Acquired Immune Deficiency Syndrome and the Lung

John A. Rankin, M.D., F.C.C.P.;* Ronald Collman, M.D.;† and Ronald P. Daniele, M.D., F.C.C.P.†

In 1981, the Centers for Disease Control reported five cases of Pneumocystis carinii pneumonia in five previously healthy male homosexuals. Prior to this report, Pneumocystis carinii pneumonia occurred mainly in severely immunosuppressed patients who were receiving chemotherapy for cancer or organ transplants. Subsequently, numerous additional reports began to emerge describing opportunistic pneumonias and infections in male homosexuals, intravenous drug users, hemophiliacs, and in Haitians; many of these patients also manifested an unusual and aggressive form of Kaposi sarcoma. Thus, what first appeared to be a medical curiosity has loomed as one of the most pernicious epidemics of our century. It is a disease that appears to be uniformly fatal and is predicted to afflict as many as 270,000 individuals in the USA by 1991.1

From the outset it was recognized that the cause of these unusual opportunistic infections was related to a severe and progressive derangement of the systemic immune system, leading to its designation as an acquired immune deficiency syndrome (AIDS). Despite its dominant manifestations in the lung, most studies of AIDS have been aimed at elucidating the immune abnormalities at the systemic level; relatively little information has been gathered on the effects of this disease on the host defenses of the lung.

The purpose of this review will be first to identify what is currently known about the impact of this virus and disease on the immune apparatus of the lung, and then to discuss the pulmonary manifestations and management in the patient with AIDS. For interested readers, there have been several excellent general reviews dealing with the epidemiology, clinical features and systemic aspects of immunopathogenesis.2-5

PULMONARY IMMUNE ABNORMALITIES

Much of our current knowledge of the immunologic abnormalities present in the lungs of patients with AIDS comes from studies using bronchoalveolar lavage (BAL). Early in the epidemic, it was appreciated that BAL was an important tool for the diagnosis of Pneumocystis carinii pneumonia,6,11 and it was recognized that both clinical and research purposes could be served by the judicious use of this BAL fluid. Also noticed early on in the epidemic was that patients with AIDS were particularly prone to infections that are predictive of a defect in the macrophage/monocyte-T-cell axis. These include infection with the parasites Pneumocystis carinii and Toxoplasmosis gondii, with the fungi Cryptococcus neoformans and Candida albicans, with certain bacteria such as the Mycobacterium species, and certain viruses such as Cytomegalovirus. Although abnormalities in T-cell immunity were appreciated first, more recent studies reveal that humoral immune components as well as cell-mediated immune components of the immune system are defective in this disease.12

At least four separate centers have reported results of analyses of cellular components of BAL fluid from patients with AIDS.13-16 A review of these data provide insight into some of the immunologic events occurring in the lower respiratory tracts of patients with AIDS. The cellular data collected in these studies are summarized in Table 1. Alveolar macrophages, in all of these studies, were present in normal quantities. Clearly then, the high incidence of pulmonary infection is not due to a numerical deficiency of macrophages.

By traditional staining methods, such as Wright’s stain, macrophages from AIDS patients are not distinguishable from those of normal individuals. Are these cells functionally intact and, if not, is the defect an intrinsic cell abnormality, or is it due to a lack of lymphokine activation of the macrophage? The answer is not known. However, one can speculate from studies using peripheral blood monocytes,17-19 precursors of the alveolar macrophage, or Langerhans’ cells,20 macrophage-like cells in the skin, that alveolar macr-
phages from patients with AIDS do not function normally and that this defect is likely to be due in part to a deficiency in macrophage conditioning by lymphokines. Macrophages and monocytes are antigen-presenting cells and are required for optimal immune responses to pathogenic organisms. Recent studies of the normal immune system reveal that antigen presentation is tied intimately to the expression of class II histocompatibility antigens on the surface of monocytes.21 One report suggests that many patients with AIDS have decreased numbers of circulating HLA-DR+ monocytes;19 another reports that Ia expression is actually increased.22 However, additional studies have found that antimicrobial function of peripheral blood monocytes is intact in patients with AIDS.23,24 Monocyte incubation in vitro with human gamma-interferon (gamma-IF) reconstitutes HLA-DR positivity to near normal levels19 and incubation with lymphokines or interferon enhances antimicrobial activity. In addition, monocytes from patients with AIDS respond to and show enhanced activity against intracellular pathogens in response to in vitro activation with gamma-IF or when gamma-IF is administered in vivo.25 These observations form part of the rationale for the use of these substances in attempts to bolster the weakened immune system of patients with AIDS. Macrophage/monocyte antigen presenting capabilities also may be adversely altered in patients with AIDS, in part because of inadequate conditioning by lymphokines such as gamma-interferon. Indeed, additional data reveal that peripheral blood monocytes from both AIDS patients and from homosexuals with lymphadenopathy and abnormal immune profiles do not respond normally to chemotactic stimuli.17 Furthermore, one study demonstrates that peripheral blood monocytes from AIDS patients do not regulate T-cell responses normally.16 Hence, monocyte defects may arise secondary to decreased numbers and defective function of lymphocytes which do not produce normal amounts of some lymphokines.21 The mono-
cyte/macrophage defects observed to date appear explicable on the basis of the loss of helper-inducer lymphocytes and the consequent lack of sufficient lymphokines, such as gamma-IF, which are essential for effective macrophage handling of pathogenic organisms.

