# Successful Treatment of Pneumocystis Carinii and Nocardia Asteroides in a Renal Transplant Patient

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**A successfully treated case of Pneumocystis carinii pneumonia in a renal transplant patient is described, the diagnosis being confirmed by percutaneous needle biopsy. Treatment with pentamidine isethionate, 4 mg/kg for 14 days, was successful, with no adverse effects on the transplanted kidney. In addition, Nocardia asteroides was isolated from the sputum, and was successfully treated with sulfisoxazole. The patient remains well after ten months; his transplanted kidney continues to function adequately.**

**Percutaneous needle biopsy of the lung should be employed promptly in such cases when conventional measures fail to establish the diagnosis.**

Recent attention has been directed to the increasing incidence of opportunistic infections in patients whose defense mechanisms have been altered by immunosuppressive, adrenal corticosteroid and antimetabolite therapy, by neoplastic diseases or by a deficiency in gamma globulin [1–4]. The data of Hill [5] revealed that among forty-four renal transplant patients who died twenty-five days or more after surgery, death was clearly related to infection in 86 per cent. The responsible organisms were considered, for the most part, unusual; Nocardia, Aspergillus, Candida, gram-negative bacteria, Histoplasma and Pneumocystis carinii.

In many instances, these opportunistic organisms may be recoverable from sputum, blood or pleural fluid; however, a significant number of cases remain undetected by these means, and many of these treatable infections are recognized only at postmortem study. For example, Rifkind [4] observed in an autopsy series of renal transplant patients treated with immunosuppressive therapy that of fourteen patients with pulmonary fungal involvement, appropriate sputum cultures revealed the offending fungus in only six (43 per cent). The key to survival in these subjects is prompt, accurate antemortem diagnosis, thus permitting rapid institution of specific therapy. When conventional measures fail to establish the pulmonary pathogen, lung biopsy should be performed promptly. As this case will emphasize, a percutaneous needle biopsy of the lung can provide a rapid, relatively safe modality for establishing an etiology in these critically ill patients.

Pneumocystis carinii pneumonia, formerly considered a disease solely of premature or debilitated infants, is now documented to be an increasing infectious problem in older children and adults under treatment for hematopoietic or lymphoreticular malignancies, receiving immunosuppressive therapy after renal transplantation or in those with gamma globulin abnormalities [6–21]. Similarly, No-

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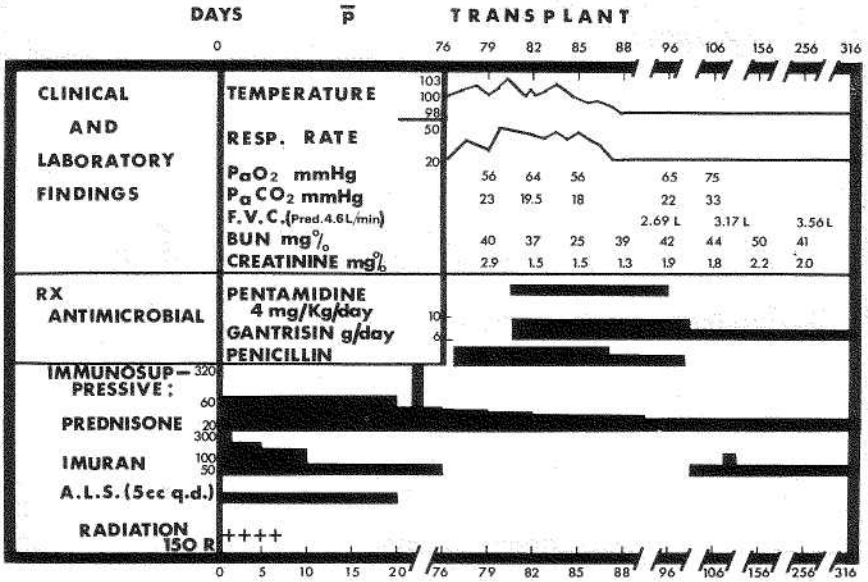


*Figure 1. Scheme of clinical, laboratory and therapeutic data. See text.*

cardia asteroides appears to be occurring more frequently, primarily in patients debilitated by other diseases, and especially in those who are receiving large doses of corticosteroids [22–26].

