Pneumocystis Pneumonia:

The Importance of Early Open Lung Biopsy

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Pulmonary infection due to *Pneumocystis carinii* is now recognized as the leading cause of death from infection in patients with a hematologic malignancy who are in remission. Effective treatment requires suspicion of the infection in susceptible patients and rapid identification of the organism. In most patients, open lung biopsy performed through a small anterior thoracotomy provides immediate identification or exclusion of the organism, thus allowing treatment of infected patients and avoidance of inappropriate therapy in patients without the disease. We feel that the use of early thoracotomy, in spite of the fact that it exposes these very ill patients to a major surgical procedure and general anesthesia, is ultimately the safest therapeutic course.

SPECIFIC IDENTIFICATION of nonbacterial causes of pneumonia is often difficult since the offending agent is usually not recognizable by examination of the sputum or bronchial washings. When the pneumonia appears as a diffuse process, profound hypoxia is not uncommon and patient survival depends not only on respiratory support but on early diagnosis and prompt therapy. The thoracic surgeon is being called upon more frequently to assist in the care of these critically ill patients, and specifically to obtain lung tissue of sufficient quantity and quality to permit an accurate diagnosis.

Pulmonary infection with *Pneumocystis carinii* is one example of a nonbacterial pneumonia which is usually diagnosed only by microscopic examination of lung tissue. Since 1969, more than 80 patients with Pneumocystis pneumonia have been treated at the National Cancer Institute, and this experience has been described previously by DeVita and associates in several publications.[2,3,13,14] This report will review 9 patients with Pneumocystis pneumonia seen over the last two years and will summarize the current diagnostic and operative approach which is employed in our clinic.

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Clinical Material

During the last two years we have performed diagnostic lung biopsy in 9 patients with pulmonary infections due to *Pneumocystis carinii*. The patients ranged in age from 5 months to 55 years, and 6 of the 9 patients were male (Table 1).

Underlying Disease Process (Tables 1 and 2)

Seven of the 9 patients with Pneumocystis pneumonia had a hematologic malignancy. At the time of lung biopsy, Patient 1 was thought to have Wegener's granulomatosis but the diagnosis was later changed to histiocytic medullary reticulosis. Eight of the patients had been receiving immunosuppressive therapy; all of these patients had received combination chemotherapy; corticosteroids had also been included in their treatment regimen and 6 patients manifested the clinical syndrome within 6 weeks of the last steroid dosage. One patient was the recent recipient of a bone marrow transplant, and one patient had received total lung irradiation two weeks prior to developing pneumonia.

Signs and Symptoms (Table 2)

The most common symptoms were fever, nonproductive cough, malaise, and breathlessness. Auscultation of the chest revealed no characteristic findings. Preoperatively 8 of the 9 patients had profound hypoxia with

TABLE 1. *Underlying Disease Process in Nine Patients with Pneumocystis Pneumonia*

Patient No.	Age/Sex	Underlying Disease Process	Additional Pulmonary Disease	Outcome
1	46 M	Histiocytic medullary reticulosis—active	None	Recovered
2	14 M	Acute lymphocytic leukemia—in remission	None	Recovered
3	23 M	Acute lymphoblastic leukemia—active	None	Recovered
4	31 F	Undifferentiated lymphoma—in remission	None	Recovered
5	55 F	Nodular mixed lymphoma—in remission	None	Recovered
6	5 mo. M	Swiss type agammaglobulinemia	None	Recovered
7	14 F	Acute lymphocytic leukemia (recent bone marrow transplantation)	Pulmonary Aspergilloma	Expired
8	13 M	Acute myelocytic leukemia—active	Extensive leukemic infiltrate	Expired
9	30 M	Ewing's sarcoma with pulmonary metastases (2 weeks post 2100 R. total lung irradiation)	Interstitial fibrosis	Expired

respiratory alkalosis. Anemia, leukopenia, and/or thrombocytopenia were present in each patient.

Radiographic Findings

The chest roentgenogram in all 9 patients showed a diffuse bilateral pulmonary infiltrate. Early in the disease the infiltrate, which is central in location, is often minimal and may not be appreciated as clinically significant (Fig. 1). Pulmonary nodularity, pneumothorax, and/or pleural effusion were not present in any patient.

Operative Management

Eight of the 9 patients with suspected Pneumocystis infection underwent a limited anterior thoracotomy. One patient, a 14-year-old boy with acute lymphocytic leukemia (#2 on Table 1) and adequate platelets, had a closed needle biopsy of the lung. Although the biopsy was positive, it resulted in a complete pneumothorax which was treated by closed tube thoracostomy. He subsequently required mechanical ventilation over a 9 day period which was complicated by a persistent air leak.

