dle aspirate has been reported to increase yield of finding granulomas at the time of transbronchial biopsy, particularly in patients with stage I chest radiographs.12,13

The question raised by this report is how comfortable can we be with the diagnosis of sarcoidosis based on fine-needle aspirate? Until the cause or causes of sarcoidosis are identified, one will always have questions about the reliability of a diagnosis supported by histology. In actuality, there is no “gold standard” in diagnosis. There is only support for the diagnosis. This is why WASOG recommended the criteria of finding noncaseating granulomas in two or more organs.

Winterbauer et al14 reported several years ago that the finding of bilateral hilar adenopathy and right paratracheal node enlargement in an asymptomatic individual was specific for sarcoidosis. This has proved correct in > 95% of cases and remains a cost-effective method of approaching the asymptomatic individual.15 Patients with erythema nodosum, along with uveitis, and hilar adenopathy are very likely to have sarcoidosis. Other features that, when found together with a biopsy showing granulomas, make sarcoidosis highly likely are lupus pernio, uveitis, seventh-nerve paralysis (Bell’s palsy), and characteristic maculopapular skin lesions.16 Another factor that supports the diagnosis is the length of observation. The longer one observes a patient who presents with asymptomatic hilar adenopathy who remains asymptomatic, or is observed until radiographic resolution, the more convincing the diagnosis.

The diagnosis of sarcoidosis relies on the clinician putting together several pieces of information. This includes the clinical and radiographic patterns, histology, and a search for other potential causes of granulomas. The use of needle aspirate, either transbronchial or percutaneous, provides support but never absolute proof of diagnosis. It provides a peek into the patient’s inflammatory response. In some cases, a peek may be as good as a stare.

Robert P. Baughman, MD, FCCP
Cincinnati, OH

Michael C. Iannuzzi, MD, FCCP
Detroit, MI

Dr. Baughman is Professor of Medicine from the Division of Pulmonary and Critical Care Medicine, University of Cincinnati Medical Center; and Dr. Iannuzzi is Professor of Medicine from Pulmonary and Critical Care Medicine, Henry Ford Health Sciences Center.
Correspondence to: Robert P. Baughman, MD, FCCP, University of Cincinnati Medical Center, 231 Bethesda Ave, Room 6004, Cincinnati, OH 45267-0564; e-mail: bob.baughman@uc.edu

Can We Make Sense Out of Cytokines?

Even the most experienced clinicians and scientists become uneasy when asked to explain cytokines, since these molecules have such wide-ranging biological effects. A recent MEDLINE search revealed > 193,816 citations referable to cytokines in the last decade, and > 1,700 in the last month alone. While it would be useful to put this immense body of

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information into a context to make it more usable for physicians in the care of their patients, this is not an easy task.

Is there a unifying definition of cytokines? Most reviews and textbooks do not even attempt to provide one, but rather refer to their functions and physical characteristics. Cytokines are a diverse group of proteins, produced by a wide variety of cells.\(^1\) They usually influence adjacent cells (paracrine), but may act on cells throughout the body (endocrine) and on the secreting cell itself (autocrine). Functions are mediated through receptors already present in low density on the cell surfaces or through upregulation of new receptors.\(^2,3\)

The role that cytokines play in the regulation and modulation of immunologic and inflammatory processes is striking. While we often classify cytokines by their individual effects on aspects of cellular function, such as chemotaxis, proliferation, maturation, differentiation, or apoptosis, it is more useful to understand “networks” of cytokines that act cooperatively to control normal physiologic activity and disease-related threats to homeostasis.\(^4\) Additionally, multiple cytokines may act simultaneously or in progressive waves as disease processes progress. There is significant redundancy both functionally and temporally among the actions of cytokines, so that no single cytokine alone is likely to be responsible by itself for controlling a specific cellular function or physiologic process.

What has cytokine biology taught us about the pathogenesis of disease? First, we know that this group of proteins is involved in regulating normal physiologic responses. Even though excess or decreased cytokine production may be associated with disease, there are probably no cytokines that are not involved in normal immunoregulation of physiologic processes.