Several pieces of evidence reveal that at least some monocytes/macrophages in patients with AIDS are infected with HIV-1. First, HIV-1-like retrovirus particles have been observed in lymph node macrophages from two patients with AIDS.26 Second, normal peripheral blood monocytes can be infected in vitro27-29 and HIV-1 can be recovered from the monocytes of infected patients.27 Infection of these cells probably occurs via the T4 antigen which is present at low levels on their surface.28 Viral budding and infection, however, are less compared to that of T-cells.29 Third, human pulmonary macrophages can be infected in vitro with HIV-1.30 Moreover, when infected, these cells produce small quantities of virus that were able to infect allogenic peripheral blood mononuclear leukocytes.30 Interestingly, the infected macrophages were more resistant to the cytopathic effects of the virus than lymphocytes. Pulmonary macrophages from a few patients with AIDS harbor or spontaneously produce low levels of virus,30 suggesting the presence of infection in vivo. Thus, macrophages are a target for HIV-1 infection and are potential sources for viral dissemination.

An additional manner by which macrophage function may be adversely affected is by infection with opportunistic organisms such as cytomegalovirus (CMV). This pathogen frequently is isolated from lung secretions of patients with AIDS. Alveolar macrophages from a guinea pig model of CMV pneumonia demonstrate marked decreases in oxygen consumption and hydrogen peroxide production,31 suggesting that the bactericidal properties of these cells may be affected adversely.

Studies to date on lung lymphocytes largely are
The major finding by all groups who have studied patients is that both the percentage of total cells that are lymphocytes and the total number of lymphocytes in BAL are increased significantly (Table 1). Subtyping of these cells using commercially available monoclonal antibodies reveals that the majority of these cells are suppressor-cytotoxic lymphocytes. The percentage of helper-inducer lymphocytes in BAL is decreased, but because there is an absolute increase in lymphocyte numbers, the total helper-inducer cell quantity may be low, normal or elevated. It is particularly noteworthy that these findings occur in patients who at the same time have decreased numbers of peripherally circulating helper-inducer and suppressor-cytotoxic lymphocytes and especially in view of the fact that HIV-1 selectively destroys helper-inducer cells. One potential explanation for these observations is that lymphocytes of both subtypes are sequestered in the lung. Alternatively, it is possible that local expansion of lymphocytes, especially of the suppressor-cytotoxic variety, occurs in the lower respiratory tract for, as yet, unknown reasons. Functional studies of lymphocytes retrieved by BAL are needed to answer these questions. The cell profile of lavage cells from patients with the AIDS-related complex (and therefore by definition without opportunistic pulmonary infections) is similar, confirming that the findings in patients with the most severe manifestations of the disease are primary and not secondary to infection with opportunistic pathogens.

A small subset of AIDS patients demonstrate increased numbers of neutrophils in BAL (Table 1). In these patients, no consistent association with a particular pathogen exists. Rats treated with corticosteroids will develop Pneumocystis pneumonia. The occurrence of bacterial pneumonia in this animal model is associated with a marked influx of neutrophils into the lungs, and appears to afford protection against the development of Pneumocystis pneumonia, suggesting that this cell may have a protective role. Examination of patients with AIDS with an increased number of neutrophils in their lavage fluid, however, does not support a protective role for this cell in human Pneumocystis pneumonia.

