the most recent 28 patients were treated by thoracoscopic operations (ie, video-assisted thoracoscopic surgery [VATS]). This is to their credit. Certainly, most mesothelial and thymic cysts can be handled by VATS. Bronchogenic cysts, which are the most likely cysts to require treatment for symptoms, in contrast, are often associated with a fibrotic reaction that makes VATS dissection difficult. Martinod and associates,6 for example, had to convert to thoracotomy in 7 of 20 such cases that were initially approached by VATS, two because of significant bleeding. The mean hospital length of stay in this report was 5 days for the VATS group and 8.5 days for the open surgery group. Of the 20 patients reported on by Zambudio and colleagues,7 5 had complications, one of which was phrenic nerve paralysis after the resection of a mesothelial cyst.

In summary, the belief that all mediastinal cysts in adults should be treated surgically requires reconsideration. Malignancy is not an issue. The cyst is often not related to the presentation. Modern imaging is highly accurate in delineating simple cysts. Resection is not without hazard. For classic simple cysts, unlike some indeterminate pulmonary nodules, for example, follow-up in many cases need not be frequent or expensive. The use of words such as tumor, the possibility of missing cancer, the fear of future catastrophe, and claims that an operation is always catastrophic, and claims that an operation is always unnecessary is the only option appear to me to cloud a rational approach to mediastinal cysts. Nonetheless, any mediastinal cyst that is not classically “simple” or is one that is clearly causing symptoms warrants intervention. In many cases, percutaneous aspiration or mediastinoscopy may obviate the need for thoracotomy or VATS.8–10

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The Etiologic Agent of Sarcoidosis

What If There Isn’t One?

Yesterday I evaluated a new patient with sarcoidosis who asked whether the disease was caused by her work as a short-order cook. The week previously, a patient wondered whether his work in a textile mill caused his sarcoidosis, while another was convinced that her sarcoidosis resulted from furniture polish fumes. In the past, I would have given my standard answer to such queries: although we do not know what causes sarcoidosis, there is no evidence suggesting an excessive number of cases in short-order cooks, textile workers, and those exposed to furniture polish. In short, these patients’ exposures had been unlikely culprits in the development of their disease.

This is no longer my answer to my patients’ questions, and the provocative article by Reich in this issue of CHEST (see page 367) explains the reason for abandoning it. There is mounting evidence suggesting that the “cause” of sarcoidosis does not relate to a specific exposure but rather to an abnormal host immunologic response to one of several exposures.

A necessary interplay between specific combinations of exposures and host responses in the pathogenesis of sarcoidosis would explain why so many studies have come to conflicting conclusions regarding the etiology of the disease. For example, two studies1,2 using polymerase chain reaction techniques have detected mycobacterial DNA in the lung tissue of 44% and 50%, respectively, of sarcoidosis patients, while other studies3–6 have established that mycobacterial DNA was rare or absent in sarcoidosis. As stated by Reich, one study linked sarcoidosis to human-made mineral fibers,7 whereas another

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large study of human-made mineral fiber workers found no such association.8 Although some studies have shown a higher prevalence of *Propionibacterium acnes* and Chlamydia species in the lungs of sarcoidosis patients than in control subjects,9,10 these findings have not been universal.11,12

Our current understanding is that the development of sarcoidosis requires at least the three following major events: exposure to an antigen; acquired cellular immunity directed against the antigen mediated through antigen-presenting cells and antigen-specific T-lymphocytes; and the appearance of immune effector cells that promote a non-specific inflammatory response.13 More specifically, alveolar macrophages from patients with pulmonary sarcoidosis show enhanced antigen-presenting capacity by the enhanced expression of human leukocyte antigen (HLA; major histocompatibility complex)-class II molecules, which is probably induced by an interaction with the sarcoidosis antigen and possibly interferon (INF)-γ.14 These macrophages recognize, process, and present the putative antigen to CD4+ T cells of the T helper (Th)-1 type.14 These activated macrophages produce IL-12, which induces a lymphocyte shift toward a Th-1 profile and causes T lymphocytes to secrete INF-γ. These activated T cells release IL-2 and chemotactic factors that recruit monocytes and macrophages to the site of disease activity.14 IL-2 is also activated and expands various T-cell clones.15 INF-γ is able to further activate macrophages and to transform them into giant cells, which are important building blocks of the granuloma.14,16