Eight patients with Pneumocystis pneumonia were treated with pentamidine isethionate, 4 mg/kg/day intramuscularly, and renal complications from the drug were not encountered. Patient 5 was successfully treated with the combination of pyramethamine and sulfa.[14] Prolonged postoperative ventilatory assistance was required in 4 of the 9 patients (Table 2).

Patient Survival

Six patients recovered from the disease and 3 patients died in the postoperative period. Patient 7 died 24 days after lung biopsy, after the pneumonia had fully resolved; death resulted from hepatic failure secondary to serum hepatitis and massive gastrointestinal bleeding. This patient is of additional interest because of a pulmonary aspergilloma (Fig. 2a) which had been present for several months prior to the onset of pneumonia. The development of fever, hypoxia, and the typical chest x-ray (Fig. 2b), in spite of heavy growth of Aspergillus in the sputum, prompted us to perform open lung biopsy which demonstrated *Pneumocystis carinii*.

Two of the 9 patients (Patients 8 and 9) died of respiratory insufficiency. It is of interest that both of these patients had significant additional pulmonary pa-

TABLE 2. *Clinical Features of Nine Patients with Pneumocystis Pneumonia*

	Number of Patients	Per Cent
Symptoms		
Fever	8	89
Nonproductive cough	8	89
Shortness of breath	5	56
Malaise	4	44
Chest pain	1	11
Immunosuppression		
Combination chemotherapy	8	89
Corticosteroids (within 6 weeks)	6	67
Laboratory findings		
Hypoxemia (Po_2 < 80 mm Hg)	8	89
Anemia (Hg < 10 gm/100 ml)	6	67
Leukopenia (WBC < 3,500/mm^3)	5	56
Thrombocytopenia (platelets 80,000/mm^3)	5	56
Postoperative ventilatory assistance		
None	4	44
<7 days	1	11
>7 days	4	44
Outcome		
Complete recovery	6	67
Expired—pulmonary related	2	22
Expired—nonpulmonary cause	1	11

thology identified by lung biopsy (Table 1) and that no residual Pneumocystis organisms were present at postmortem examination. Patient 8 was a 13-year-old boy with acute myelogenous leukemia which had not responded to treatment. Lung biopsy demonstrated a diffuse leukemic infiltrate as well as Pneumocystis infection. Patient 9, a 30-year-old man with pulmonary metastasis from Ewing's sarcoma, had undergone total lung irradiation (2100 R) two weeks prior to developing a pulmonary infiltrate. Pulmonary fibrosis was also identified in this patient.

There were no significant postoperative complications in the 8 patients who underwent open thoracotomy. Specifically, there were no instances of postoperative hemorrhage, significant air leak, empyema, pneumothorax, or wound infection.

Discussion

Pneumocystis carinii is an unusual organism which until recently has not been grown in culture. It is the most common cause of death from infection in patients with a hematologic malignancy who are in remission.[3,9] It is difficult to classify, but is generally believed to be a protozoan. With appropriate staining techniques, the organisms are easily found in infected lung, characteristically lying clustered in alveolar lumens. The individual cysts are 5 to 8 μ in diameter, and are round, oval, or, most characteristically, cup or crescent-shaped. The walls of the alveoli are usually thickened by hypertrophic alveolar lining cells, interstitial edema, and a variable mononuclear cellular infiltrate often containing plasma cells. Special stains are essential to see the organism and establish the diagnosis (Fig. 3).

The typical patient with Pneumocystis infection fits a general pattern. Usually the patient is in remission from a hematologic malignancy, and often immunologic suppressive drugs, especially corticosteroids, have been recently discontinued. Dyspnea and fever are common presenting complaints, and early in the course of the disease the chest radiograph may appear normal. The acute form of the disease, which is most common in cancer patients in remission, follows a rapid and predictable course. A bilateral, central, pulmonary infiltrate develops, and as the patient's dyspnea worsens, hypoxia with respiratory alkalosis is evident on blood gas determinations. Unless the disease is treated, death occurs because of respiratory insufficiency.

