Clinical Investigation

Pneumocystis carinii Pneumonia Treated With α-Difluoromethylornithine

A Prospective Study Among Patients With the Acquired Immunodeficiency Syndrome

JEFFREY A. GOLDEN, MD, *San Francisco;* ALBERT SJOERDSMA, MD, PhD, *Cincinnati, and* DANIEL V. SANTI, MD, PhD, *San Francisco*

Pneumocystis carinii *pneumonia is a protozoal infection that, in the setting of acquired immunodeficiency syndrome (AIDS), is often lethal and unresponsive to conventional therapy with trimethoprim-sulfamethoxazole or pentamidine. In the present study, we have prospectively assessed the use of α-difluoromethylornithine (DFMO), an inhibitor of polyamine biosynthesis, in the treatment of* P carinii *pneumonia in patients with AIDS who were intolerant or unresponsive to conventional drugs. Improvement by both clinical and objective criteria was observed in six patients who completed six to eight weeks of DFMO therapy. Expansion of these early trials of DFMO is warranted.*

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Pneumocystis carinii, although a ubiquitous protozoan, causes disease only in immunocompromised hosts.[1-3] *P carinii* pneumonia is the most common lethal infection in patients with acquired immunodeficiency syndrome (AIDS).[1,4,5] Although *P carinii* pneumonia usually responds to treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine in patients who do not have AIDS, these drugs are often inadequate or cause severe toxic reactions when used to treat *P carinii* pneumonia in patients who do have AIDS.[6-13] For such patients there is an immediate need for a safe and effective agent for treating *P carinii* pneumonia.

α-Difluoromethylornithine (DFMO) reduces intracellular polyamines by specific and irreversible inhibition of ornithine decarboxylase. Although polyamines are ubiquitous in living cells and are important in cell growth and replication, DFMO is well tolerated and remarkably nontoxic in animals and humans.[14,15] DFMO is an impressive antiprotozoan agent that has been used with dramatic success to treat infection by African trypanosomes in both animals and humans.[14,16,17] DFMO has also been shown to inhibit the protozoa *Eimeria tenella*, the exoerythrocytic form of *Plasmodium berghei*, *Trichomonas vaginalis* and *Giardia lamblia*.[14,18-20] Because *P carinii* is generally considered to belong to the protozoan subkingdom,[9,21] we felt that DFMO might be useful in treating *P carinii* pneumonia.

DFMO has also exhibited effects in the laboratory setting that might, in principle, benefit patients with AIDS. First, patients with AIDS are frequently infected with cytomegalovirus, an agent that itself may contribute to immunosuppression.[22,23] DFMO reportedly blocks the replication of human cytomegalovirus in cell cultures of human diploid fibroblasts.[24] Second, AIDS is fundamentally a disorder of the immune system. Improving immunocompetence in AIDS patients would be considerably important.[25] Recently, polyamine synthesis has been shown to play a role in the production of suppressor T cells, and mice treated with DFMO have had an increase in the ratio of helper-to-suppressor T cells.[26]

In this report, we describe the results of an initial clinical trial that used DFMO to treat *P carinii* pneumonia in six AIDS patients who were refractory or intolerant to

From the Departments of Medicine (Dr Golden), Biochemistry and Pharmaceutical Chemistry (Dr Santi), University of California, San Francisco, and Merrell Dow Research Institute, Cincinnati (Dr Sjoerdsma). Dr Santi is a Burroughs Wellcome Scholar in Molecular Parasitology.

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Reprint requests to Jeffrey A. Golden, MD, UC, San Francisco, Room 539-A, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT
AIDS—acquired immunodeficiency syndrome
DFMO—α-difluoromethylornithine
Pa_{O_2}—partial pressure of oxygen
Pa_{CO_2}—partial pressure of carbon dioxide
TMP-SMX—trimethoprim-sulfamethoxazole

TMP-SMX and pentamidine. Our findings suggest that DFMO may be an important new agent for the treatment of *P carinii* pneumonia in patients with AIDS.

Methods

The protocol for assessing DFMO therapy for *P carinii* pneumonia was approved by the University of California Committee on Human Research. All patients who participated in the study gave informed consent. Only patients with AIDS and a diagnosis of *P carinii* pneumonia confirmed by biopsy were eligible. AIDS was defined as the occurrence of a life-threatening opportunistic infection or Kaposi's sarcoma in patients younger than 60 years with no known cause for immunodeficiency.[4,5] Other eligibility criteria were refractoriness or life-threatening toxic reactions to pentamidine and TMP-SMX. Refractoriness was defined as a worsening clinical course, including dyspnea, elevated temperature, increased infiltrates on roentgenograms of the chest and worsening arterial blood-gas values. In addition, patients were eligible only if they were expected to survive for at least two weeks when they were deemed refractory to treatment.

The initial dose of DFMO was 6 grams per sq m of body surface area per day, divided in three orally given doses, for eight weeks. In the event of toxicity, administration of the drug was to be discontinued. If the specific toxic manifestation disappeared when DFMO therapy was discontinued, the therapy was to be restarted at a lower dosage: 4 grams per sq m per day given orally.

To assess the benefit and toxicity of DFMO, baseline and follow-up data were collected from the following sources: medical history, physical examination, routine blood analysis as well as enumeration of helper and suppressor T-cell subsets,[27] arterial blood gas determinations (specimens were taken while the patient breathed room air), chest roentgenograms, audiologic evaluation, gallium lung scan and fiberoptic bronchoscopy. Gallium lung scans were done 48 hours after intravenous injection of gallium 67 citrate at 100 μCi per kg. Pulmonary gallium uptake was evaluated as follows: grade 1, less than or equal to that in the adjacent soft tissue; grade 2, greater than that in adjacent soft tissue; grade 3, equal to that in the liver, or grade 4, greater than that in the liver. Resolution from grade 3 or 4 diffuse gallium uptake to grade 1 or focal grade 2 was interpreted as successful therapeutic response.[28-33] Flexible fiberoptic bronchoscopy was carried out by methods previously described.[34] Bronchoalveolar lavage specimens were taken by wedging the bronchoscope into a segmental bronchus and instilling five aliquots of 20 ml of normal saline to obtain a bronchoalveolar lavage sample of at least 30 ml.