It is also recognized that systemic humoral immunity is abnormal in patients with AIDS. Albumin is synthesized only in the liver, and its presence in increased quantities in BAL fluid of patients with AIDS compared to normal subjects (Fig 1) suggests that the integrity of the alveolar-capillary membrane

**Figure 1.** BAL and serum proteins. Total albumin retrieved in the BAL of patients with AIDS compared to normal subjects (panel A). IgG, IgA, IgM levels in BAL and blood of patients with AIDS and normal controls (panel B). Shaded areas represent the mean ± 2 SD of values for 25 normal controls. Triangles indicate smokers and circles indicate nonsmokers. Levels of albumin in panel A are the total milligrams of albumin retrieved (mg/ml in concentrated BAL × volume of concentrated BAL). In panel B immunoglobulin levels in BAL and blood are expressed as a ratio of immunoglobulin (mg) to albumin (mg). All p values refer to the comparison between patient values and normal controls. (Reproduced with permission from Young KR Jr, Rankin JA, Naegel GP, Paul ES, Reynolds HY. An immunologic analysis of bronchoalveolar lavage cells and proteins in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1985; 103:522-33.)
is compromised. As a result, some serum proteins escape into the alveoli. Quantification of some of the lung humoral immune components sampled by BAL reveals that patients with AIDS have significant increases in IgG and IgA, but not IgM (Fig 1). It is likely, therefore, that some of the increase in BAL immunoglobulin may be due to transudation from the intravascular space. It is also possible, however, that local production by plasma cells in the lung may be an additional source. AIDS patients demonstrate hyperactive peripheral blood B cells that are spontaneously secreting immunoglobulin. Similar studies with cells retrieved by BAL reveal that the lungs also may be an important site of immunoglobulin production.

In an early study of two patients with AIDS and Pneumocystis pneumonia, IgG, IgA and IgM antibodies to Pneumocystis were observed in BAL fluid. However, in this study antibody to this parasite also was observed in normal control subjects and control subjects with idiopathic interstitial lung disease. The number of patients examined was too small to permit statistical comparisons with control subjects. More recently, in collaboration with Drs. Linda Piñer and K. Randall Young, Jr., these studies have been expanded to a larger number of AIDS patients with Pneumocystis pneumonia. The results revealed that the level of IgG anti-Pneumocystis antibody was significantly higher in normal healthy adults (Table 2). However, the mean levels in AIDS patients were similar to those in a control group of noninfected patients with sarcoidosis or idiopathic pulmonary fibrosis. These observations support previously reported data on studies of peripheral blood which indicate that B cells are polyclonally and nonspecifically activated and unable to respond appropriately to antigenic stimuli. Also noteworthy is that serum IgG anti-Pneumocystis antibody levels in patients with AIDS were not significantly different from levels in either control group, at a time when BAL levels were increased (Table 2).

In summary, the patient with the most severe form of HIV-1 disease possesses complex immunologic abnormalities which encompass all arms of the immune system. Studies of the lungs of these patients using BAL have revealed insights into defects not obvious from studies of peripheral blood. The pronounced incidence and wide variety of opportunistic lung infections in patients with AIDS provides a unique opportunity to investigate local pulmonary immune capabilities and responses in this disease and expand our overall understanding of lower respiratory tract defenses.

**Clinical Pulmonary Manifestations**

The infectious agents causing pulmonary disease most frequently in patients with AIDS are listed in Table 3. In general, the presence of infection with any of these organisms is particularly frequent in patients with major defects in the macrophage-T-cell axis of systemic immunity. Most of these pathogens can endure in macrophages and monocytes. The actual killing of these organisms depends on intact lymphocyte immune responses which, in part, control macrophage/monocyte antibacterial activity.

The most commonly recognized pulmonary pathogen in patients with AIDS is *Pneumocystis carinii*, which causes pneumonia at least once in 50-90 percent of all patients. Data are mounting in support of the hypothesis that infection with this organism is due to reactivation of latent infection.

The clinical presentation of Pneumocystis pneumo-

---

**Table 2—Anti-Pneumocystis Carinii Antibody in Bronchoalveolar Lavage Fluid and Serum from Patients with AIDS***

<table>
<thead>
<tr>
<th></th>
<th>AIDS</th>
<th>Normals</th>
<th>ILD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Pn C Ab‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAL</td>
<td>130.5±</td>
<td>36.1</td>
<td>150.8±</td>
</tr>
<tr>
<td>(n=6)</td>
<td>±54</td>
<td>±16.1</td>
<td>±46</td>
</tr>
<tr>
<td>Serum</td>
<td>57.5</td>
<td>63.9</td>
<td>83.1</td>
</tr>
<tr>
<td>(n=5)</td>
<td>±36</td>
<td>±22</td>
<td>±22</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SEM.
†ILD = interstitial lung disease (sarcoidosis, idiopathic pulmonary fibrosis).
‡Expressed as the reciprocal IgG titer/IgG level mg/ml.
§p<0.001 compared to normal controls.