We present a successfully treated case of histologically diagnosed Pneumocystis carinii pneumonia in a renal transplant patient. The diagnosis was confirmed by percutaneous needle biopsy, and the patient was treated with pentamidine isethionate. The course was additionally interesting due to the simultaneous recovery of Nocardia asteroides from the sputum. This was also successfully treated.

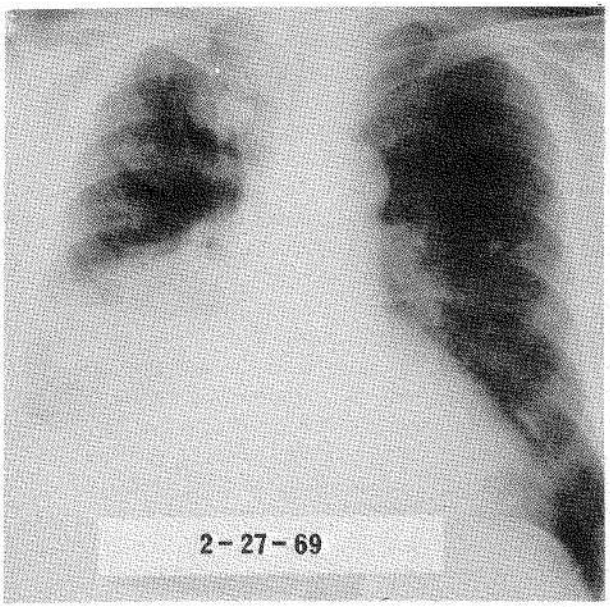


*Figure 2. Chest roentgenogram obtained on admission revealing a dense infiltrate in the lower lobe of the right lung and minor right apical changes.*

## CASE REPORT

A forty-nine year old man, a purchasing agent, was admitted to the Boston City Hospital on February 27, 1969, with complaints of fever, weakness, cough with yellow sputum, and marked shortness of breath.

Bilateral staghorn calculi and pyelonephritis were diagnosed in 1963. Renal failure developed in 1967, and the patient had been maintained on intermittent hemodialysis. A bilateral nephrectomy was performed in April 1968 and on December 12, 1968, he received a cadaveric renal transplant. Immunosuppressive therapy (Figure 1) consisted of prednisone, Imuran®, antilymphocytic serum and local radiation to the transplanted kidney. After the transplantation, he was treated successfully for an episode of acute tubular necrosis with intermittent hemodialysis, and for a Serratia bacteruria with kanamycin. He was discharged on the fiftieth day after the transplant (February 1, 1969) with a blood urea nitrogen of 46 mg/100 ml, and a serum creatinine level of 1.8 mg/100 ml.

Two weeks after discharge (February 15, 1969) he experienced a dry cough followed by progressive fatigue, temperatures of 100° to 103°F, and production of yellow-green sputum. Just prior to admission, dyspnea developed with minimal exertion. He had been a cigarette smoker until six years previously but denied symptoms of pulmonary disease. No occupational or geographic pulmonary exposure could be established, and a chest roentgenogram obtained in December 1968 was clear except for old right costophrenic angle blunting.

Physical examination on admission revealed a middle-aged man who appeared acutely ill, chronically wasted and profoundly weak. The temperature was 101°F, pulse rate 120/minute, blood pressure 140/90 mm Hg and respiratory rate 24 breaths/minute. The skin was pale, and there was no cyanosis. Chest examination revealed dullness, decreased breath sounds and rales over the base and mid-axillary area of the right lung. The transplanted kidney, palpable in the right lower quadrant, was nontender, and the bilateral flank incisions were healed.