Results

Nine patients participated in the study between July 1983 and July 1984. Two patients elected to stop all supportive measures and therapy after one day of treatment with DFMO and died within 72 hours. A third patient was treated with DFMO for four days but he subsequently elected to resume pentamidine therapy, which had resulted in thrombocytopenia five months earlier; he had a slow and incomplete recovery during the subsequent month of pentamidine therapy with no recurrent thrombocytopenia. Six patients completed six to eight weeks of DFMO therapy.

Reports of Cases

Patient 1

A 34-year-old white homosexual man was admitted to hospital on July 18, 1983, after two weeks of progressive dyspnea and nonproductive cough. The only abnormality on physical examination was oral mucosal candidiasis. Arterial

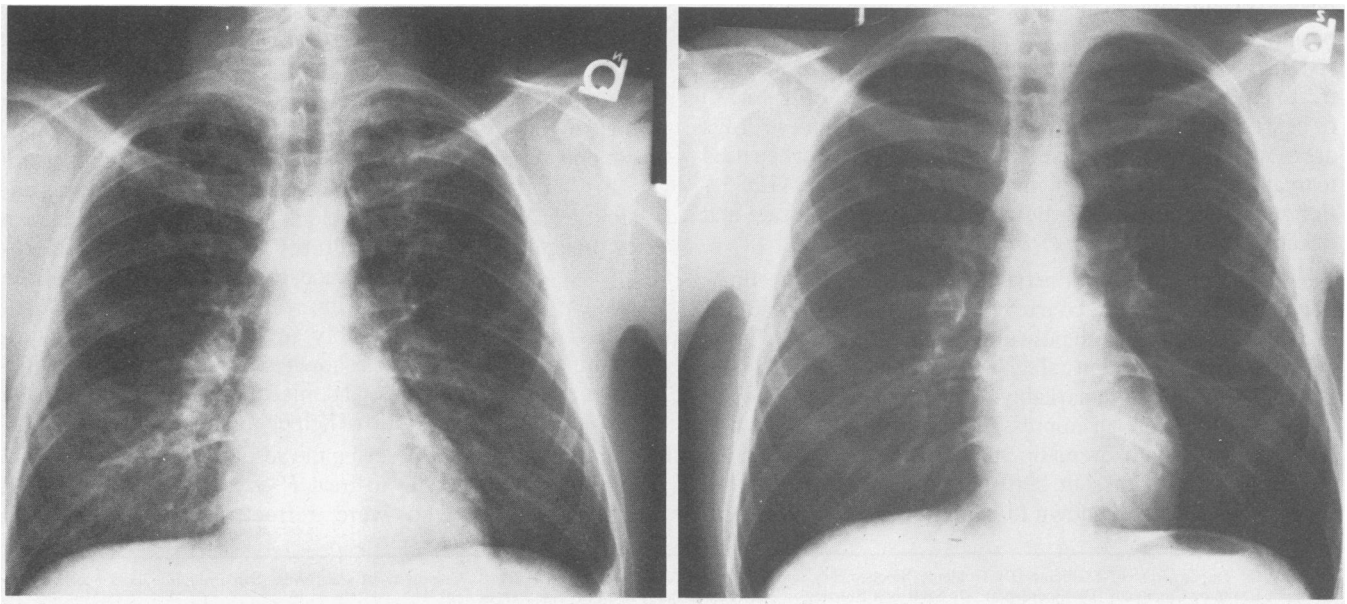

Figure 1.—Chest roentgenograms in patient 1, before **(left)** DFMO therapy showing diffuse infiltrates and after **(right)** 25 days of DFMO therapy showing resolved infiltrates.

blood gases (room air) were as follows: partial pressure of oxygen (Pao_2) 68 mm of mercury, partial pressure of carbon dioxide ($Paco_2$) 39 mm of mercury and pH 7.44. A chest roentgenogram showed bilateral infiltrates, and transbronchial biopsy showed *P carinii* pneumonia.

The patient was initially treated with TMP-SMX. After nine days a diffuse erythematous rash developed and the patient became febrile; TMP-SMX was replaced by pentamidine therapy. Four days later the infiltrates on the chest roentgenogram showed some resolution, and both the fever and diffuse rash diminished. However, on day 7 of pentamidine therapy, the patient's temperature again rose as high as 40°C (104°F) and a chest roentgenogram showed increased infiltrates (Figure 1). Arterial blood gas studies done while the patient was breathing room air showed Pao_2 50 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.44; while he was breathing 5 liters of oxygen per minute via nasal prongs, Pao_2 was 65 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.35. On day 8 of pentamidine therapy, bronchoscopy confirmed the persistence of *P carinii* pneumonia. At this time the patient was considered unresponsive to pentamidine therapy: he had increased temperature, worsening arterial blood gas values, increased infiltrates on chest roentgenograms and grade 4 diffuse uptake on a gallium scan (Figure 2). TMP-SMX therapy was reinstituted but caused an immediate hypotensive reaction that required treatment with dopamine. On August 8, DFMO therapy was initiated. By the fourth day of DFMO therapy, the patient became less dyspneic; his temperature returned to normal and remained so throughout the rest of his hospital stay. After one week of DFMO therapy, findings on chest roentgenograms improved and subsequent chest roentgenograms showed progressively less infiltrate (Figure 1). Arterial blood gas values (room air) also improved after one week of therapy: Pao_2 92 mm of mercury, $Paco_2$ 41 mm of mercury and pH 7.43. The patient was discharged from hospital after 11 days of DFMO therapy.