---

**Table 3—Types of Pulmonary Infection in AIDS**

<table>
<thead>
<tr>
<th>Organism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protozoa</td>
<td></td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>7, 9-11, 13, 38-41</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>44-47, 51, 58, 77</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>9</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>71</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>8, 66, 68</td>
</tr>
<tr>
<td><em>Aspergillus species</em></td>
<td>7, 42, 51</td>
</tr>
<tr>
<td><em>Mycobacterium avium-intracellulare,</em></td>
<td>9, 13, 51, 57, 59-64</td>
</tr>
<tr>
<td><em>Legionella</em>, <em>Klebsiella</em>, <em>Hemophilus</em></td>
<td>9, 51, 55, 72-74</td>
</tr>
<tr>
<td><em>Streptococcus</em>, <em>Staphylococcus</em>, <em>Mycoplasma</em>, <em>Branhamella</em>, <em>Pseudomonas</em>, <em>Enterobacter</em></td>
<td>70</td>
</tr>
</tbody>
</table>

AIDS and the Lung (Rankin, Collman, Daniele)
nia in AIDS is characterized by chronic but nonspecific respiratory symptoms—usually present for weeks to several months prior to diagnosis. These symptoms include nonproductive cough, fever and dyspnea. Auscultation of the chest may reveal inspiratory crackles, but frequently reveals normal breath sounds. The respiratory rate is elevated depending on the stage of the infectious process. Room air arterial oxygen tension usually is low but may be normal, and quantification of the alveolar-arterial difference in PaO₂ particularly with exercise, may be a more sensitive indicator of active disease. Abnormalities in lung function consistent with diffuse alveolar disease include reductions in total lung capacity and vital capacity, increased expiratory flow rates, and a reduced single breath diffusing capacity for carbon monoxide. The most frequent chest roentgenographic abnormality is diffuse and bilateral alveolar/interstitial infiltrates that may remain stable, improve, or progress rapidly over a few days. Occasionally, unilateral interstitial infiltrates are present. Cystic or honeycomb lesions also can be seen. Patients presenting with completely normal chest roentgenograms have been reported, but localized consolidation is distinctly atypical. Pleural effusions and hilar adenopathy are more commonly associated with Kaposi's sarcoma, and may be seen in patients with tuberculosis or infection with atypical mycobacteria. Data reported at a National Heart, Lung and Blood Institute workshop identified that gallium scanning had a sensitivity of 98 percent but only a 47 percent specificity. Normal scans at the time of Pneumocystis infection are rare but do occur (Rankin, personal observations).

More than one pathogen is often isolated from the lungs of patients with AIDS. Cytomegalovirus (CMV) only occasionally causes clinical and chest roentgenographic pneumonia by itself. Most frequently, it is found in addition to other pulmonary pathogens. The precise incidence of CMV pneumonia is difficult to ascertain from the literature as it depends upon how one defines the condition. In the largest reported series of pulmonary complications of AIDS, cytomegalovirus infection was diagnosed either by culture or by virtue of its characteristic cytopathic changes in 74 of 441 patients. Mycobacterium avium-intracellulare can be grown from lung specimens in many patients with AIDS. Not surprisingly, this species and other atypical mycobacteria also may be isolated from blood and multiple organ sites.

Pulmonary infection with several fungi may occur. Cryptococcus predominates but Histoplasma, Aspergillus and Coccioidioides infection are reported. Patients with AIDS have a high incidence of oral and esophageal candidiasis. The isolation of this fungus from sputum, therefore, in most cases is not indicative of pulmonary infection. Indeed, few reports of pneumonia due to Candida exist in this patient population. Pulmonary infection with Toxoplasma, Legionella, and other bacterial species, Nocardia, Listeria and Cryptosporidia do occur. There are few clinical characteristics specific for these infections. Consequently, lung tissue or secretions must be obtained to diagnose any or all of them.