The typical clinical picture outlined above is not always encountered. The disease occurs in cancer patients who are being treated with chemotherapy without response, in patients who have been receiving corticosteroids or immunosuppressive drugs for nonmalignant diseases (systemic lupus erythematosis, rheumatoid arthritis, transplant recipients, etc.), and in patients

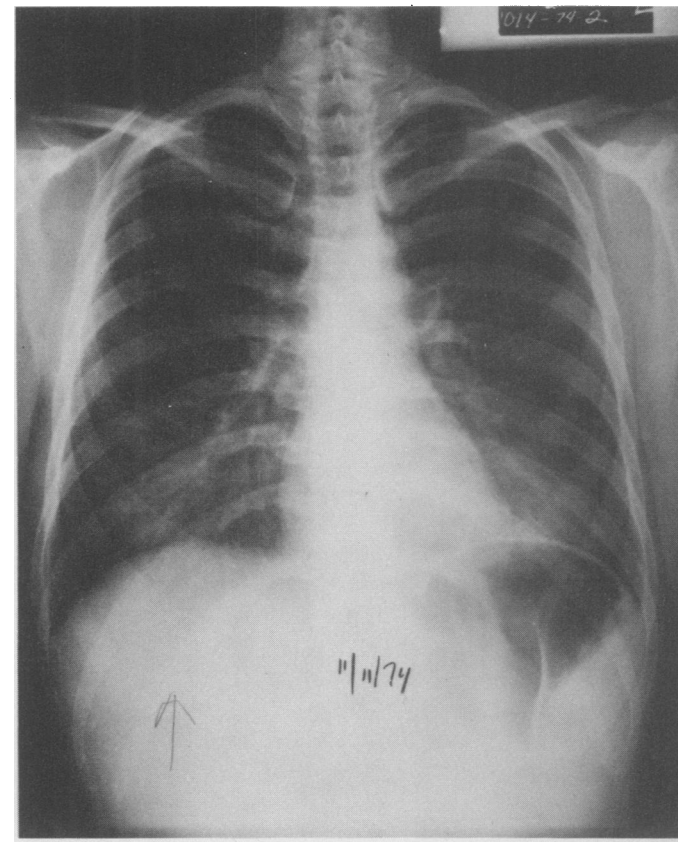

FIG. 1. The predominant roentgenographic finding in early Pneumocystis pneumonia is a bilateral central infiltrate with sparing of the apices and bases. Profound hypoxia may be present with only minimal radiographic changes.

with congenital or acquired immunologic deficits. In the latter group of patients, Pneumocystis tends to occur as a more indolent, chronic process. Sporadic epidemics of the disease have been reported in newborn nurseries[1,5] and in cancer hospitals.[3,10,11]

The differential diagnosis includes virtually every cause of diffuse pulmonary infiltrate, but viral pneumonia, pulmonary edema, malignant lung infiltrates, and interstitial pneumonitis and vasculitis due to Aspergillus, *Pseudomonas aeruginosa,* drug toxicity, or reaction to radiation therapy are most commonly considered. Although Pneumocystis organisms reside in the alveoli, they are often not found in the bronchi or even the bronchiolar system, and so analysis of sputum, endotracheal aspiration or lavage, or even deep endoscopic bronchial washings seldom reveal the organism. The diagnosis, therefore, usually depends on microscopic identification of the organism in lung tissue.

All surgically invasive procedures, however, carry a risk of hemorrhage and/or pneumothorax and these risks are almost always amplified in the patient with suspected Pneumocystis infection. Almost all the patients that we have seen with the disease have been hypoxic, with reduced pulmonary compliance, and many have been sig-