The hematocrit was 22 per cent, and the white blood cell count was 11,800/cu mm. Examination of the urine revealed 1+ glycosuria and 600 mg protein/L. The urine sediment contained 2+ white blood cells and bacteria, which on culture yielded Serratia >100,000 colonies/cu ml. The blood urea nitrogen was 52 mg/100 ml, creatinine 2.9 mg/100 ml, serum sodium 120 mEq/L, potassium 4.7 mEq/L, chloride 108 mEq/L, carbon dioxide combining power 10.5 mEq/L, calcium 7.8 mg/100 ml, phosphorus 2.7 mg/100 ml, random blood sugar 296 mg/100 ml. The serum total protein was 5.6 gm/100 ml (albumin 2.7 gm), serum glutamic oxalacetic transaminase 32 units and uric acid 4.2 mg/100 ml.

Initial blood cultures grew D. pneumococcus, type 17. A gram stain of the sputum revealed gram-positive diplococci, while sputum culture grew B. pyocaneus, Staph aureus, group B streptococci with beta hemolysis, D. pneumococci and Neisseria flava.

The chest roentgenogram obtained on admission revealed a diffuse alveolar type of infiltration in the lower lobe of the right lung and minimal infiltrates in the apical portion of the upper lobe of the right lung (Figure 2). The left lung appeared essentially clear. Based upon the blood, sputum and urine cultures, penicillin (6 million units/day), nafcillin and gentamycin were administered. Over the next four days the patient continued to exhibit daily fever spikes, the respiratory rate rising to 40/minute and pulse rate to 124/minute. On the fourth hospital day bilateral rales were noted, and on the next day there was atrial flutter with a ventricular rate of 156/minute. A chest roentgenogram at this time revealed progression of the infiltrates in the right lung, and also diffuse infiltrate in the left lung (Figure 3).

On March 3, 1969, physical examination revealed profound dyspnea, cyanosis and fine crepitant rales over all lung fields. The sputum showed gram-positive branching filamentous organisms that were in part acid-fast (Figure 4). The organisms were consistent with Nocardia (subsequently documented as N. asteroides) for which 10 gm/day of Gantrisin was administered. While breathing room air, an arterial pH was 7.42, $PaO_2$ 64 mm Hg, and $PaCO_2$ 19.5 mm Hg. Despite the recovery of Nocardia and pneumococci, the clinical setting also suggested P. carinii pneumonia. The intra-

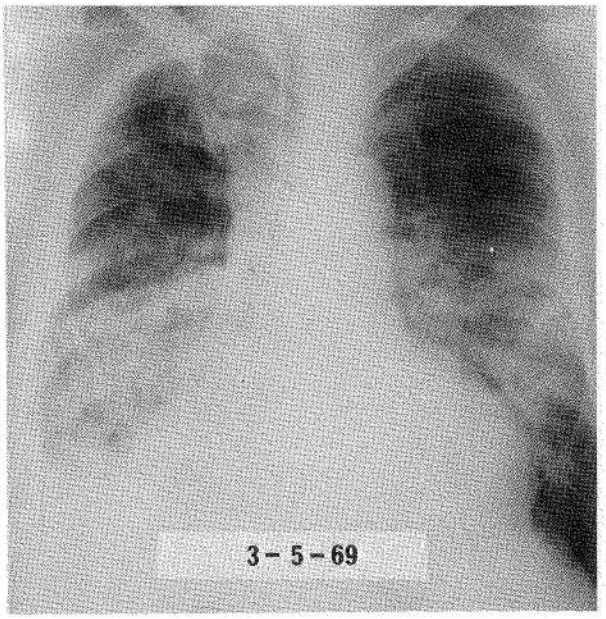


*Figure 3. Portable chest roentgenogram obtained at time of percutaneous lung biopsy revealing infiltrates in the mid-zone of both lungs and in the lower lobe of the right lung.*