Pulmonary infection with pyogenic bacteria also represents a problem for the individual with AIDS. Any organism that is pathogenic for persons with an intact immune system may cause pneumonia in the AIDS patient (Table 2). The clinical presentation of bacterial pneumonia is similar to that seen in other immunocompromised hosts. While the overall incidence of lung infection with opportunistic organisms exceeds that due to the pyogenic bacteria, the clinician should not forget that bacterial pneumonias do occur in patients with AIDS, that they represent a serious threat to the host, and that they require aggressive evaluation and therapy.

DIAGNOSTIC PROCEDURES

Several similar algorithms outlining the diagnostic approach to pulmonary complications in AIDS exist. They are based on extensive experience with AIDS or represent the combined experiences of several institutions. The exact approach at different institutions should vary slightly based on local experience with the disease and the reliability of available diagnostic tests. Examination of induced sputum is the procedure of choice for the initial evaluation of Pneumocystis carinii pneumonia (PCP) in patients with AIDS. Investigators with extensive experience in this use of sputum report that as many as 70 percent of patients with PCP can be diagnosed by this method. Inductions with hypertonic saline solution (3-5 percent), the careful preparation of the patient, processing of the specimen, and reading by an individual with experience undoubtedly contribute to this success rate. Clearly, the patient benefits from the avoidance of more invasive and costly procedures. In hospitals not set up to procure and analyze sputa for PCP, the choice of sputum examination versus fiberoptic bronchoscopy should be left up to the physician caring for the patient.

Ample data support the use of fiberoptic bronchoscopy with brush biopsy, bronchoalveolar lavage and transbronchial biopsy as the initial invasive procedure aimed at diagnosing pulmonary disease in AIDS patients. Fiberoptic bronchoscopy in patients with AIDS has a high yield for diagnosing lung infectious complications, particularly Pneumocystis carinii infection. If initially nondiagnostic, a repeat bron-
choscopic examination frequently will establish the diagnosis. The yield of bronchoalveolar lavage and transbronchial biopsy in PCP are each about 90 percent, and together are greater than 95 percent. These yields are lower for all opportunistic infections as a group. Brush biopsy is occasionally also useful, but less often than bronchoalveolar lavage and transbronchial biopsy.

Experience with the use of bronchoalveolar lavage to diagnose pulmonary infections in patients with AIDS has been particularly rewarding. It is essential to point out the difference between bronchoalveolar lavage performed, and bronchial washing, or airways lavage as washings are sometimes referred to. This latter procedure is performed through a nonwedges—more proximally positioned—bronchoscope tip with smaller volumes of fluid. Therefore, bronchial washings preferentially sample airways. By contrast, the instillation of a minimum of 100 ml of saline solution is required during bronchoalveolar lavage if a sample representative of alveolar material is to be obtained. Since Pneumocystis carinii is predominantly an alveolar process, it is logical that sampling alveolar material would be more likely to reveal pathogenic organisms. Like many procedures, the exact diagnostic yield will depend on the experience of the bronchoscopist and the availability of facilities and personnel to handle the specimens. The processing of BAL fluid is straightforward. In our centers, BAL fluid is first filtered through a single layer of sterile gauze to remove large aggregates of mucus and centrifuged at 500 × G for 10 minutes to sediment cellular material. The supernatant is saved for research purposes and viral culture and the cells are resuspended in a physiologic solution at 1-5 million cells/ml. A cytocentrifuge is utilized to make slides that are Gram or Wright-Giemsa stained which permits rapid identification of Pneumocystis organisms. Additional slides are sent for Grocott staining to confirm the diagnosis. In a recent unpublished review of our experience, we found that Gram stains revealed Pneumocystis in all but one of 40 cases that were positive on silver staining (Rankin, personal observations). Not all patients with negative BAL results for Pneumocystis had open lung biopsies to rule out false-negative results, but clinical follow-up of cases made the diagnosis very unlikely. Hence, Gram-staining of BAL cell preparations is a rapid and sensitive method for identifying Pneumocystis. BAL has several potential advantages over bronchial brushings and transbronchial biopsies. First, it can be performed quickly. For example, once an endotracheal tube is in place, a 100 ml lavage can be completed and the bronchoscope removed in less than 5 minutes. This may be particularly important in critically ill patients such as those on mechanical ventilation. Secondly, BAL does not cause pulmonary hemorrhage and therefore is particularly suited for patients with coagulopathies. Third, BAL does not cause pneumothorax. Indeed, the only observed complications of this procedure include fever and slight deterioration of gas exchange. The introduction of new infection is possible but rarely occurs.

