CHEST

EDITORIALS

## In Pursuit of Pneumocystis Carinii

The clinician confronting a critically ill patient with a diffuse, infiltrative pneumonitis is faced with a variety of diagnostic possibilities. In recent years, an increased awareness of so-called opportunistic infections has further strained the differential diagnosis and its attendant demands. Since specific therapy is available in many instances, it has become axiomatic that the definitive pathogen be established.

In this light, such predatory organisms have assumed increasing significance in patients with compromised cellular immune mechanisms, including the following causes: immunosuppressive drugs, adrenal corticosteroids, antimetabolites, antimicrobials, diabetes mellitus, collagen vascular disease, cardiac or renal homotransplantation, debilitating or neoplastic disease, and gamma globulin deficiency disorders. Many excellent reviews have dealt with this problem, sufficing to indicate that both typical and rare infectious agents may be causative.[1,2] Among the bacteria, certain Gram-negative bacilli such as *Mycobacterium tuberculosis* or staphylococci are important considerations. Considerable attention is now focused on select mycoses, generally considered harmless or saprophytic, which may become pathogenic under any of the above cited circumstances. Particularly interesting has been the documentation of invasive Aspergillus species and *Nocardia asteroides*, although Candida, Cryptococcus and Mucor, among others, have been incriminated. Such fungal infections may arise with alarming rapidity and be lethal unless prompt and specific diagnoses are established. While somewhat characteristic radiographic features may suggest the possibility of nocardiosis, aspergillosis, or cryptococcal infection by focal bronchopneumonia, cavitation, or necrosis, careful scrutiny of expectorated materials, bronchoscopic washings, or even biopsy is necessary to specifically demonstrate their presence. It is important to realize that their absence by microscopic examination of pathologic secretions does not necessarily rule out their tissue existence, which may be discovered on subsequent culture or at the time of lung biopsy or postmortem examination. Compounding the matter is the possibility of a viral interstitial pneumonitis, particularly the medium-sized DNA members of the herpes virus group including Varicella-zoster virus, herpes simplex, and cytomegalovirus. The latter has been most implicated in patients with abnormal defense mechanisms. Although there is a high rate of recovery in some series of patients with renal transplantation on whom autopsy was performed (approximately 50 percent), the antemortem diagnosis by cytologic technique, tissue biopsy, culture or rising complement-fixing antibody titers is presently frustrated by lack of definitive therapy.[3]

Finally, the diagnostic problems associated with *Pneumocystis carinii* infestation are highlighted by the report of Hodgkin, Andersen and Rosenow in this issue of *Chest* (see page 551), which focuses on the parasitic group of opportunistic pathogens. Well known to European pediatricians dealing with premature infants, debilitated children, or those with immunologic disorders, *Pneumocystis carinii* has been recognized with greater frequency in the United States in a variety of immunosuppressed patients, in particular those endangered by hematologic, lymphoproliferative or neoplastic disease, or homotransplant recipients. A basic underlying feature of these cases is the use of immunosuppressant or adrenal corticosteroid drugs.

The clinical, radiographic and pathologic features of published cases reveal a similar pattern. Following an appropriate interval of immunosuppressant therapy, dyspnea, pyrexia, an irritative cough, and progressive pulmonary infiltration with variable auscultatory findings develop. The onset of the illness may be florid or insidious in nature, with a course fulminant and lethal if untreated. A diffuse interstitial and alveolar pattern spreading from the perihilar zones into the middle and lower lobes of the lungs is commonly observed on the chest x-ray film. As might be expected in association with a reduced lung compliance, the usual gas exchange abnormalities arise by ventilation/perfusion inhomogeneity as manifested by hypoxemia and hypocapnia; hypercapnia is an unusual finding until late in the course. Regrettably, these findings are rarely useful in identifying the causative process. It

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is by specific lung histology that the characteristic features of the lesions are revealed, consisting of both an inflammatory process in the interstitium and a prominent foamy intra-alveolar latticelike exudate within which the characteristic cysts of *Pneumocystis carinii* can be demonstrated with appropriate stains such as toluidine blue or methenamine silver.

Currently, the methods of establishing this specific diagnosis are of paramount importance. There are presently no dependable means of isolating *Pneumocystis carinii* nor are serologic assays generally available, although a nonspecific evaluation of cold agglutinins has been reported which can also occur in cytomegalovirus infections.[4] In the appropriate clinical setting, *a high index of suspicion* is needed to initiate the appropriate investigations. Essentially, the diagnosis is established by identifying the cysts of the protozoan in the lung or its pathologic secretions. Although its isolation from sputum secretions has been reported, and must be considered pathognomic if so recovered, most patients do not raise significant volumes of sputum. Thus, in the past few years the emphasis has been on recovery by lung biopsy with opinions divided on the matter of open thoracotomy vs. percutaneous needle biopsy. As far as can be determined, open biopsy, despite its attendant morbidity, generally carries a high diagnostic yield. Alternatively, the percutaneous route, either by cutting or aspiration biopsy, has been favorably viewed because of its applicability in critically ill patients with marginal pulmonary reserve, and to a lesser extent because it is expeditious; the adequacy of tissue recovery by needle biopsy may be extrapolated from large series of diffuse lung disorders to average from 80 to 90 percent. However, even here complications of bleeding or pneumothorax and false-negative results have occurred.[5]

Alternative, high yield, diagnostic procedures with low morbidity are clearly desirable. The morbidity of transtracheal aspiration is low, but from available American data so too is the specimen yield. Repsher et al[6] have recently reviewed their experience with endobronchial brush biopsy in a series of 19 patients suspected of having *Pneumocystis carinii*. The diagnosis was confirmed in ten cases, although false-negative results may have been present in another five of their patients. In their hands the procedure was considered safe and well tolerated, even by severely ill patients. Finally, the approach presented by Hodgkin, Andersen and Rosenow involves the use of transbronchoscopic lung biopsy. The transbronchoscopic biopsy was effective in documenting *Pneumocystis carinii* in 7 of 522 patients who underwent this procedure, with a reported zero false-negative rate, although we are uncertain as to actual documentation in the remaining 515 patients. This is not a new technique, having been recently used by Andersen[7] in diffuse pneumonopathies, with a tissue yield of 82 percent. As the authors appropriately advise, this population sample of seven patients is too small from which to draw adequate conclusions or to compare with other diagnostic approaches. The discussion of this paper also highlights other relatively unsuccessful methods for the detection of *Pneumocystis carinii*.

What may we conclude? First, that infectious problems continue to demand sound diagnostic attitudes. Secondly, uncommon or unusual invaders are more frequent as the result of augmented supportive therapy or immunosuppression, by disease or therapy. Thirdly, empirical therapy is rarely warranted in these potentially grave infectious, diffuse, interstitial (intra-alveolar) disorders, although in select circumstances such empirical decisions may be required, at least initially. The availability of effective chemotherapy in the form of pentamidine isethionate, or more recently reported pyrimethamine and sulfadiazine, as well as the host toxicity of pentamidine are valid reasons to support this premise in treating patients with *Pneumocystis carinii*. Moreover, although it is infrequent, such immunocompromised patients may be susceptible to infection with more than one "unusual" organism.[8] Fourthly, a specific diagnosis should be obtained by the procedure with the "highest yield and lowest morbidity" as the primary determinant. In this regard several approaches concurrently appear acceptable for the diagnosis of *Pneumocystis carinii* pneumonia; the most effective or appropriate technique will ultimately rest with local expertise and other individual considerations.

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