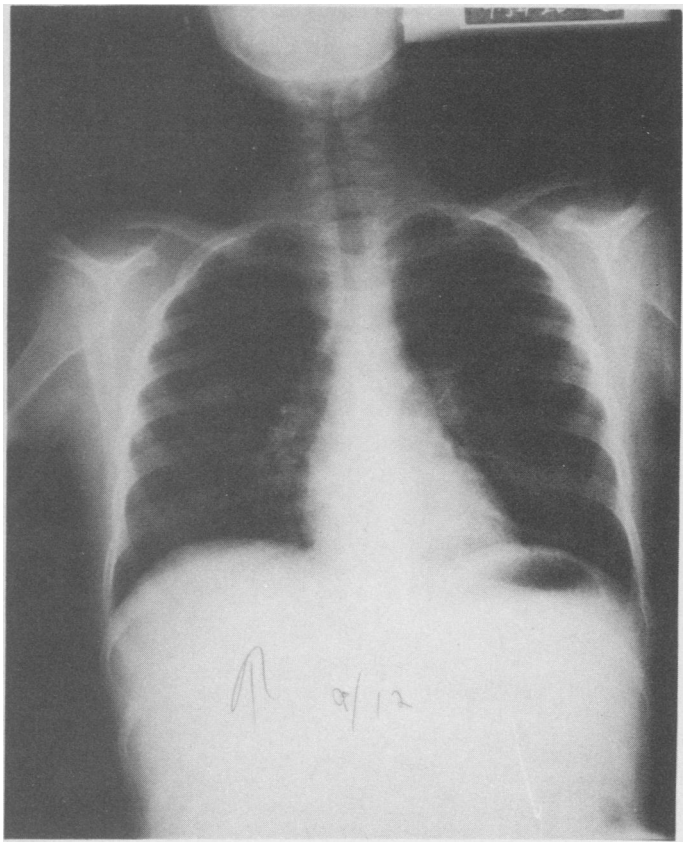

FIG. 2a. Chest x-ray in patient 7 taken 3 months prior to Pneumocystis pneumonia. The patient had Aspergillus in her sputum and the typical radiographic signs of an aspergilloma in the right upper lobe.

nificantly thrombocytopenic. In this situation, empiric therapy with pentamidine isethionate appears to be an attractive alternative to lung biopsy. It is our opinion that this course, i.e., treatment without a tissue diagnosis, should be avoided whenever possible since not only is there the risk of treating the patient for the wrong disease, but also of exposing him to a drug (pentamidine) which has appreciable renal toxicity[2] and may, in itself, cause pulmonary fibrosis.[4,7,8]

When a patient is suspected of having Pneumocystis pneumonia, we proceed with the following general protocol. The patient is admitted to the hospital and a baseline chest roentgenogram and arterial blood gas analysis are obtained. As mentioned above, the early chest x-ray may be normal, but in the majority of patients, it usually shows bilateral, central infiltrates with relative sparing of the apices and bases. The infiltrate is interstitial in appearance and significant pleural effusion is uncommon. Pneumothorax, hilar adenopathy, pleural thickening, and unilateral or lobar involvement are not characteristic of Pneumocystis pneumonia, although early in the disease one lung may be more involved than the other. Radiographic changes then generally progress over the next 24–36 hours to dense bilateral pulmonary infiltration (Fig. 2b). Other laboratory tests are usually not helpful in making a diagnosis.

We concur with Tyras and associates[12] that as soon as there is reasonable suspicion that a patient is suffering from Pneumocystis pneumonia, lung biopsy is indicated. Bronchoscopy is usually not carried out since the organism is recovered only rarely in the bronchial washings, and transbronchial parenchymal biopsy carries a high risk of bleeding when platelets are reduced. Closed needle biopsy has been successful in some cases, but the risk of hemorrhage (particularly in adults) and/or pneumothorax may carry a risk equivalent to thoracotomy. Children can sometimes be given a sufficient number of homologous platelets to make a closed biopsy safe, but lack of cooperation on the part of the child, and the risk of delayed hemorrhage as the platelet count falls often make the risk of the procedure prohibitive. Low pulmonary compliance almost always leads to pneumothorax after closed biopsy, with the risk of continued air leak, especially if mechanical ventilation with continuous positive airway pressure is contemplated.

Perhaps the greatest disadvantage of a closed biopsy is the small quantity of lung tissue obtained. If the Pneumocystis organism is not seen, there is still unwillingness to rule out the presence of the disease