Open lung biopsy remains the most sensitive and specific (albeit the most invasive) of the available procedures for diagnosing pulmonary disease in patients with AIDS. This procedure should be reserved for patients in whom one—and possibly two—carefully performed and adequate fiberoptic bronchoscopic examinations were not diagnostic or in patients with coagulopathies where BAL was nondiagnostic and a transbronchial biopsy contraindicated. It is rarely useful in patients who deteriorate after treatment for a diagnosis established previously by bronchoscopy. One disadvantage of open lung biopsy is that it cannot be easily repeated more than once without considerable risk to the patient.

**TREATMENT OF INFECTIOUS PULMONARY COMPLICATIONS**

Antimicrobial therapy exists for many of the pulmonary opportunistic infections seen in AIDS patients. Unfortunately, such therapy frequently is not completely effective unless some ability by the host exists to mount an appropriate immunologic response. Guidelines for treatment of the infectious complications in AIDS patients have been borrowed from experience with opportunistic infections in patients with more traditional causes of immunodeficiency. In many cases, adequate experience and controlled trials are lacking.

At this time, trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine are used most frequently in the treatment of Pneumocystis carinii pneumonia. Experience with large numbers of patients in the pre-AIDS era revealed that the efficacy of both agents was equal. In non-AIDS patients with Pneumocystis pneumonia, TMP-SMX was the drug of choice chiefly because of its lower incidence of side effects. However, patients with AIDS treated with TMP-SMX have an incidence of side effects equaling that observed in patients treated with pentamidine. In a prospective, randomized trial, the two agents were equivalent both in efficacy and incidence of adverse effects. Sixty percent of patients treated initially with either agent had to cross over to the other agent because of major toxicity or drug failure. Therefore, the choice of one agent over the other as the initial therapy depends on other factors. Patients with pre-existing renal disease might benefit from treatment with TMP-SMX first because of pentamidine's potential for nephrotoxicity. TMP-SMX requires relatively large volumes of fluid for intravenous administration, and therefore,
pentamidine may be the drug of choice in patients requiring fluid restriction. Furthermore, pentamidine might be used first in patients with a history of possible allergic reactions to sulfa drugs or severe leukopenia with or without anemia. There is little evidence that administration of folic acid along with TMP-SMX lessens hematologic complications in AIDS patients.

The appropriate duration of therapy with either agent has not been established. A minimum of two weeks of therapy is standard. Several investigators have found Pneumocystis carinii cysts present in lung specimens for weeks to months after a successful course of therapy, and therefore, some prefer a total of three weeks of therapy. There are no good studies on the incidence of recurrence of infection in patients treated for two versus three weeks. In addition, the cyst forms observed do not represent the active form of the parasite. Consequently, their continued presence may simply reflect delayed clearance of organisms.

Additional unanswered questions include whether or not patients not responding to one agent should be switched to the other or whether the other agent should be added. In one study on rats, the combination of TMP-SMX and pentamidine was no more efficacious than either agent alone. However, the rat model of Pneumocystis carinii pneumonia differs significantly from disease in humans.

Recent results of an open trial for treatment of PCP in patients with AIDS suggest oral dapsone along with trimethoprim is reasonably safe and possibly as effective as either TMP-SMX or pentamidine, but appears to offer no clear advantage as initial therapy. Therapy with difluromethylornithine holds promise but is experimental. Trimetrexate, a new antineoplastic agent, has been shown very recently to be an effective and particularly safe drug for the treatment of Pneumocystis carinii pneumonia. Further studies should determine whether this agent will become the drug of choice for the initial therapy of Pneumocystis carinii pneumonia. Currently, dapsone, difluromethylornithine and trimetrexate may be of use in the patient who is either intolerant of or fails therapy with both pentamidine and TMP/SMX.

The use of aerosolized pentamidine for the treatment of PCP may represent an advance in our therapeutic approach. Recent preliminary reports suggest that treatment with aerosolized pentamidine can cure PCP in patients with AIDS without the high incidence of side effects seen with systemic therapy. There may be, however, a higher incidence of early relapse with inhaled therapy, and its role in patients with severe disease has not been examined.

Corticosteroids used in conjunction with antimicrobial chemotherapy appear to be a promising adjunct in treating severe PCP. PCP infection in AIDS has an acute mortality rate of 15 percent and up to 90 percent when associated with respiratory failure. Response to chemotherapy is slow with a mean response time of four to seven days; clinical deterioration during the first days of treatment is common. Recent nonrandomized series have suggested that short-term high-dose corticosteroids during the first few days or week of antimicrobial therapy may lead to more rapid improvement and decreased mortality, particularly in patients with severe disease and respiratory failure.