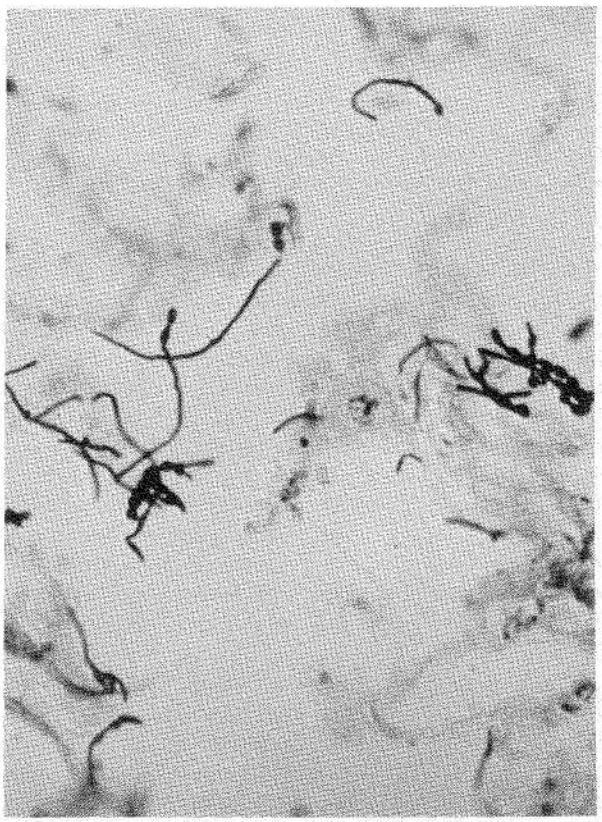

*Figure 4. Gram stain of representative sputum specimen. Gram-positive, branching, filamentous fungi documented to be Nocardia asteroides are clearly demonstrated. Original magnification × 1,000.*

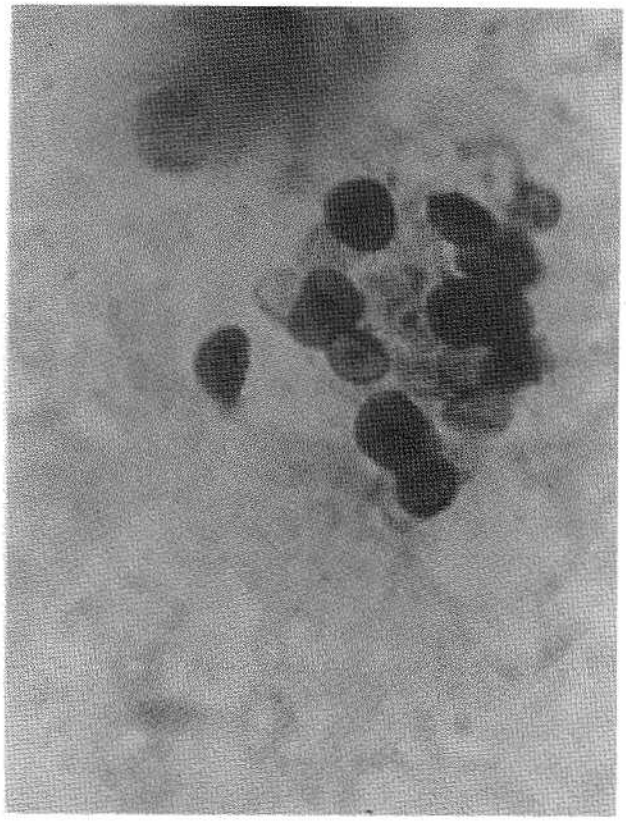

*Figure 5. Toluidine blue stain of tissue imprint obtained from percutaneous lung biopsy. P. carinii cysts appear as dark round bodies. An internal structure can be seen within some cysts. Original magnification × 1,000.*

