setting except for sicker patients (as characterized by low pH, persisting tachypnea, hypoxemia, etc).

Other minor questions about the guidelines regarding the exclusion of certain patients can be raised. For example, patients with pneumothoraces are excluded, with no provision for inclusion once appropriate drainage has been instituted. Also, patients with upper airway obstruction were excluded, yet a historically controlled trial[1] has indicated that NPPV is very effective at avoiding intubation in patients with postextubation respiratory failure, a group of patients in whom temporary upper airway obstruction related to glottic swelling is fairly common. Upper airway obstruction might be considered a relative contraindication, depending on the severity of the obstruction.

Despite these concerns, the guidelines created by Sinuff et al represent an important step toward the formulation of widely applicable guidelines for the implementation of NPPV. As the authors acknowledged in their discussion, guideline creation is a dynamic process. Modifications are made as new evidence becomes available, and in response to evaluations and experience. In addition, guidelines need to be tailored to individual institutions, taking into account staff and technical resource availability, and other unique characteristics. Sinuff et al have established that NPPV guidelines influence clinician behavior and thereby can facilitate the standardization of techniques. In this respect, guidelines are clearly helpful. On the other hand, unless they can be shown to improve the efficiency of resource utilization and/or patient outcomes, they also can be a hindrance, with the potential for needlessly increasing resource utilization. At present, the guidelines for NPPV should be considered a work in progress, with a strong endorsement awaiting better evidence of efficacy.

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Induced Sputum Analysis For T Helper Type 2 Cell Regulation

Closing the Loop

The past decade has seen notable progress in our understanding of allergic asthma. Despite clear advances in dissecting the molecular and genetic factors that contribute to the asthmatic phenotype, morbidity and mortality from asthma, especially in industrialized nations, is increasing.[1,2] However, there is cause for optimism in the development of new diagnostics and therapeutics. The application of techniques in molecular biology, specifically the investigation of the control of gene transcription, has become routine and accessible. With these applications, we have greater understanding of the early steps in the development of the immune response that is central to expression of the asthmatic phenotype.

Along with this new knowledge comes a myriad of potential new therapeutic targets. Two global controllers of transcriptional programs that define the two types of CD4+ helper T cells, T helper (Th) type 1 and Th2, have now been identified. γ-Interferon-producing Th1 cells are essential for acquired host defense against many infectious agents. The transcription factor that regulates the development of Th1 cells is T-bet.[3] Th2 cells are responsible for humoral immunity. The transcription factors that dictate their development are GATA-3 and c-Maf.[4,5] Th2 cells are defined by their synthesis of interleukin (IL)-4, IL-5, IL-9, and IL-13. While both types of Th cells are important for a fully developed acquired immune system, there are circumstances in which the inflammation that accompanies the immune

response is deleterious. The tissue destruction that accompanies granuloma formation in *Mycobacterium tuberculosis* is an example of Th1-mediated inflammation, while the atopic diatheses associated with allergic rhinitis, conjunctivitis, dermatitis, and asthma are examples of Th2 immune responses that are destructive. Notably, Th2 cells are recruited to the airways, and their products have been identified in cases of human asthma.[6] Along these lines, the overexpression of the Th2 cell-derived cytokines IL-9 and IL-13 in mice is sufficient to induce all the characteristics of asthma.[7,8]

In this issue of *CHEST* (see page 2074), Taha and colleagues identify key factors in the cellular differentiation of Th2 cells from induced sputum. The findings confirm our current understanding of Th2 cell development in atopic asthma and provide the background for the phenotypic characterization of expectorated immune cells in many lung diseases.

This translational study compared the prevalence of the Th2 differentiation transcription factors GATA-3 and c-Maf, the Th2 cytokine transcription factor STAT-6, and the Th2 cytokine receptor components IL-4Rα and IL-5Rα in sputum T cells of eight asthmatic individuals and eight healthy individuals. Thus, all phases of Th2 cytokine generation (*ie*, Th2 differentiation signals GATA-3 and c-Maf to IL-4, IL-5, and IL-13 generation, which leads to IL-4Rα and IL-5Rα ligation, which leads to STAT-6 signaling, and to the further expansion of Th2 cells) were inspected, providing a cell-by-cell picture of the "complete loop" of Th2 cell events. All five of these markers were significantly increased in asthmatic patients compared to control subjects. The tight regulation of the Th2 cell-driven response is evident in the significant but relatively small increase in the percentage of immunoreactive cells (approximately 3 to 12%).