As an outpatient, after a total of 30 days of treatment with DFMO, the patient remained free of dyspnea on exertion, and the chest roentgenogram was normal. A gallium lung scan showed resolution to grade 1 (Figure 2), and arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.37. Transbronchial biopsy showed no evidence of *P carinii* pneumonia and no *P carinii* cysts were evident in the bronchoalveolar lavage specimen. Cytomegalovirus was not cultured from the lung in either the initial or this post-DFMO bronchoscopic evaluation. The patient arbitrarily decided to stop DFMO therapy after seven weeks.

DFMO may have caused hematologic side effects. Although the hemoglobin level and the platelet count remained unchanged, the leukocyte count fell from 6,100 per μl before DFMO therapy to 2,200 per μl after 14 days of therapy. The leukocyte count later increased spontaneously but never exceeded 3,000 per μl during the course of therapy. During the seven months after therapy, the leukocyte count remained in the range of 2,500 to 3,000 per μl. Also, serial audiologic evaluations, including a study done one month after the completion of DFMO therapy, showed normal hearing acuity.

Initial immunologic evaluation on July 1, before DFMO therapy, showed 48% T cells (normal, 65% to 85%) with 12% helper T cells (normal, 40% to 60%) and 28% suppressor T cells (normal, 20% to 40%); the helper:suppressor ratio was 0.4 (normal, 1.2 to 2.3). Evaluation after DFMO therapy showed 53% T cells, with 14% helper T cells, 42% suppressor T cells and a helper:suppressor ratio of 0.34. The patient was asymptomatic after discontinuation of DFMO therapy for the seven months he was followed by one of the authors (J.G.).*

*One year following DFMO therapy patient 1 was admitted to a community hospital with fulminant *P carinii* pneumonia. Although he was not a candidate for our protocol because of the severity of his pneumonia, his physician treated him with DFMO on a compassionate basis. The patient's condition rapidly deteriorated and he died. No autopsy was carried out.

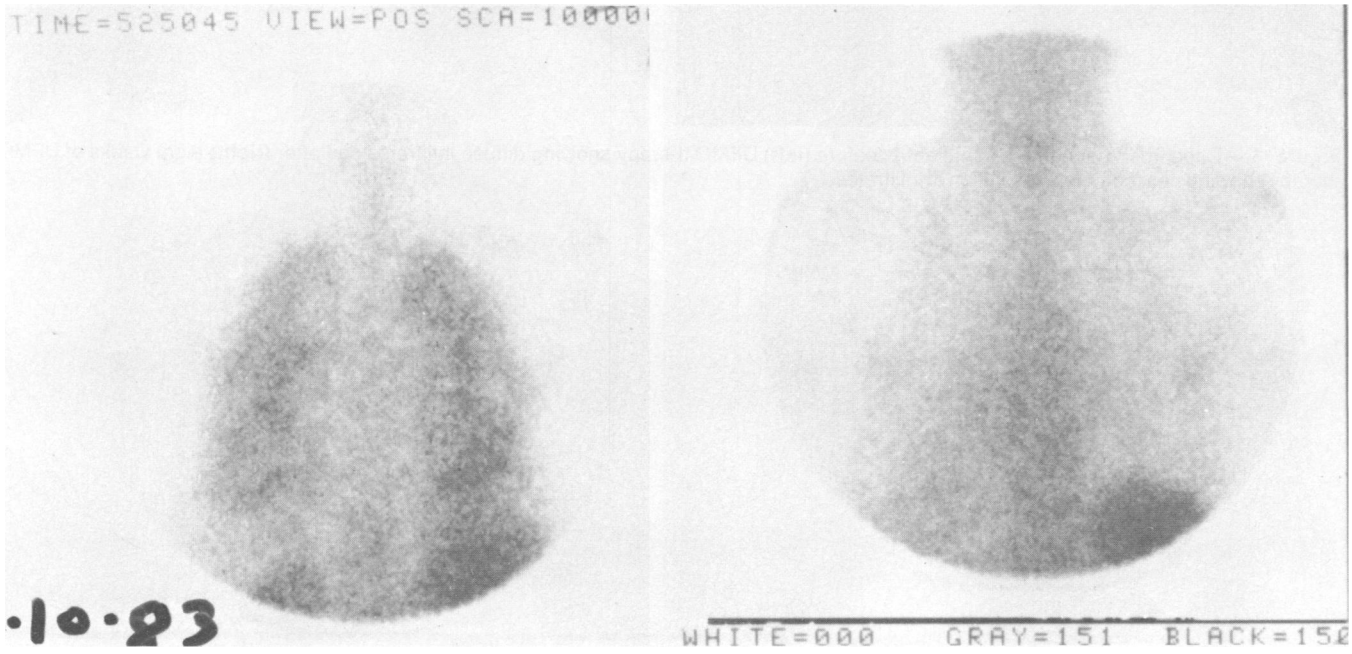

Figure 2.—Gallium lung scans, posterior view, in patient 1, before **(left)** DFMO therapy showing diffuse gallium uptake and after **(right)** one month of DFMO therapy showing resolution of gallium uptake.

Patient 2

A 36-year-old white homosexual man was admitted to hospital on September 23, 1983, because of dyspnea for two days and nonproductive cough for one week. The patient also had had three weeks of watery diarrhea and fever associated with an 11-kg (25-lb) weight loss. On physical examination, he appeared to be in a toxic condition with acute respiratory distress, breathing 40 times per minute, and had a temperature of 38.5°C (101.3°F); oral examination showed mucosal candidiasis. Arterial blood gas values (room air) were Pao_2 56 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46. A chest roentgenogram showed bilateral hazy infiltrates.