muscular administration of pentamidine isethionate, 4 mg/kg, was initiated; the following morning a percutaneous pulmonary needle biopsy of the lower lobe of the right lung was performed without complications. A core of grey-white tissue, 1 mm by 1 cm was obtained. Touch imprints of this material, stained with toluidine blue and methenamine silver, revealed organisms consistent with P. carinii (Figure 5). Gram stain, acid-fast stain and crystal violet stain of the imprint revealed no other oragnisms. Subsequent bacterial and fungal cultures were sterile. Examination of the lung biopsy specimen revealed chronic inflammation, fibrosis and foamy macrophages with no evidence of pneumocystis or Nocardia.

The following day the atrial flutter was converted electrically. The fever, tachypnea and tachycardia persisted for another four days, and the $PaO_2$ decreased to 56 mm Hg. By the fifth day of pentamidine and sulfisoxazole therapy clinical improvement occurred. The patient became afebrile, respirations fell to 20/minute. The vital signs remained normal thereafter, and the chest film showed clearing. By March 20, 1969, Nocardia was no longer seen in the sputum and the Gantrisin dosage was decreased to 6 gm/day. By March 24 he was clinically well, the roentgenogram showed marked clearing, the $P_aO_2$ was 75 mm Hg, and a forced vital capacity was 2.69 L (58 per cent of predicted). The patient was discharged on the following medications: prednisone (now tapered to 22 mg/day), Imuran 50 mg/day (which had been discontinued during his acute illness) and Gantrisin 6 gm/day.

During the patient's fourteen days of pentamidine treatment his renal functions were carefully monitored. The urine volume, osmolality, sodium and potassium remained unchanged. There was no glucosuria, no significant proteinuria, and the sediment revealed only 4 or 5 white cells. The blood urea nitrogen ranged between 30 and 40 mg/100 ml and the creatinine 1.6 and 2.6 mg/100 ml.

Since discharge, the patient's condition has improved progressively. There has been no sputum production, the dyspnea has resolved, the chest roentgenogram remains essentially clear, and the vital capacity has risen to 3.56 L (78 per cent of predicted).

The transplanted kidney continues to function adequately; the sediment remains benign, the urine cultures are sterile, the blood urea nitrogen ranges between 40 and 50 mg/100 ml, creatinine 1.5 and 1.8 mg/100 ml, and the creatinine clearance is 70 ml/minute. The patient was last seen on January 12, 1970 (ten month follow-up) at which time he was found to be clinically well. There were no pathogens on sputum examination, and the chest roentgenogram remains stable (Figure 6).

## COMMENTS

Our patient presented with nonspecific pulmonary symptoms of three weeks' duration. D. pneumoniae was initially isolated from sputum and blood cultures, and additional sputum examinations and cultures consistently revealed Nocardia, for which penicillin and sulfisoxazole were administered. Because of the patient's profound dyspnea, tachypnea, hypoxemia and rapidly progressive changes as noted on roentgenograms despite this regimen, and in the clinical context, P. carinii pneumonia was also suspected. A percutaneous pulmonary biopsy, employing a Franklin modification of the Vim-Silverman needle, and following the technic described by Krumholz et al. [27], confirmed this clinical impression. After four days of specific pentamidine therapy, there was dramatic clinical improvement.

## PNEUMOCYSTIS CARINII

P. carinii was first clearly recognized as a rat parasite by Carini in 1910. It has been classified as a protozoan of the class Sporozoa. To date, it has not been cultured, nor has a pure antigen been isolated.