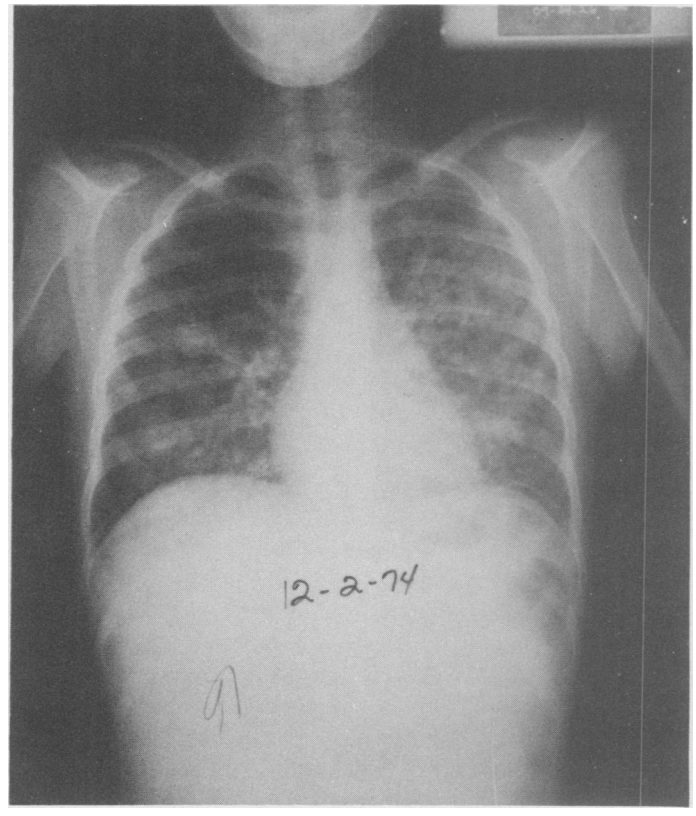

FIG. 2b. Chest x-ray in patient 7 following the onset of dyspnea and fever. In spite of continued heavy growth of Aspergillus in the sputum, open lung biopsy was performed which demonstrated *Pneumocystis carinii*.

because the small piece of lung obtained may not have been representative. Similarly, the pathologist is reluctant to examine frozen sections for fear of wasting tissue which may be needed for final permanent sections. Thus, a negative closed procedure may waste several days in arriving at an absolute diagnosis, inclusive or exclusive, of Pneumocystis pneumonia.

Our policy is to carry out thoracotomy and lung biopsy promptly. Besides providing adequate lung tissue for all desired studies, open biopsy has other advantages. Through a small anterior thoracotomy, direct observations of the texture and appearance of the lung parenchyma can be made, and the presence or absence of pleuritis and significant pleural or pericardial effusion can be ascertained. Absolute hemostasis is achieved, no residual air leak remains, and dependent pleural drainage is afforded.

It has been our practice to operate on an urgent, but not emergent, basis, usually on the day following hospital admission. This routine has several advantages: the patient can be fasted overnight, reducing the risk of aspiration during intubation; the anesthesiologist has an opportunity to see and evaluate the patient; blood and/or platelets can be obtained and accurately cross-matched; postoperative care arrangements (ICU, respiratory care unit, ventilators, etc.) can be made; the pathologist can be notified to be available at the time of biopsy; and the operation is carried out by a surgical team that is fully prepared for a rapid, safe, operative procedure.

It is rare that a patient needs to be intubated preoperatively, and usually oxygen by mask is sufficient to correct the hypoxia present early in the course of the disease. When a component of pulmonary edema is suspected, preoperative digitalization and/or diuretic administration is indicated. We are not reluctant to begin treatment with pentamidine isethionate *before* a tissue diagnosis is made, and often have started the drug 12–18 hours prior to the actual lung biopsy. In no instance has this resulted in a "false negative" biopsy; in fact Pneumocystis has been demonstrated in lung tissue at autopsy after 6 days of full-dose pentamidine therapy.

If the patient has been receiving steroids for any length of time, preoperative steroid coverage is given as in any major operation. If the platelet count is less than 50,000, it has been our policy to have fresh platelet transfusions administered just prior to the operation.

When the patient reaches the operating room, a percutaneous radial arterial catheter is placed—both for monitoring arterial pressure and for the analysis of arterial blood gases postoperatively. A central venous line is positioned and, if necessary, a Swan-Ganz catheter can be placed to measure pulmonary artery wedge pressure.

Generally, we prefer a nasotracheal tube for the administration of general anesthesia. Many patients will need some form of ventilatory support in the postoperative period, and a nasotracheal tube is much more comfortable for this purpose. Copious secretions are not a component of Pneumocystis pneumonia, and the relatively smaller internal size of a nasotracheal tube (which makes suctioning somewhat more difficult) is not a serious drawback.