Because the patient was too ill for bronchoscopy, a presumptive diagnosis of *P carinii* pneumonia was made. Pentamidine therapy was initiated because the patient had previously had a severe Steven-Johnson reaction to sulfa-drug therapy. A bronchoalveolar lavage specimen taken 48 hours after admission showed *P carinii* cysts. Also, cytomegalovirus was cultured from the lavage specimen. Transbronchial biopsy was not done at this time because the patient was too ill and uncooperative.

The patient remained in a toxic condition with temperatures of 38.5°C to 39°C (101°F to 102°F) during six days of pentamidine therapy. On day 6 of the therapy, roentgenogram of the chest showed that the pneumonia had progressed since the patient was admitted (Figure 3), and arterial blood gas values (room air) had worsened, with Pao_2 35 mm of mercury, $Paco_2$ 34 mm of mercury and pH 7.45. A gallium lung scan showed diffuse grade 4 uptake (Figure 4).

In view of the progressive *P carinii* pneumonia, the patient was considered unresponsive to pentamidine therapy. On September 28, oral DFMO therapy was initiated. Because of persistent diarrhea, on October 5 the drug was administered intravenously at 4 grams per sq m per day in three divided doses; on October 8, the dosage was increased to 5 grams per sq m per day.

On day 3 of DFMO therapy, the patient was subjectively improved. He became afebrile on day 6 and his gas exchange also improved; arterial blood gas values (room air) were Pao_2 54 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.42. With continued DFMO therapy, the patient had progressively less dyspnea, his temperature did not rise above 38°C

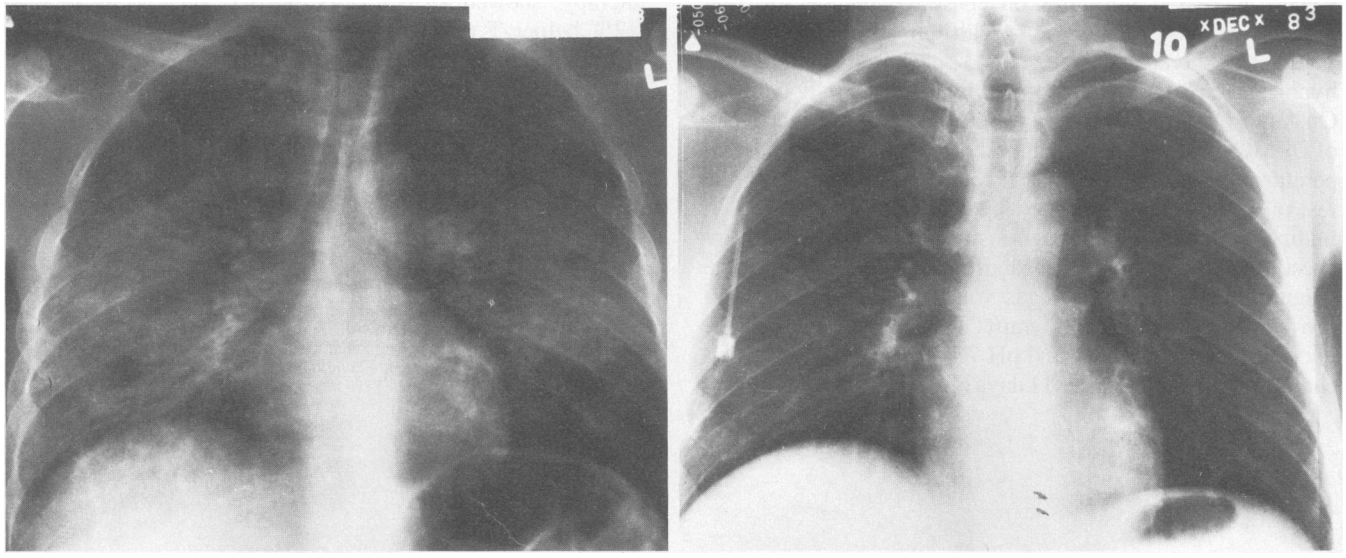

Figure 3.—Chest roentgenograms in patient 2, before **(left)** DFMO therapy showing diffuse infiltrates and after **(right)** eight weeks of DFMO therapy showing near complete resolution of infiltrates.