Rössle, early in the 1920's, described a type of chronic interstitial pneumonia occurring in infants that was associated with large numbers of plasma

cells; and Van der Meer and Brug [28] in 1942 first showed P. carinii in human lung disease. P. carinii pneumonia was then extensively described in the European literature in the 1940's as occurring primarily in premature and debilitated infants [29]. Since the early reports in the United States [30] and England [31] in 1955, this disease has since been recognized under the following clinical circumstances: (1) renal transplant patients receiving immunosuppressive therapy, (2) hematopoietic and lymphoreticular malignancies on adrenal corticosteroids or cytotoxic agents, (3) immunoglobulin deficiency states. There are only two well documented cases in adults in the absence of underlying disease [32,33]. Subclinical P. carinii pneumonitis was described by Sheldon [34] who suggested that in the normal host P. carinii infections are of low virulence, thus implying that host-resistance factors must be severely compromised before the parasite can produce clinically manifest disease.

Activation of latent colonization has been clearly demonstrated in animals [17,35]. For example, the organisms have been found in the lungs of healthy rats and rabbits, albeit in very low numbers, becoming activated by alteration of the host's resistance with adrenal corticosteroids, antimetabolites, antimicrobial or chemotherapeutic agents. These exacerbations in animals are confined to the lung, which appears to be the case in man; the pathology is also quite similar. Recently, however, a case of generalized P. carinii infection in a patient with severe idiopathic hypoproteinemia has been described [36], and P. carinii have also been identified in lymph nodes and spleen [37].

The pertinent pathologic features of P. carinii pneumonia include (1) a chronic interstitial pneumonia, (2) prominent alveolar septal cells (cuboidal or flat) and amorphous foamy exudate (which can extend into the respiratory bronchioles), (3) absence of tissue necrosis and a paucity of polymorphonulcear cells, (4) lymphocytic and particularly plasma cell interstitial infiltration, (5) absence of fibrosis, and (6) absent pleural involvement.

The 4 $\mu$ size, spherical intra-alveolar cysts stain readily with Gomori's methenamine silver or Grawe's modification of the toluidine blue stain [38]. We observed that tissue imprints revealed many more organisms than did fixed sections; in fact, in our case the tissue sections were negative for P. carinii. Other investigators appear to express a similar preference for touch preparations of biopsy material [7,19,29,39].

Rifkind [8] studied arterial blood gas data in five cases of P. carinii pneumonia. Oxyhemoglobin saturation values ranged from 90.5 to 44.5 per cent. The partial pressures of carbon dioxide were normal or slightly low. In another report [32], the pulmonary compliance was markedly decreased to 0.02 L/cm $H_2O$ (normal 0.2 L/cm $H_2O$). The clinical course of relentless progression appears associated with increasingly severe hypoxemia. Although unclarified at present, the hypoxemia seems to be due to a diffusion defect and/or venous to arterial shunting.

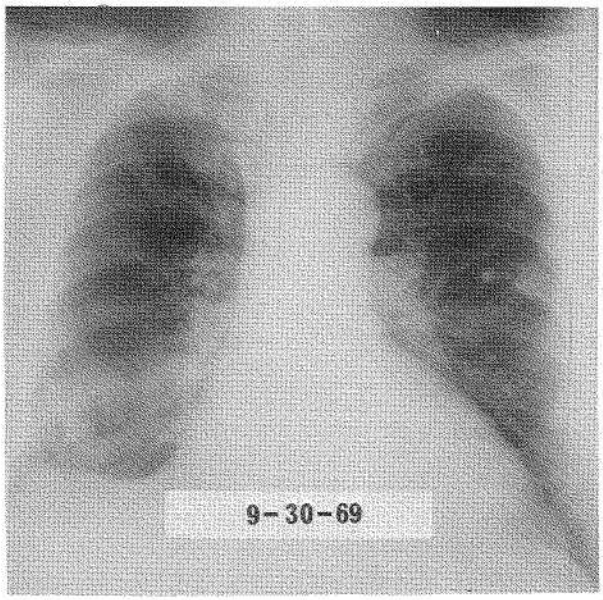


*Figure 6. Six month follow-up chest roentgenogram showing resolution of P. carinii infiltrates, appearing essentially the same as the pretransplantation film.*

The clinical presentation of P. carinii infections is often insidious and includes a nonproductive cough, dyspnea, cyanosis and a low grade temperature. Sputum production is not a major feature of this disease; if present, other associated pathogens should be suspected. With progressive involvement, fever may exhibit a high spiking pattern, severe tachypnea and cyanosis may develop, and death frequency results from progressive respiratory failure. Lung auscultation often reveals only a few scattered rales; thus a useful clinical observation is the dissociation of physical findings, which are sparse, and the roentgenologic changes, which are gross.