The prototypical disease, which opened a window into cytokine biology, is “sepsis,” which in the experimental situation was best defined as endotoxemia. Although the expression of cytokines, such as tumor necrosis factor (TNF)-\(\alpha\) and interleukin (IL)-1\(\beta\), is elevated in the septic process, these proinflammatory mediators are important in driving the initial inflammatory response, encompassing leukocyte mobilization, coagulation alterations, and tissue repair in response to an invading organism. It is thought that an overexuberant proinflammatory cytokine response has a central role in the septic process. Elevated circulating levels of IL-1\(\beta\), TNF-\(\alpha\), and IL-6 correlate with increased mortality and poor outcome in patients with sepsis, but are not reliably predictive of outcome in individual patients.\(^5\)

In ARDS, high levels of cytokines, such as IL-6, are present both locally in the lung and systemically.\(^6\) It is hypothesized that the lung itself can be an important cytokine-producing organ, such as when lung infection or inflammation is poorly contained; in these cases, pulmonary release of cytokines leads to elevations in their systemic levels.\(^7\) Recently, ventilator-induced lung injury, associated with the use of larger tidal volumes, has been shown to be associated with increased pulmonary cytokine production that then leads to elevations in circulating concentrations.\(^8\) Stretch of myocytes and epithelial cells in vitro results in cytokine release.\(^9\) In animal models and in recently conducted randomized controlled clinical trials, strategies that limit tidal volumes and plateau pressures demonstrate decreased release of proinflammatory cytokines when such “lung protective strategies” are used.\(^10\) Thus, appropriate mechanical ventilation techniques may improve outcome by reducing the generation of cytokines in the lung, which then spill into the systemic circulation.

A similar relationship between alterations in cytokine expression and clinical outcome has been demonstrated in critical illnesses other than ARDS and sepsis. For example, both TNF-\(\alpha\) and IL-1\(\beta\) are persistently elevated in severe cases of pneumonia, and the degree of their elevation reflects the severity of illness and likelihood of survival.\(^6\) In pancreatitis, IL-1\(\beta\), IL-6, and TNF-\(\alpha\) are detected at the site of abdominal inflammation, even prior to radiographic evidence of disease.\(^11\)

The cytokine response in asthma also has been demonstrated to correlate with disease severity and prognosis.\(^12\) In this case, the effect of cytokines may be specifically related to upregulation of eosinophilic differentiation and migration of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5. IL-4 plays an important role in regulating IgE synthesis by B-lymphocytes, and alterations in IL-4 production are present in asthmatic patients. GM-CSF and interferon-\(\gamma\) increase antigen presentation by airway macrophages.\(^2\) The role of growth factors on myofibroblasts and airway smooth muscle is being explored as the progressive airway remodeling that characterized chronic asthma is further examined.

Has this improved pathophysiologic understanding of the role of cytokines in the pathobiology of disease permitted more efficacious treatment? Therapy directed at cytokine response has yet to be shown to have a significant impact on clinical outcome despite the apparent potential of these agents to modify disease. Anti-TNF therapies have recently been approved for rheumatoid arthritis and inflammatory bowel disease, and clearly ameliorate symptoms associated with these disease processes. However, the long-term effects of such anti-TNF
therapies on outcome in patients with rheumatoid arthritis or Crohn’s disease remain unknown at present.

Unfortunately, neither monoclonal antibody to TNF-α nor the administration of soluble TNF-receptor immunoadohesins were found to be effective in sepsis.13 There are multiple possible reasons for the failure of anti-TNF therapies to be effective in sepsis. An important concern in targeting patients with organ system dysfunction associated with severe infection is the heterogeneity of this population, where many of the patients did not show evidence of increased TNF-α release.

The series initiated in this issue of CHEST (see page 1162) will deal with cytokines at the interface of infectious and inflammatory disease. These contributions are aimed at explaining the roles of cytokines as well as factors influencing cytokine expression, such as the transcriptional factor nuclear factor-κB and reactive oxygen species, in normal homostasis and in disease. It is clear that by modifying the production and effects of cytokines, we are entering a new frontier in the application of biology to treatment of disease. We hope that this series will help convey the potential importance that such approaches may hold for diseases that are resistant or even impervious to our present therapies.

Alan M. Fein, MD, FCCP
Manhasset, NY
Edward M. Abraham, MD
Denver, CO

Dr. Fein is Professor of Medicine and Director, Center for Pulmonary and Critical Care Medicine, North Shore University Hospital; Dr. Abraham is from the Division of Pulmonary Science, University of Colorado Health Sciences Center.

Correspondence to: Alan M. Fein, MD, FCCP, Professor of Medicine, Director, Center for Pulmonary and Critical Care Medicine, North Shore University Hospital, 300 Community Dr, 4th Floor, Levitt Building, Manhasset, NY 11030; e-mail: amf49@aol.com

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4th Floor, Levitt Building, Manhasset, NY 11030; e-mail: amf49@aol.com