A multidisciplinary approach to diagnosis is a widely accepted principle in modern medicine. Most physicians and pathologists in particular adhere to this tenet and apply it to their daily practices. It may be fair to say that in any perusal of pathology reports generated at most US institutions, a good number of them would include phrases or sentences such as “clinical correlation recommended” or “this diagnosis cannot be made on histopathologic grounds alone, further interpretation is needed in light of clinical and radiographic findings.” Although pleas have been made in the past to bring clinicians and pathologists together, it is still unusual to see “clinical papers” in a pathology journal or to read a pure pathology article in a clinical journal. Hypersensitivity pneumonitis (HSP) is a multifaceted respiratory disease that may mimic almost any interstitial lung disease, some pulmonary infections, some cases of bronchiolar disease, and even cases of diffuse fibrosing diseases of the lung. Initially recognized only in farmers and pigeon breeders, HSP is now known to represent a rather broad group of complex, immunologically mediated lung disorders brought about by exposure to a variety of environmental, occupational, and recreational agents, resulting in a wide variety and sometimes substantial numbers of affected individuals, that is, workers in the textile and automotive industries.

Because of its clinical complexity, broadening spectrum of affected individuals, and still incompletely understood pathogenesis, HSP is particularly suitable for discussion using the previously cited multidisciplinary approach to diagnosis of pulmonary disease.

This special section in this issue of the ARCHIVES addresses clinical, histopathologic, and immunologic aspects of HSP. The special section is made up of 4 separate articles: my commentary and perspectives offered by 3 experienced physicians—a pulmonologist, a histopathologist, and an immunologist. Recognizing that HSP is clinically challenging, Dr Madison notes the disease can be quite variable in its clinical presentation, severity, and natural history and calls attention to the importance of considering HSP in the differential diagnosis of patients with interstitial lung disease because HSP is often treatable through avoidance of exposure to relevant antigen(s). The important question of whether a lung biopsy is needed for diagnosis is also explored by Dr Madison in his clinical article. In that regard he states: “When a clinical history identifies an offending antigen, positive precipitins are identified, and clinical and radiographic findings are consistent with HSP without suggesting another disease process, many clinicians would agree that invasive procedures are not always necessary.” However, when the clinical presentation is not typical and serologies, chest imaging studies, and inhalation challenges are not conclusive and the diagnosis still remains uncertain, lung biopsy will be indicated. To me, this is encouraging as it means that, at least for the time being, pathologists will continue to play a role in the diagnosis of this intriguing disease.

In his article focusing on the histopathology of HSP, Dr Barrios notes most lung biopsies are obtained during the subacute or chronic stage of the disease, as patients may not seek medical attention during its earliest acute phase. Consequently, most knowledge of the pathology of HSP is derived from biopsies performed during the subacute (or chronic) stage. In its subacute stage, there is typically a chronic bronchiolocentric, interstitial inflammatory process, which when occurring alone may mimic the idiopathic form of nonspecific interstitial pneumonitis. Also occurring in the subacute stage are loose or poorly formed granulomas, which often consist only of scattered multinucleated giant cells, with or without cholesterol clefting. Although this histopathologic triad (bronchiolocentricity, interstitial pneumonitis, loose granulomas) can be seen in about 70% to 80% of cases that come to biopsy, its presence is not absolutely necessary to make a diagnosis. In fact, there is a trend to “relax” the diagnostic criteria in HSP with only 2 of the 3 elements of the triad being needed for diagnosis, provided that sufficient clinical-radiographic and/or serologic compatible data are at hand. Youerkolis et al have gone one step further with their well-documented report of patients presenting with a pattern of nonspecific pneumonitis as the sole histopathologic expression of HSP, a clinically relevant issue because failure to distinguish HSP from idiopathic nonspecific interstitial pneumonia and to eradicate the provocative exposure may result in progression of the disease to a far more serious phase of pulmonary fibrosis. Once the disease progresses to its final fibrotic stage, the question may be asked: Is it possible to recognize the chronic stage of the disease? Citing features reported in a recent study, Dr Barrios notes...
that subpleural patchy fibrosis resembling usual interstitial pneumonia with isolated giant cells, a pattern of linear fibrosis resembling non-specific interstitial pneumonitis, and irregular fibrosis with peribronchiolar distribution would facilitate the recognition and diagnosis of HSP in its chronic stage but again only in light of appropriate clinical, radiologic, and serologic findings.

Hypersensitivity pneumonitis is an immunologically induced lung disease with features indicative of both immune complex-mediated and T-cell-mediated immune responses. Although much progress has been made in the understanding of these immune responses, there remains a number of unexplained features. In his immunopathology article, Dr Woda examines the pathogenesis of the disease, calling attention to 3 such unexplained features, namely why only some of the exposed individuals develop clinical disease, what triggers acute episodes after prolonged periods of sensitization, and what factors cause the disease to progress. In terms of susceptibility, there appears to be good evidence that individuals with a TH1 dominant response are more likely to develop clinical disease.

Do clinicians and practicing pathologists need to be well informed about these and other issues regarding the pathogenesis of HSP? The answer to this rhetorical question is a qualified yes, for a couple of reasons: first, of course, our inherent and compelling need “to know” and second, evidence provided by Ando et al15 and others suggesting these T-cell-mediated immune responses appear to be more crucial than previously suspected. As for T-cell-mediated responses, TH1/TH2 and TCD1/TCD2 cytokines produced by CD4+ and CD8+ T cells appear to play important roles in the development of granulomatous inflammation in the lung, an important element of the previously cited histopathologic triad of the disease. Another somewhat rhetorical question comes up: Is there a need to have a clinical discussion in an eminently pathology journal? Again, the answer is a categorical yes. Writing on the subject of clinician-pathologist interactions, Dr Andrew Churg1 stated: “In the best of all possible worlds, pulmonologists, thoracic surgeons, and pathologist would sit down and discuss each patient before a biopsy is performed.” To this group, the input of a radiologist and/or immunologist may also be sought, for example, in the interpretation of borderline imaging studies or in the interpretation of CD4/CD8 cell ratios in bronchoalveolar lavage specimens obtained from patients with suspected but not proven HSP.

In closing, in this special section of the ARCHIVES we bring together the perspectives of a clinician, a surgical pathologist, and an immunopathologist on a disease process that has a widening spectrum of patients, is no longer just for farmers and pigeon breeders, and is therefore of much interest not only to those interested in pulmonary disease but to practitioners of medicine at large. Whether you deal routinely with this entity in your daily practice or see it only in an occasional biopsy, we hope this review will be of value to you.

References
Armando E. Fraire, MD, is professor of pathology in the Department of Pathology of the University of Massachusetts Medical School, Worcester, where he also serves as director of the Autopsy Service. Dr. Fraire took his initial training in medicine as an intern at the University Hospital, Monterrey, Mexico, and most of his postgraduate training in pathology at Baylor College of Medicine, Houston, Tex. While at Baylor he worked under Drs. Harlan J. Spjut and the late S. Donald Greenberg. He credits Dr. Greenberg as a major influence in his career and for his lifelong interest in diseases of the lung. Dr. Fraire has been an invited speaker at numerous pathology meetings in the United States and abroad and has authored more than 80 articles in major national and international journals, mostly focused in pulmonary pathology. In addition, he has written or cowritten a number of chapters in pathology and thoracic oncology textbooks. Currently, he serves as an environmental pathology section editor for the Archives of Pathology & Laboratory Medicine.