There are no distinctive x-ray patterns of this disorder. The most common appearance is that of hazy, ground glass, diffuse, bilateral, interstitial infiltrates with predominant opacification in the perihilar zones and lung bases. Early roentgenographic findings may precede clinical events. This picture may be confused with pulmonary edema or other disorders which produce a butterfly pattern on roentgenograms. Nocardia may rarely produce a similar roentgenologic pattern but should generally not be confused with pneumocystis infections.

Diagnosis is established by identifying the protozoan either in the lung or its secretions. Since these patients do not produce significant sputum, tracheal lavage has been advocated as an approach. Ivady

et al. [40], basing their views upon vast experience with premature and feeble infants, prefer smears of tracheal mucus obtained by aspiration through a laryngoscope. Using this technic they have identified organisms as early as seven to ten days prior to changes noted on roentgenograms and clinically. Although P. carinii has been identified in fixed sections of hypopharyngeal material recovered from an infant, most investigators believe that the organism rarely, if ever, appears in the sputum [41]. Because of the inability to identify the organism in sputum, lung biopsy is recommended to establish the diagnosis. In cases of P. carinii pneumonia, open lung biopsy, although an accepted approach, has been reported to be associated with problems commencing with anesthesia and continuing through the postoperative period. In some cases assisted ventilation was required postoperatively because of severe respiratory distress [11,18]. Percutaneous lung biopsy is an alternative approach, having been successfully employed in obtaining specimens for organism identification with only minor complications [6,7,12,42]. To date, we have successfully employed percutaneous pulmonary needle biopsy in two renal transplant patients to confirm the presence of P. carinii pneumonia. There were no complications other than transient hemoptysis (5 to 10 cc). Robbins [18], however, mentions a case in which nondecompressable pneumothorax and death followed needle aspiration of a lung infected with P. carinii. At the present time, our experience parallels that of others, in that percutaneous lung biopsy is a rapid, useful diagnostic modality with minor morbidity and mortality for problems of diffuse pneumonopathy [27,43]. This procedure is especially germane in critically ill patients suspected of having P. carinii pneumonia, who often are poor surgical candidates.

In the English literature, there are twelve cases of P. carinii pneumonitis, proved at biopsy, in which the patients were treated successfully [6,7,11,13,15,16,18,19], later deaths being attributed to other causes. One patient was successfully treated with hydroxystilbamidine, another with amphotericin and large doses of corticosteroids [13,16]. The other ten patients received pentamidine isethionate, a diamidine with trypanosomicidal activity, found to be effective in man and animals [44]. Ivady, the first to use the drug in man (1950), observed that from the sixth day of treatment degeneration of the pneumocystis became more and more prominent; by the tenth day, the organisms had almost disintegrated and thereafter were no longer demonstrable. In infants, with a dose of 4 mg/kg over twelve to fourteen days, the clinical effect became apparent four to six days after the initial injection, the only side effects being "occasional erythrocyturia and anemia." The mortality rate decreased from 50 to 3 per cent [40].

The drug, administered intramuscularly, occasionally causes pain at the injection site, and tissue slough has been reported [7]. Nausea and vomiting, dizziness, hypotension, tachycardia and hypoglycemia have also been described. Megaloblastic bone marrow changes, possibly related to an antifolate effect of the drug, have been described [18]. Of particular concern to our patient with renal transplantation are the recent reports of possible nephrotoxicity. DeVita et al. [6] reported a case of apparent renal tubular dysfunction, questionably secondary to doubling the dose of pentamidine for two days. In a second case the patient experienced one day of oliguria with full recovery; however, nephrotoxic antibiotics may have been added factors. Our patient received 4 mg/kg intramuscularly for fourteen days without renal injury, as measured by daily urine output, urine electrolytes, urine sediment and blood urea nitrogen and creatinine levels.

