Cytokines, Metabolism, and Nutrition: Overview (43422)

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Just a few years ago, the mechanisms underlying the metabolic alterations associated with infection and inflammation were rather mysterious. Then, a series of startling discoveries suggested that these pathways would soon be unraveled with a clarity that might permit targeted interventions. This was based on extensive information derived from the *in vitro* study of certain peptide mediators released during infection and inflammation, particularly interleukin (IL)-1 and tumor necrosis factor, and more limited *in vivo* investigations in certain animals concerning their effects on host metabolism. These data are reviewed in the paper by Bistrian and colleagues in this symposium.

While the view that these two cytokines are the signals to reorganize metabolic priorities during infection and inflammation remains the most likely mechanism for these events, more recent studies have identified many more mediators with overlapping properties and both up- and down-regulatory controls. In addition, it has been found that responses *in vivo* may not parallel those obtained *in vitro*, as reviewed in the paper by Grunfeld and Feingold in this symposium, which complicates the interpretation of the earlier data. While the two initially described metabolic regulators (IL-1 and tumor necrosis factor) continued to hold center stage as the best and most likely candidates for the role of conductor of the metabolic response to infection and inflammation, it is still too early to be absolutely certain of even this. The paper by Dinarello in this symposium suggests some of the technical and biological reasons for this. For example, he discusses the many pitfalls in the accurate assay of cyotkines and how readily unphysiological experimental conditions can lead to spurious results. In addition, Dinarello demonstrates the clear separation of transcription from translation of the IL-1 gene and he discusses the difference in the nature of the signals required for these two steps in the ctyokine pathway. The strong implication is that studies that do not assess both steps in gene activation may lead to inappropriate conclusions, and that in vitro studies that do not select the correct stimuli for cytokine pathway activation may lead to incorrect assumptions on *in vivo* events.

Drs. Tracey and Cerami then go on to discuss another critical issue in cytokine biology, the importance of systemic versus tissue levels of cytokines, in this case tumor necrosis factor in the pathogenesis of septic shock, and infection-induced cachexia. Not surprising, the data suggest that tissue levels are the relevant parameter to evaluate in order to understand mechanisms of disease. Unfortunately, this is the more difficult area to approach by investigative methods, especially in humans.

The final paper in this sympopsium, by Yamada *et al.*, reveals the role of cytokine cascades in the regulation of cholesterol metabolism and its possible application to atherosclerosis. They report that human monocyte colony-stimulating factor, which is regulated by other cytokines, such as IL-1, alters the metabolism of cholesterol by human monocyte-derived macrophages, both *in vitro* and *in vivo* using the genetically hyperlipemic Watanabe rabbit model. In both cases, recombinant human monocyte colony-stimulating factor results in the efflux of cholesterol from macrophages, and in the uptake of cholesterol by plasma high density lipoprotein. The effect of the cytokine to increase the binding of high density lipoprotein to specific macrophage receptors may underlie this response.

Papers in other symposia from the Conference on Molecular and Comparative Nutrition suggest that cytokines may play a key role in many nutritional and metabolic responses *in vivo*. With the development of molecular tools to study these situations, and an increased understanding of the regulatory influences involved in cytokine activation and action, we can expect a period of rapid increase in knowledge. The discovery of natural cytokine inhibitors, such as receptor antagonists or soluble cytokine-binding proteins, suggests that regulation of both cytokine activation and action is an important facet of normal metabolism, and that abnormal cytokine regulation may be involved in disease pathogenesis. The present availablilty of cloned recombinant regulatory molecules will allow us to study

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the importance of cytokine pathways *in vivo*, and promises the development of new strategies to treat disease or modulate certain pathophysiological responses in the intact host. Attempts are already being made to alter human cytokine responses by dietary measures, such as feeding fish oil diets, or by the administration of the recombinant IL-1 receptor antagonist molecule. We await the results of these pioneering studies with great interest and anticipation of a major new way to treat many different human diseases.