Therefore, the evidence suggests that the immunologic process that leads to sarcoidosis begins when an antigen is presented by a macrophage via HLA class II molecules to a T lymphocyte. This induces a Th-1 T-lymphocyte response whereby cytokines are released that result in granuloma formation. Scandinavian investigators17 have demonstrated a strong association of a specific class of lung T cells bearing Vα2.3 T-cell-antigen receptors in patients with clinically active acute sarcoidosis. These patients express HLA-DR3, DQ2. These results suggest that a single antigen paired with a single antigen-presenting molecule may trigger the immunologic response that results in this sarcoidosis phenotype.13 However, many other sarcoidosis patients have more than one T-cell clone or no increase in oligoclonal T cells.13 In addition, different sarcoidosis phenotypes are associated with different HLA class II molecules.18 These data support the concept that there are multiple sarcoidosis antigens or epitopes recognized by different T-cell clones that are paired with different HLA class II molecules.13

Reich further speculates that the granulomatous response of sarcoidosis represents an “immunologic fallback position” in persons who are unable to clear the immunologic agents in a more efficient manner. The data to support this conjecture are minimal. Reich’s foundation for this concept consists of one abstract19 that examined the intradermal injection of Kveim reagent. In that study, healthy subjects demonstrated features of delayed hypersensitivity, including infiltrates of Th and suppressor cells with markers of activation (eg, Tac+ and Leu9+) and dendritic Langerhans cells (eg, OKT6 and RFD+) with strong HLA-DR expression 11 and 18 days after intradermal injection. In contrast, Kveim-positive sarcoidosis patients failed to develop this response. These findings suggest that the granulomas of sarcoidosis may be the result of a sluggish delayed hypersensitivity response, which subserves the antigen, allowing it to remain undetected or to be inadequately cleared from tissue.

Although a paucity of investigational data supports the model of ineffective clearance of putative sarcoid antigens by the sarcoid granuloma, Reich cites an abundance of clinical evidence. This concept would explain why corticosteroids might promote the relapse of sarcoidosis20–22 by possibly further inhibiting the already sluggish granulomatous response. It would also explain why patients who have a brisk immunologic response, such as those with erythema nodosum, have a good prognosis. And, it would explain why individuals with combined variable immunodeficiency, many of whom have an associated deficiency in T lymphocytes, have a high rate of developing sarcoidosis.23

However, the concept that sarcoidosis granulomas are inefficient at clearing antigens does not explain all the clinical aspects of the disease. For instance, it does not explain the sarcoidosis-like reaction that can occur when highly active antiretroviral therapy is given to HIV-infected patients.24 It is likely that the antigens that cause sarcoidosis are present in the HIV-infected individual who has a low CD4+ count. However, the CD4+ lymphocyte number and function is inadequate to mount a significant Th-1-induced granulomatous response until highly active antiretroviral therapy is administered.25 Therefore, in this example, sarcoidosis develops in a better constituted immune system, not in a more defective one. Inefficient clearance by sarcoid granulomas also would not explain the development of sarcoidosis in allografts following transplantation,26 as supposedly these transplanted organs would be free of the antigen in the excised tissues that caused the granulomatous response. Possibly, granulomas are formed in this instance by the immunologic response cross-reacting with allograft tissue instead of an antigen.
Regardless of the answers to these concerns, it is sobering to consider Reich’s argument that there is not any one single agent and that there is not one discrete immunologic defect that causes sarcoidosis. For sarcoidosis to occur, patients may have to experience a specific interaction between one or several exposures and one or several abnormal immunologic responses. If this model is correct, it will be extremely difficult to prove. And perhaps the absence of proof for any etiology of sarcoidosis may be the most compelling argument supporting Reich’s hypothesis. We still have not figured out the cause of sarcoidosis perhaps because there is not just one cause.

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Treatment of Pulmonary Arterial Hypertension

A Step Forward

No great improvements in the lot of mankind are possible, until a great change takes place in the fundamental constitution of their modes of thought.

John Stuart Mill, 1873

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of the pulmonary vascular bed. If untreated, PAH progresses to