While the increased expression of Th2 cytokine receptors and transcriptional regulators confirm the major phenotype of asthmatic airway inflammatory cells, the differential colocalization of cell-specific markers and cytokine receptor markers on cells expressing GATA-3, STAT-6, and c-Maf is particularly interesting. Nearly 90% of GATA-3-expressing cells are accounted for by T cells and eosinophils, but only about two thirds of cells expressing STAT-6 and c-Maf were accounted for by these cell types. Even considering the redundancy of transcriptional regulators, this finding highlights the likely contribution of nonimmune airway cells in cytokine synthesis. As expected, a high percentage (70%) of cells coexpressed STAT-6 and IL-4Rα. The fact that only 10% expressed IL-5Rα is consistent with the fact that IL-5Rα receptor activation is linked predominantly to STAT-5. Furthermore, the percentage of GATA-3/IL-4Rα-coexpressing cells is relatively low, so that many cells coexpressed c-MAF and IL-5Rα even though c-MAF is a specific inducer of IL-4. Taken altogether, these findings demonstrate that there are subpopulations of Th2 cells and that polarization is neither homogeneous nor linear.

The use of induced sputum for immune cell analysis requires some comment. Presumably, these cells have migrated into the airways. The implication is that the immune cells in sputum were at some time an important part of the airway inflammatory response and that this small sampling is representative of that response. Unfortunately, we do not know how the complexion of the sampled sputum population of T cells compares to intraepithelial and subepithelial immune cells. We do not know what percentage of effector cells is not represented, either because they do not transmigrate into the alveolar spaces or because they are lost (*eg*, by apoptosis) before they exit the airways, where they can be sampled by sputum induction. Similar criticisms can be made of the population of cells obtained by BAL. Thus, neither method provides a perfect window into airway epithelial biology. However, if paradigms for sputum T-cell phenotypes can be determined that serve as reliable markers of prognosis or therapeutic efficacy, the convenience of induced sputum as a source of T cells for study makes it a potentially powerful tool. The study by Taha et al demonstrates that all the cell-by-cell molecular techniques that are now used in experimental model systems are applicable to T cells in sputum. The authors attempt to address the conundrum posed in infectious airway diseases (in which we are never completely certain that upper airway contamination has not tainted our assessment of the bacteriology of the sputum) by selectively studying the T cells in sputum on a cell-by-cell basis. Unfortunately, we do not know whether T cells from the nasopharynx skew our interpretation of the inflammatory process in the lower respiratory tract. Further studies with these more sophisticated cell-specific techniques are required to be certain of the validity of the sampling technique.

Several additional questions remain that studies of this design could clarify. While the Th1 transcriptional controller T-bet has been reported[9] to be nearly absent in asthmatic bronchi and to be present in the airways of control subjects, it is also clear that the Th1 cytokine interferon-γ can be identified in asthmatic airways and BAL fluid. Since the Th1/Th2 polarization in humans is less discrete than that in mice, it will be important to determine a cell-by-cell analysis of the expression of interferon-γ and T-bet in asthmatic patients along with the factors measured in this study. Mice lacking T-bet spontaneously

develop an asthmatic phenotype.[10] If Th1 cells play an important modulatory role in airway Th2 inflammation,[11] then the simultaneous measurement of both Th1 and Th2 cells may give greater insights into the factors that determine asthma severity. Exposure to environmental factors that predispose a person to Th1 responses early in life have been postulated to play a role in limiting the responses to Th2-dependent allergens, but no direct evidence exists that this relationship plays a role in the severity of asthma in any individual person. Before defining pro-Th1-based therapies or anti-Th2-based therapies for asthma, objective evidence of the existence of the cells responsible for airway inflammation will be necessary for diagnosis and monitoring therapy. The types of measurements on sputum T cells that are defined in the article by Taha et al are just what will be necessary.

In summary, the investigation of Taha et al is important for several reasons. First, it validates the applicability of noninvasive sampling of airway secretions for descriptive studies in asthma[12] and other airway diseases.[13] In addition, the novel ability to phenotype individual cells simultaneously for transcription factors, cytokine messenger RNA, and cytokine receptors provides the potential for frequent monitoring of asthmatic subjects to customize treatment. Nevertheless, cautious optimism is warranted. The noninvasive nature of induced sputum comes at the price of partial sampling of the inflammatory response. T cells constitute a very small minority of expectorated nonsquamous cells (approximately 2%). It is likely that prior to the application of induced sputum as the sole "surrogate" for more invasive sampling methods, it will need to be validated in pilot studies in a disease-specific fashion. Once validated, the potential for the application of this noninvasive technique to clinical practice is great, not only in asthma but in many other lung diseases. The future holds promise.

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To Screen or Not To Screen

A Volatile Issue in Lung Cancer

Whether at international medical forums, within the halls of local hospitals, in medical offices, or in the lay press, the debate over whether or not to screen for lung cancer continues, even though the public demands guidance and few problems frustrate physicians more than their inability to prevent deaths from the disease. Affecting close to 200,000 people annually in the United States, this devastating malignancy is the most common cause of cancer death worldwide. Previously considered an affliction of