Of the twelve surviving patients described in the literature, concomitant with pentamidine administration, two patients were treated successfully while receiving larger doses of steroids, three patients were treated successfully while on a decreasing steroid schedule. At the present time there is no firm evidence that it is necessary to increase, decrease or discontinue the administration of corticosteroids in order to treat P. carinii pneumonia. This point will require further clarification.

## NOCARDIA

This genus of fungi typically presents as gram-positive, partially acid-fast, filamentous appearing forms with fine branching hyphae that tend to break up into bacillary or coccal fragments. These grow aerobically on routine culture medium, distinguishing it from other anaerobic species. Worldwide in distribution, Nocardia appears to colonize man directly via the inhalation route. Most investigators contend that Nocardia is a saprophyte in man, thus its presence in sputum indicates ongoing pathogenicity requiring appropriate therapy [23,45,46]. Nocardia asteroides is the most common species infecting man, manifesting primarily as a bronchopulmonary disorder, although systemic dissemination is an added complication. The course may be either acute or chronic, localized or disseminated, and may resemble acute pneumonitis, chronic tuberculosis, lung abscess or neoplasm.

Prior to sulfonamide therapy the mortality rate was estimated at about 75 per cent [22]; at present the over-all mortality is cited at about 50 per cent. This value may be somewhat misleading in that nocardiosis usually occurs in those who are seriously ill with other diseases, especially in those receiving large doses of adrenocortical steroids [22,24,25,45,47–49]. The incidence of nocardiosis appears to be increasing, perhaps attributable to the improved

survival of patients with serious underlying disorders, to the increased use of adrenal corticosteroids and to increasing diagnostic acumen. Sulfonamides are currently the drugs of choice [50], first successfully administered in 1944 by Benbow et al. [51]. Strauss and associates [52] in 1951 demonstrated with animal protection studies that sodium sulfadiazine imparted almost 100 per cent protection to infected mice. Sulfadiazine has been the most frequently employed sulfonamide, provided in dosages to attain serum concentrations of 8 to 12 mg/100 ml [22]. Successful treatment has been reported with sulfisoxazole [22, 53], sulfamethoxine [22], sulfanilamide [53] and triple sulfate [53,54]. Thus, any of the available sulfonamides yielding adequate and sustained blood concentrations appear equally effective by present criteria. Sulfa drugs should be continued for at least two or three months, and if chronic disease persists, for one year or longer. Sulfisoxazole (Gantrisin) is rapidly excreted, relatively highly soluble in urine, only infrequently produces hematuria or crystalluria (0.2 to 0.3 per cent) and is associated with a low risk of anuria [55]. We therefore prefer sulfisoxazole in the hope of minimizing any added insult to transplant kidneys.

Other antibiotics suggested for treatment of Nocardia include penicillin [56], penicillin combined with streptomycin [57], penicillin and chlortetracycline [58], chloramphenicol [59] and cycloserine [60]. A review of the literature, however, offers no unequivocal criteria as to which antibiotic, if any, should be used in conjunction with sulfonamides.

Finally, this case additionally serves to emphasize that patients with compromised immunologic defense mechanisms may be suspectible to infection with more than one "unusual" organism. In a review of twenty-three deaths after transplantation, 83 per cent of the patients with systemic fungal infections had a concomitant infection, usually pneumonia or septicemia; of these, five were due to P. carinii, the others being bacterial [4]. Cytomegalovirus was also frequently observed in the postmortem lung examination in this series, but was considered not to be a direct cause of death.

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