Reduction of the early, inflammatory response has been postulated as a possible beneficial mechanism. Prospective, randomized, controlled studies are needed to define the role for short-term steroids in the treatment of PCP in patients with severe lung dysfunction.

Because PCP has a recurrence rate of 30-50 percent per year in patients with AIDS, chronic oral TMP/SMX at reduced dosage is commonly used as a prophylactic treatment against recurrence. It is generally effective but frequently complicated by adverse reactions. Preliminary results suggest that long-term therapy with dapsone, pyrimethamine-sulfadoxine (Fansidar) and inhaled pentamidine may offer alternative effective prophylaxis.

At this time, no effective therapy for cytomegalovirus pneumonia exists. An acyclovir analogue 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG) has short-term beneficial effects on CMV pneumonitis in some patients. However, relapses frequently occur soon after therapy is stopped. In another report of its use in bone marrow transplant recipients, the response was disappointing. The treatment of fungal infections has been somewhat effective. Amphotericin B alone or in combination with fluconazole should be used in accordance with guidelines for therapy of fungal infections in other immunocompromised hosts.

The Centers for Disease Control recommends that tuberculosis be treated with three drugs. Preferably, this includes the use of the bactericidal agents isoniazid and rifampin, and for the initial two months of therapy either ethambutol in cidal concentrations or pyrazinamide. The optimal duration of therapy is unknown, but it is recommended that treatment continue for a minimum of nine months and for at least six months after sputum culture conversion. If INH or rifampin is not included in the regimen, therapy should continue for a minimum of 18 months and 12 months after sputum conversion. The treatment of Mycobacterium avium-intracellulare is more difficult as this organism is resistant to many antituberculosis agents. No particular regimen appears very effective. A trial of therapy may be indicated for symptomatic patients growing this organism from multiple sites and a deteriorating clinical condition. The success rate in
these individuals also has been disappointing. Ansa-
mycin and clofazimine are two agents with good in
vitro activity against M avium-intracellulare. They
have been used alone or along with additional antitu-
berculosis agents. Of course, the incidence of side
effects increases with the number of agents used. The
successful long-term use of several agents in a chron-
ically ill patient with AIDS rarely is accomplished.

As for any immunocompromised host, pneumonia
due to community-acquired organisms tends to re-
respond more favorably to therapy than infection due to
organisms acquired nosocomially.73 Pneumonitis ther-
apy is similar to that utilized for other immunocom-
promised hosts.