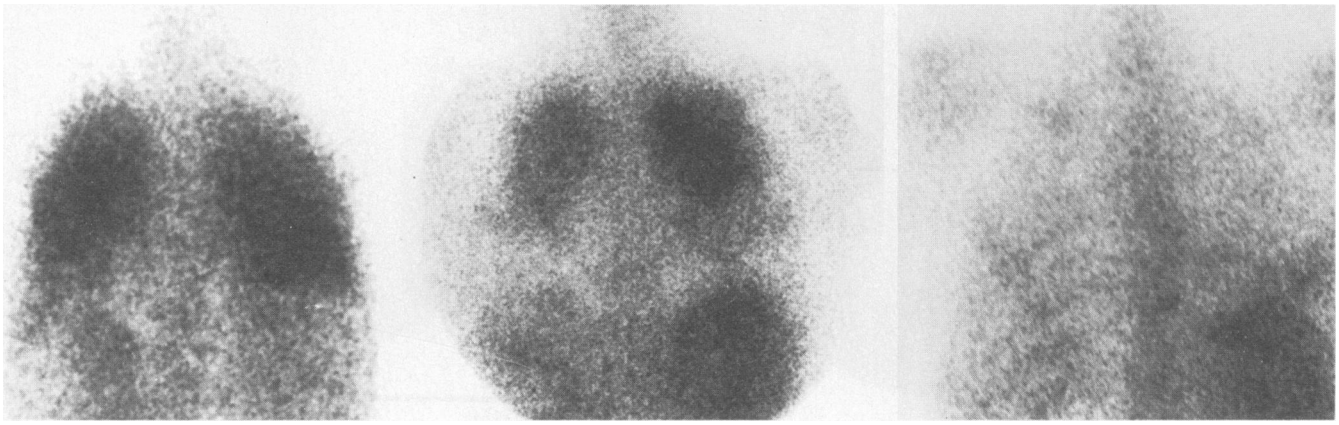

Figure 4.—Gallium lung scans, posterior view, in patient 2, before **(left)** DFMO therapy, after **(center)** four weeks of DFMO therapy and after **(right)** eight weeks of DFMO therapy showing progressive resolution of diffuse gallium uptake during therapy.

(100.4°F) and findings on roentgenograms of the chest slowly improved. However, pancytopenia developed slowly during the course of DFMO therapy. Before this therapy, the complete blood count included hemoglobin, 10.4 grams per dl; hematocrit, 30%; leukocyte count, 5,100 per μl, and platelet count, 302,000 per μl. After 27 days of therapy, the values were hemoglobin, 8.3 grams per dl; hematocrit, 25%; leukocyte count, 3,100 per μl, and platelet count, 54,000 per μl. At this time, we discontinued DFMO administration. Four days later, the leukocyte count had fallen to 1,400 per μl and the platelet count had fallen to 27,600 per μl. A bone marrow biopsy at that time showed erythroid hypoplasia, normal megakaryocytes and some myeloid immaturity. There was no circulating antiplatelet antibody.

At this time, arterial blood gases (room air) were Pao_2 72 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46. A chest roentgenogram showed resolution of the prior diffuse infiltrates, with infiltrates persisting only in the upper lung fields bilaterally. A gallium lung scan showed resolution to grade 1 in the lower lung fields and grade 3 uptake in both upper lung fields (Figure 4). A bronchoalveolar lavage specimen showed *P carinii* cysts; a transbronchial biopsy showed persistent *P carinii* pneumonia. The patient's immunologic state showed no change at this time. Before DFMO therapy, the patient had 12% helper T cells (normal, 39% to 53%), 42% suppressor T cells (normal, 18% to 27%) and a helper:suppressor ratio of 0.3 (normal, 1.8 to 2.4); these values did not change following DFMO therapy.

The patient's hematologic state improved one week after DFMO therapy was discontinued; the leukocyte count was 3,300 per μl and the platelet count was 330,000 per μl. DFMO therapy was reinstituted at 4 grams per sq m per day by oral administration, and continued at this dosage until the eight-week course was completed. At this time, findings on a chest roentgenogram were nearly normal (Figure 3). A gallium lung scan (Figure 4) showed dramatic improvement with focal grade 2 uptake localized to the middle of the right lung. Arterial blood gas values (room air) were Pao_2 70 mm of mercury, $Paco_2$ 33 mm of mercury and pH 7.44. No cysts of *P carinii* were found in the bronchoalveolar lavage specimen and only scattered cysts were found in the transbronchial biopsy specimen. Cytomegalovirus was cultured from the bronchoalveolar lavage specimen.

The patient was discharged from hospital and did well for three months. However, he was readmitted March 30, 1984, with a one-week history of dyspnea and severe diarrhea associated with a 9-kg (20-lb) weight loss. On physical examination he was cachectic-appearing with 32 respirations per minute, oral mucosal candidiasis and funduscopic findings consistent with cytomegalovirus retinitis. A roentgenogram of the chest showed diffuse infiltrates; arterial blood gas values (room air) were Pao_2 59 mm of mercury, $Paco_2$ 31 mm of mercury and pH 7.47. *P carinii* pneumonia was diagnosed by transbronchial biopsy. After 11 days of pentamidine therapy the patient was more dyspneic; arterial blood gas values (room air) were Pao_2 33 mm of mercury, $Paco_2$ 38 mm of mercury and pH 7.50; the chest roentgenogram showed increased infiltration and the gallium lung scan showed diffuse grade 4 uptake. He was again considered unresponsive to pentamidine therapy and it was discontinued. On April 10, 1984, therapy with DFMO was begun at 6 grams per sq m per day in three divided doses given intravenously. After 11 days of DFMO administration the patient was less dyspneic and a roentgenogram of the chest showed decreased infiltration, which progressively cleared on subsequent studies. Gallium lung scans after 35 and 56 days of DFMO therapy showed dramatic progressive improvement; the latter study showed only focal grade 2 uptake. On repeat bronchoscopy after eight weeks of DFMO therapy the transbronchial biopsy specimen was negative for *P carinii* pneumonia and no cysts were found on bronchoalveolar lavage. The patient was discharged on June 13, 1984, with hyperalimentation for progressive weight loss associated with massive diarrhea that defied diagnosis. He died at home one month later.

Patient 3

A 40-year-old white homosexual man was admitted to hospital on September 23, 1983, after three weeks of progressive dyspnea on exertion and nonproductive cough, diarrhea and weight loss. During the four months before admission, he had complained of malaise and fever and had been found to have oral mucosal candidiasis, hepatosplenomegaly and a positive urine culture for cytomegalovirus.

On physical examination the patient was notably thin; his temperature was 38.5°C and he was breathing 20 times per minute. He had oral mucosal candidiasis and bilateral rales were noted on chest auscultation. Arterial blood gas values (room air) were Pao_2, 79 mm of mercury; $Paco_2$, 37 mm of mercury and pH 7.45. A roentgenogram of the chest showed bilateral infiltrates, predominantly in the upper lobes. A transbronchial biopsy of the left upper lobe revealed *P carinii* pneumonia.

