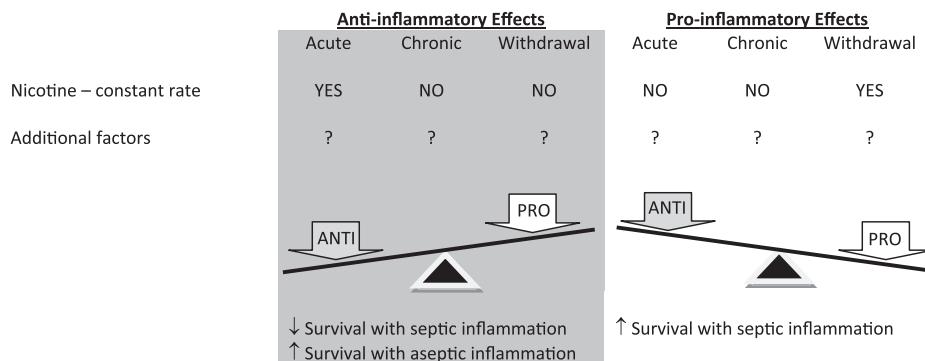
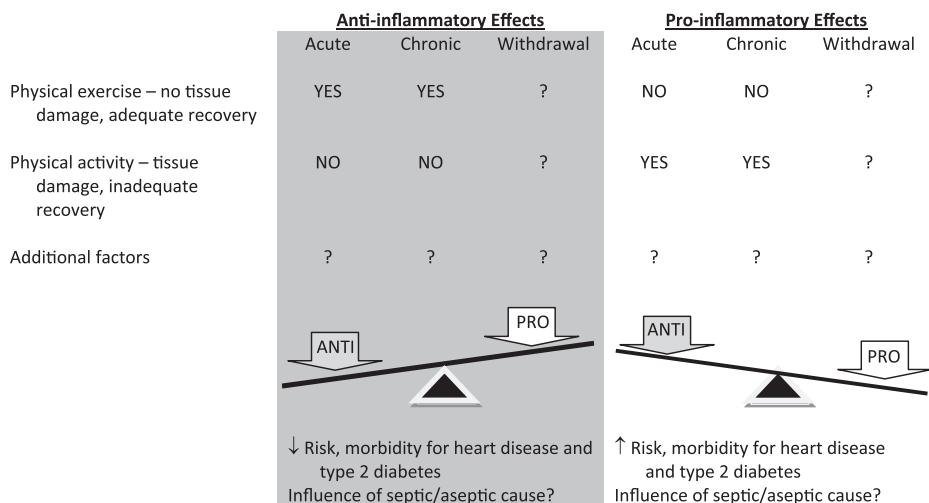


Fig. 1. Schematic illustrating the major findings of Steiner et al. (11) as an example of a common framework for factors capable of influencing the inflammatory process. Physiological influences capable of tipping the scale toward a net pro- or anti-inflammatory balance for the inflammatory process should be investigated in response to acute exposure, chronic exposure, and withdrawal. In this instance, the stimulating or inhibitory effects of nicotine exposure (acute, chronic, or withdrawal) influence the systemic inflammatory response syndrome (SIRS) to either increase or decrease survival rate depending on whether the inflammatory stimulus is septic or aseptic (11).

## MODULATION OF PERSISTENT, LOW-LEVEL INFLAMMATION

Fig. 2. Schematic illustrating application of the common framework for persistent, low-level inflammation. In this instance, the influence of physical exercise with and without tissue damage and adequate recovery has been placed in the framework as tipping the scale toward a net pro- or anti-inflammatory balance for the inflammatory process and influencing disease risk and associated outcomes (3, 6, 8, 10). The lack of information regarding the potential effects of withdrawal from habitual exercise is in question because this portion of the model has not been sufficiently investigated. An additional gap in the research pertains to lack of information as to whether the underlying cause of this type of inflammation is septic or aseptic.



limitations of research models when extrapolating to inflammation in humans. These researchers based the nicotine dose to mice on concentrations typically found in the circulation of many individuals who smoke. However, one major difference between the experiments performed by Steiner et al. and cigarette smoking is that nicotine is just one component of cigarette smoke. The net effect of cigarette smoking appears to be proinflammatory as a result of oxidative stress not caused by nicotine (12). The animal model has the advantage of allowing researchers to isolate individual variables. However, another limitation is that human beings all are unique in the collection of factors that might influence the inflammatory process. Thus, while animal models are an excellent means of determining mechanisms and effects of isolated factors, external validity is an issue to be considered.

A framework for the systematic approach to include acute exposure, chronic exposure, and withdrawal for individual factors influencing inflammation and associated outcomes is presented in Fig. 1. The major findings of Steiner et al. have been plugged into the grid. Factors from a wide range of categories can be added to this grid, e.g., physical activity, diet, disease states, drug use, socioeconomic status, psychological stresses, body composition, alcohol use, and others. Many factors need to be subdivided into unique categories. For example, the mode, duration, and intensity of physical exercise influence whether an acute bout of exercise has proinflammatory or anti-inflammatory effects (2, 6). The accumulation of physical activity over time, as in exercise training or what might be considered chronic exercise, also can be pro- or anti-inflammatory depending on the degree to which recovery occurs between exercise bouts (2, 6, 10). Thus the complexity of the overall picture integrating multiple influences with appropriate attention to the characteristics of each variable is overwhelming. However, placing existing research findings into the proposed grid and using this approach in future investigations may yield patterns helpful in deciphering the overall picture. To this end, the same grid modified for persistent, low-level inflammation is presented in Fig. 2. Two categories of physical exercise have been inserted into the model, and the lack of information regarding withdrawal effects is apparent. Addi-

tional research is needed to determine whether the interactions of variables produce additive or synergistic effects.

In sum, the process of inflammation influences a spectrum of outcomes from beneficial adaptations to rapid death. Increasing our understanding of the influence of a collection of individual factors influencing the process is a research area of great importance. A systematic approach seems warranted given the wide range of factors that impact inflammation. The recent work of Steiner et al. (11) differentiating effects of acute exposure, chronic exposure, and withdrawal from a single variable on inflammation of both septic and aseptic origins provides a potential framework to serve as a starting point for this systematic approach. From low-level inflammation to SIRS, common pathways and patterns generated by this approach at both ends of the inflammation spectrum may provide clues to more effective strategies for preventing the unintended consequences of inflammation and to guide future research.

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