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Kushner I. The phenomenon of the acute phase response. *Ann. NY Acad. Sci.* 389:39-48, 1982. [Case Western Reserve University, Cleveland Metropolitan General Hospital. Department of Medicine, Cleveland, OH]

This review article provided an overview of the many systemic, metabolic, and physiologic changes that occur in vertebrates following inflammatory stimuli—"the acute phase response," in the broad sense—and then focused more sharply on changes in the liver, and, particularly, on the reorchestration of the pattern of plasma protein synthesis by hepatocytes during inflammatory states. It concluded with brief discussions of future research directions and of several clinically relevant questions. [The SCI® indicates that this paper has been cited in more than 505 publications.]

The Acute Phase Response

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This article served as an introduction to a conference sponsored by the New York Academy of Sciences, in 1981, entitled "C-Reactive Protein and the Plasma Protein Response to Tissue Injury," which I had organized together with John Volanakis and Henry Gewurz. Because of recent progress in a number of related fields, we thought that the time was ripe for a conference that, we hoped, would stimulate interest in C-reactive protein and the acute phase response. In this review, I tried to impart my sense of the biologic and pathophysiologic significance of the acute phase response as a setting aside of many of the normal regulatory homeostatic mechanisms and their replacement by new "set points," which appear to represent a rapidly achieved group of primary adaptive and defense mechanisms. The conference achieved its objective. Interest in this subject expanded greatly and a number of investigators were attracted to the field; the subsequent frequency of citation of this

article, I believe, has largely been due to its timeliness.

My interest in this subject dates back about 40 years, to when I was a medical student and was exposed to Hans Selye's concept of a general adaptation syndrome. My imagination was stimulated by the idea that the group of metabolic and endocrine changes which occurred in response to a wide variety of damaging agents represented a fundamental nonspecific adaptive process. My personal involvement in studies of the acute phase response began in earnest in 1958, when I joined Mel Kaplan as a research fellow in Cleveland and was assigned the task of detecting the source of the prototypical acute phase protein, C-reactive protein. I have been working at one aspect or another of this subject ever since.

The acute phase response has attracted considerable interest in the last few years, not only in its own right, but also because study of this dynamic process affords the opportunity to answer a number of important questions in molecular biology and cell biology that are not easily resolved in steady-state systems. One example is the fundamental biologic phenomenon of intercellular communication. It is now clear that the polypeptide signaling molecules, currently referred to as cytokines, play a key role in regulation of the acute phase response. At the same time, there is a growing realization that the cytokines constitute part of a complex signaling language in which total informational content lies not in individual cytokines, but rather in the combination and perhaps sequence of cytokines and other intercellular messengers that impact on a cell. The acute phase response represents an excellent model system in which to study the mechanisms by which a variety of soluble messenger molecules, alone or in combination, can influence expression of a large number of different genes.

I have recently been involved in the preparation of two review articles which, in a sense, update the 1982 article,¹² as well as a historical review.³

1. Ballou S P & Kushner I. C-reactive protein and the acute phase response. (Stollerman G H, ed.) *Advances in internal medicine*. Chicago, IL: Mosby Academic Press. 1992. p. 313-26.

2. Kushner I. Regulation of the acute phase response by cytokines. (Gearing A J H, Rosio J L & Oppenheim J J, eds.) *Clinical applications of cytokines: role in pathogenesis, diagnosis and therapy*. New York: Oxford University Press. (In press. 1993.)

3.----- The acute phase response: from Hippocrates to cytokine biology. *Eur. Cytokine Network* 2:75-80. 1991.

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