TMP-SMX therapy was begun on September 24. Seventeen days later, because of worsening findings on chest roentgenograms and persistent temperature elevations to 40°C, TMP-SMX was replaced by pentamidine therapy. A gallium lung scan showed diffuse grade 3 gallium uptake. The pentamidine caused side effects including pain at the injection site and hypotension. Because of the side effects, further elevation of temperature and progressive infiltrates on the chest roentgenogram, pentamidine was discontinued after two weeks. At this time the patient had fever and dyspnea on exertion, although arterial blood gases (room air) were Pao_2 100 mm of mercury, $Paco_2$ 36 mm of mercury and pH 7.48. A bronchoscopic examination was done on November 3. Transbronchial biopsy of the left upper lobe showed *P carinii* pneumonia, and the bronchoalveolar lavage specimen grew cytomegalovirus and a few colonies of cryptococci. On the day of bronchoscopy, blood cultures were positive for cryptococci. On November 5, amphotericin B therapy was initiated. DFMO therapy was begun at the same time because of temperature elevation, worsening findings on chest roentgenograms and bronchoscopic evidence of persistent *P carinii* pneumonia. At this time the hemoglobin was 10.8 grams per dl, the hematocrit, 32%; the leukocyte count, 1,300 per μl, and the platelet count, 94,000 per μl. Enumeration of T-cell subsets was not done. A gallium lung scan showed diffuse grade 3 gallium uptake unchanged from the earlier study done after 17 days of TMP-SMX therapy.

Before the initiation of DFMO and amphotericin B therapy, the patient had been persistently febrile with temperatures ranging from 38.5°C to 40°C. By the fifth day of

therapy, he felt better and was afebrile. He remained essentially afebrile for the next six weeks, after which he was discharged from hospital. It should be noted that when he became afebrile, he had received a total dose of amphotericin B of only 60 mg because of renal toxicity; during his entire hospital stay, he received only 15 mg of amphotericin B every other day, for a total dose of 340 mg. A roentgenogram of the chest taken on the eighth day of DFMO and amphotericin B therapy showed improvement. On the tenth day, however, the patient's platelet count began to fall, although the leukocyte count remained above 1,000 per μl and the hemoglobin remained at 10 grams per dl, with a hematocrit of 30%. By the 24th day of therapy, the platelet count was 35,000 per μl and the leukocyte count had fallen to 900 per μl. DFMO therapy was discontinued. One week later, the platelet count had risen to 90,000 per μl and the leukocyte count to 1,500 per μl. DFMO therapy was restarted at 4 grams per sq m per day.

Evaluation after four weeks of orally administered DFMO (24 days at 6 grams per sq m and 5 days at 4 grams per sq m) showed continued improvement in the findings on chest roentgenograms; the last film taken in hospital on December 10 was almost normal. A gallium scan on December 9 showed improvement compared with the baseline scan of November 7, 1983, with only a trace of focal grade 2 gallium uptake at the left base of the lung and no abnormalities in the right lung. Bronchoscopy on December 12 showed only a few cysts of *P carinii* in the bronchoalveolar lavage specimen. The transbronchial biopsy was negative for *P carinii* pneumonia. Viral cultures of bronchoscopically derived lung lavage and tissue were negative for cytomegalovirus. While the patient was an outpatient, the platelet count again started to fall. On December 24, with a platelet count of 50,000 per μl, DFMO therapy was again discontinued with subsequent elevation of the platelet count. Although the patient's clinical condition as an outpatient improved initially, elevated temperatures associated with progressively severe inanition subsequently developed and he died on February 6, 1984. The lung parenchyma at autopsy was hemorrhagic with intranuclear inclusions within enlarged alveolar lining cells typical of cytomegalovirus. There was no evidence of *P carinii* pneumonia or cysts. Inclusions typical of cytomegalovirus were identified in other organs: small and large intestines, liver, pancreas, thyroid, adrenals (associated with hemorrhagic necrosis) and kidney. The autopsy diagnosis was disseminated cytomegalovirus infection.

Patient 4

A 36-year-old white homosexual man with Kaposi's sarcoma was admitted to hospital on October 24, 1983, after three weeks of fever, progressive shortness of breath and nonproductive cough. Seven months earlier, he had lost 9 kg (20 lb) and suffered shortness of breath; *P carinii* pneumonia had been diagnosed by bronchoscopy. He had initially been treated with TMP-SMX but, after five days, with worsening arterial blood gas values and chest roentgenographic findings, the therapy was changed to pentamidine, to which he responded.

On physical examination on admission the patient was noted to be in moderate respiratory distress, breathing 30 times per minute, with a nonproductive cough, a temperature of 40.5°C (105°F) and oral mucosal candidiasis. Skin examination showed diffuse Kaposi's sarcoma. The arterial blood gas values (room air) were Pao_2 85 mm of mercury, $Paco_2$ 21 mm of mercury and pH 7.51. The chest roentgenogram showed diffuse interstitial infiltrates, with a dense consolidation in the upper lobe of the right lung.

On October 28, after *P carinii* pneumonia had been diagnosed by transbronchial biopsy, pentamidine therapy was begun. In addition, the bronchoalveolar lavage specimen grew cytomegalovirus. Because blood cultures were positive for *Streptococcus pneumoniae,* penicillin therapy was also initiated. The patient remained febrile, and after five days of therapy, on November 2, a diffuse erythematous skin eruption appeared, requiring that both pentamidine and penicillin administration be discontinued. The chest roentgenogram was unchanged. Arterial blood gas values (room air) were Pao_2 84 mm of mercury, $Paco_2$ 22 mm of mercury and pH 7.48. Erythromycin therapy was initiated for the streptococcal infection, but the *P carinii* pneumonia was not treated for three days. During that time the patient's cough worsened and his temperature was between 38°C and 39°C. On November 5, DFMO therapy was begun. At this time, arterial blood gas values (room air) were Pao_2 77 mm of mercury, $Paco_2$ 24 mm of mercury and pH 7.49. A gallium lung scan was not done at this time. Subset enumeration of T cells was not carried out in this patient.