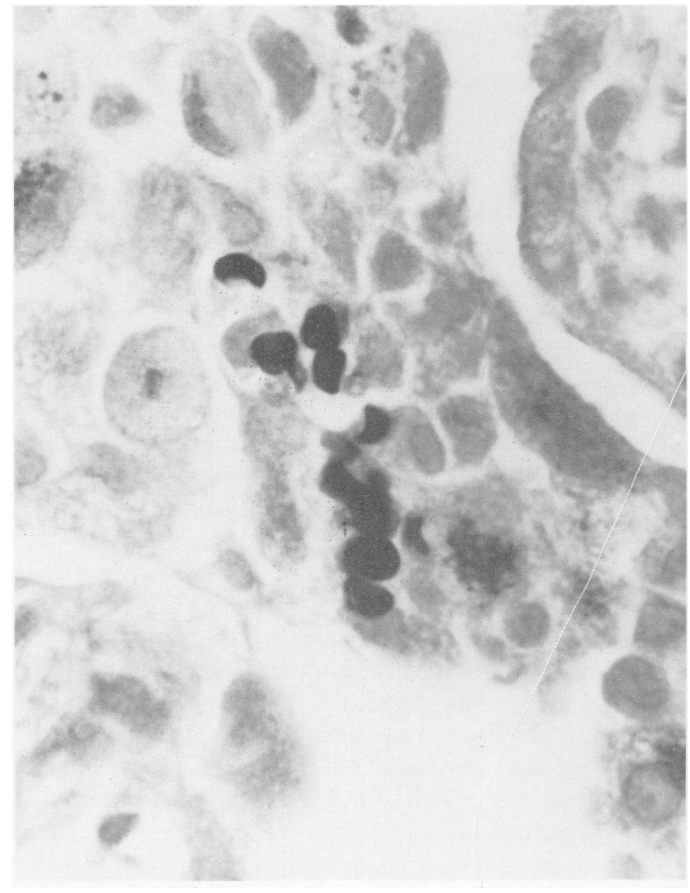

FIG. 3. Histologic section from open lung biopsy of lingula from patient with lymphoproliferative disease. Several typical pneumocysts are clustered within an alveolar lumen. (Methenamine silver stain original magnification ×1000).

A small anterior thoracotomy is performed, usually through the 4th intercostal space. When involvement is bilateral, the left side is preferred because of the smaller percentage of ventilation performed by that lung. Also the pericardium is more accessible through the left side and the lingula is easily mobilized. After assessing and culturing pleural or pericardial effusions, the mediastinum and as much lung as possible are palpated. The involved lung is then delivered through the incision, and a portion is amputated distally to a line of staples placed with an automatic stapling device. The tissue distal to the staples is then oversewn with a running suture of chromic catgut. A medium-sized intercostal catheter is inserted independently in the

mid-axillary line and placed laterally into the apex. The incision is closed in layers with heavy absorbable sutures.

Postoperatively the patient is maintained on mechanical ventilation for as long as necessary. The chest catheter is kept in place throughout the period of artificial ventilation. In some instances positive end expiratory pressure is necessary for several days, and in this circumstance the intercostal tube is prophylaxis against pneumothorax on the operative side. Standard treatment of the adult respiratory distress syndrome is carried out postoperatively, with great stress placed on diuresis, maintenance of adequate plasma albumin levels, sterile tracheal suction techniques, and frequent analysis of the arterial gases. A broad spectrum antibiotic is usually begun preoperatively and continued for 4–5 days.

Pathologic examination of the lung tissue is carried out as follows: On the day the tissue is received several touch preparations are made, half of which are promptly stained with Pneumocystis stain (a rapid cresyl violet method) and the remainder are saved to be stained the following day with the more time consuming methenamine silver method. Frozen sections are cut, stained with H&E, Pneumocystis stain, and the P.A.S. reaction, and examined microscopically for Pneumocystis, fungal, and other types of pneumonia.

The remaining lung tissue is rapidly fixed and routinely embedded and sectioned. Permanent H&E and methenamine silver stained sections are examined microscopically for the presence of organisms and histologic features not detected by the more rapid methods employed the previous day.

During this same period, we have operated upon an additional 14 patients in whom Pneumocystis pneumonia was considered a likely diagnosis but the organism was not identified. None of these patients was subsequently found to have Pneumocystis and in most of these patients, another specific diagnosis was established including viral pneumonia, pulmonary edema due to drug toxicity or other causes, malignant pulmonary infiltrates of all sorts, necrotizing pulmonary vasculitis, and various fungal pneumonitides. In all of these instances, Pneumocystis was excluded, and inappropriate therapy with pentamidine isethionate was thereby avoided.

Conclusion

Pneumocystis pneumonia is a curable disease. We feel that early diagnosis and prompt treatment will not only decrease the high mortality which has previously been associated with the disease,[12] but will also reduce the need for ventilatory and membrane lung[16] support. The attending physician must be constantly aware of the possibility of Pneumocystis infection in susceptible patients and the surgeon must be willing to obtain sufficient lung tissue in order for the diagnosis to be established rapidly. It is our belief that open lung biopsy is usually the indicated procedure. Attention to operative techniques and pre- and postoperative care will minimize the problems associated with thoracotomy in these critically ill patients.

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