REFERENCES

1 Selwyn P. AIDS: What is now known. New York: HP Publishing
   Co, 1986
2 Hoxie JA. Current concepts in the virology of infection with
   human immunodeficiency virus (HIV). A view from the Third
3 Koenig S, Rosenberg ZF. Immunology of infection with the
   human immunodeficiency virus (HIV). A view from the Third
   International Conference on AIDS. Ann Intern Med 1987; 107:409-12
4 Seligmann M, Pinching AJ, Rosen FS, Fáhey JL, Khahtov RM,
   Klatzmann D, et al. Immunology of human immunodeficiency
   virus infection and the acquired immunodeficiency syndrome.
5 Ho DD, Pomerantz RJ, Kaplan JC. Pathogenesis of infection
   317:278-86
6 Hopewell PC, Luce JM. Pulmonary involvement in the
   acquired immunodeficiency syndrome. Chest 1985; 87:104-12
7 Hartman B, Koss M, Hui A, Baumann W, Athos L, Boylen T.
   Pneumocystis carinii pneumonia in the acquired immunodefi-
   ciency syndrome (AIDS): Diagnosis with bronchial brushing,
   biopsy, and bronchoalveolar lavage. Chest 1985; 87:603-07
8 Broadus C, Date MD, Stullberg MS, et al. Bronchoalveolar
   lavage and transbronchial biopsy for the diagnosis of pulmonary
   infections in the acquired immunodeficiency syndrome. Ann
9 Murray JF, Garay SM, Hopewell PC, Mills J, Snider C, Stower
   DE. Pulmonary complications of the acquired immunodefi-
10 Stover DE, White DA, Romano PA, Gellene RA. Diagnosis of
   pulmonary disease in acquired immune deficiency syndrome
   (AIDS). Role of bronchoscopy and bronchoalveolar lavage. Am
   Rev Respir Dis 1984; 130:659-62
11 Engelberg LA, Lerner CW, Tapper ML. Clinical features of
   Pneumocystis pneumonia in the acquired immune deficiency
12 Lane HC, Masur H, Edgar LC, Whalen G, Rook A, Fauci A.
   Abnormalities of B-cell activation and immunoregulation in
   patients with the acquired immunodeficiency syndrome. N
13 Young KF Jr, Rankin JA, Naegel GE, Paul ES, Reynolds HY.
   An immunologic analysis of bronchoalveolar lavage cells and
   proteins in patients with the acquired immunodeficiency
14 White DA, Gellene RA, Gupta S, Cunningham-Rundles C,
   Stower DE. Pulmonary cell populations of the immuno-sup-
   pressed patient: Bronchoalveolar lavage findings during epi-
15 Wallace JM, Barbers RG, Oishi J, Prince H. Cellular and T-
   lymphocyte subpopulation profiles in bronchoalveolar lavage
   fluid from patients with acquired immunodeficiency syndrome
   and pneumonitis. Am Rev Respir Dis 1984; 130:796-90
16 Venet A, Clavel F, Israel-Biet D, Rouzioux C, Dennewald G,
   Stern W, et al. Lung in acquired immune deficiency syndrome: Infections and immunological status assessed by bronchoalveo-
17 Smith PD, Ohura K, Masur H, Lane HC, Fauci AS, Wahl SM.
   Monocyte function in the acquired immune deficiency syn-
18 Prince HE, Moody DJ, Shubin BI, Fauey JL. Defective
   monocyte function in acquired immune deficiency syndrome
   (AIDS): Evidence from a monocyte-dependent T-cell prolifer-
19 Heagy W, Kelley VE, Strom TB, Mayer K, Shapiro HM,
   Mandel R, et al. Decreased expression of human class II
   antigens on monocytes from patients with acquired immune
20 Belisio DV, Sanchez MR, Baer RL, Valentine F, Thorbecke
   GJ. Reduced Langerhans cell IA antigen and ATPase activity
   in patients with acquired immunodeficiency syndrome. N Engl
   J Med 1984; 310:1279-82
21 McDevitt HO. Regulation of the immune response by the
   major histocompatibility system. N Engl J Med 1980; 303:1514-
   17
22 Sei Y, Petrella RJ, Tsang P, Bekesi JG. Monocytes in AIDS.
23 Murray HW, Rubin BY, Masur H, Roberts RB. Impaired
   production of lymphokines and immune (GAMMA) interferon in
   310:838-89
24 Washburn RG, Tuzon CU, Bennett JE. Phagocytic fungicidal
   activity of monocytes from patients with acquired immuno-
25 Murray HW, Scavuzzo D, Jacobs JL, Kaplan MH, Libby DM,
   Schandler J, et al. In vitro and in vivo activation of human
   mononuclear phagocytes by interferon-gamma. J Immunol
   1987; 138:2457-62
26 Gyorkey F, Melnick JL, Sinkovics JC, Gyorkey P. Retrovirus
   resembling HTLV in macrophages of patients with AIDS
27 Ho DD, Bota TR, Hirsch MS. Infection of monocyte/macra-
   phages by human T lymphotropic virus type III. J Clin Invest
   1986; 77:1712-15
28 Nicholson JKA, Cross GD, Calloway CS, McDougal JS. In
   vitro infection of human monocytes with human T lymphotropic
   virus type III/lymphadenopathy-associated virus. J Immunol
   1986; 137:323-29
29 Gartner S, Markovits E, Markovits D, Kaplan MH, Gallo RC,
   Popovic M. The role of mononuclear phagocytes in HTLV-III/-
30 Salahuddin SZ, Rose R, Groopman JE, Markham PD, Gallo
   RC. Human T lymphotropic virus type III infection of human
31 Miller SA, Bia FJ, Coleman DL, Lucia HL, Young KR Jr, Root
   RK. Pulmonary macrophage function during experimental
   47:211-16
32 Klatzmann D, Barre-Sinoussi F, Nugeyre MT, Dauguet C,
   Vilmer E, Griscelli C, et al. Selective tropism of lymphaden-
   opathy associated virus (LAV) for helper-inducer-T-lymphocytes.
   Science 1984; 225:59-63
33 Kalish RS, Schlossman SF. The T4 lymphocyte in AIDS.