After two days of DFMO therapy, the patient felt better and became afebrile. Arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.43. By day 6 of therapy the leukocyte count had decreased from 6,600 per μl at the initiation of DFMO therapy to 2,200 per μl. The patient was discharged on November 11 on a regimen of the same oral dosage of DFMO. In follow-up as an outpatient, after ten days of DFMO therapy, his leukocyte count had further decreased to 1,900 per μl. He was feeling well and arterial blood gas values were Pao_2 99 mm of mercury, $Paco_2$ 32 mm of mercury and pH 7.44. Because of the falling leukocyte count, however, DFMO administration was discontinued after 13 days of therapy. Three days later, the leukocyte count was 2,200 per μl and DFMO therapy was restarted at a lower oral dosage (4 grams per sq m per day). It was continued at this dose, with the patient's leukocyte counts ranging between 2,000 and 2,400 per μl until the eight-week course was completed. At that time, the patient had no cough and only minimal dyspnea on exertion. He was afebrile. The leukocyte count was 2,400 per μl, platelet count 235,000 per μl and the hemoglobin 10 grams per dl; the hematocrit was 29%. Arterial blood gases (room air) were Pao_2 96 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.45. Roentgenograms of the chest showed improvement but minimally increased interstitial markings were noted. A gallium lung scan showed diffuse grade 1 uptake. Bronchoscopy showed multiple dark airway lesions consistent with Kaposi's sarcoma. The transbronchial biopsy was negative for *P carinii* pneumonia but a few cysts were evident on the bronchoalveolar lavage specimen. Cytomegalovirus was cultured from this lavage specimen. The patient did well for two months after DFMO therapy at which time elevated temperatures developed associated with severe inanition and he died. He had requested no specific or supportive therapy. An autopsy was not carried out.

Patient 5

A 45-year-old white homosexual man was admitted to hospital on March 27, 1984, after one week of dyspnea. Two years before admission he had atypical pneumonia and was treated with TMP-SMX to which a severe cutaneous reaction developed. Physical examination on admission showed diffuse adenopathy and oral mucosal candidiasis. Chest roentgenograms showed bilateral infiltrates; arterial blood gas values (room air) were Pao_2 56 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.51. Transbronchial biopsy showed *P carinii* pneumonia. On March 28 he was given TMP-SMX, which resulted in an immediate rash after the second oral

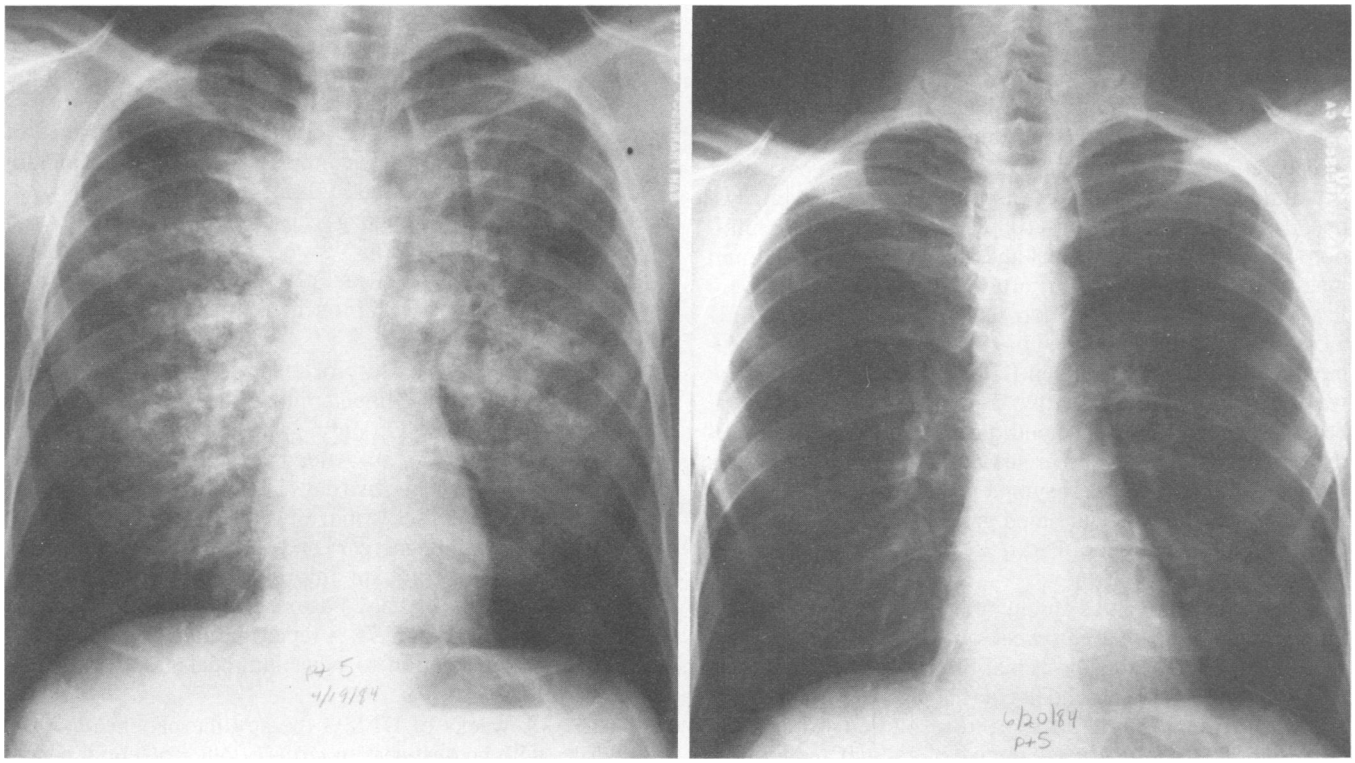

Figure 5.—Chest roentgenograms in patient 5, before **(left)** DFMO therapy for recurrent *Pneumocystis* pneumonia showing diffuse infiltrates and after **(right)** eight weeks of treatment with DFMO showing resolution of infiltrates.

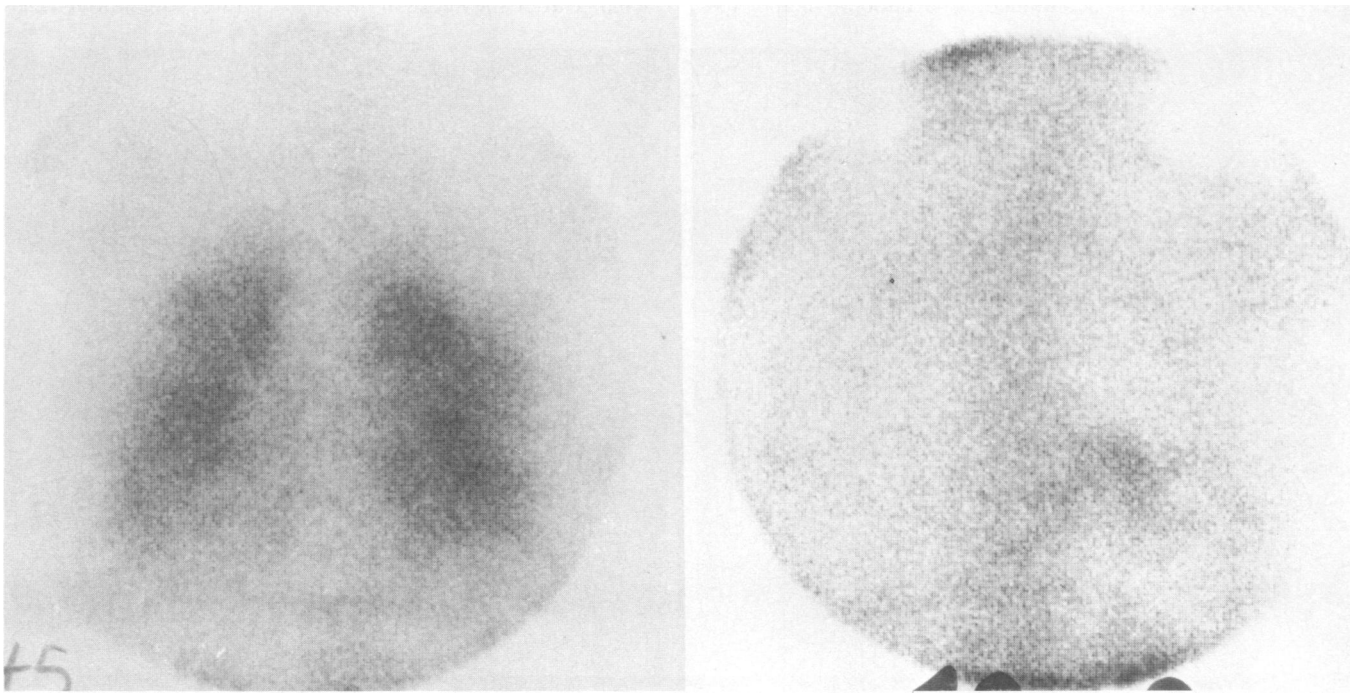

Figure 6.—Gallium lung scans, posterior view, in patient 5, before **(left)** DFMO therapy for recurrent *Pneumocystis* pneumonia showing diffuse gallium uptake and after **(right)** eight weeks of treatment with DFMO showing near complete resolution of gallium uptake.

dose; TMP-SMX therapy was discontinued and pentamidine therapy was begun. After three days of pentamidine therapy, the patient became afebrile. After five days, however, recurrent temperature elevation and rash developed, and liver function test results were abnormal. Pentamidine administration was discontinued after 14 days because of these toxicities. The patient remained in hospital for seven days with no therapy for his pneumonia. He was discharged at that time with less dyspnea, and arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 25 mm of mercury and pH 7.46. A roentgenogram of the chest showed improvement compared with a study done on admission.

The patient was readmitted three days later, ten days after pentamidine therapy had been discontinued, with severe dyspnea, temperature to 41°C (105.8°F), progressive infiltration on chest roentgenograms and a diffuse grade 4 gallium lung scan (Figures 5 and 6); arterial blood gas values were Pao_2 58 mm of mercury, $Paco_2$ 24 mm of mercury and pH 7.53. A repeat transbronchial biopsy showed *P carinii* pneumonia. The patient was given DFMO; pentamidine therapy was not reinstituted. After five days of DFMO therapy, he became afebrile; arterial blood gases were Pao_2 66 mm of mercury, $Paco_2$ 31 mm of mercury and pH 7.5. After ten days of DFMO therapy he was asymptomatic and was discharged from the hospital; arterial blood gas values (room air) were Pao_2 83 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46.

The patient did well as an outpatient; he returned to work for the last six of his eight weeks of DFMO therapy. The post-DFMO repeat transbronchial biopsy showed no *P carinii* pneumonia, and bronchoalveolar lavage was negative for cysts. A gallium lung scan showed resolution with only a focal right lower lobe grade 2 uptake of gallium and a roentgenogram of the chest showed no abnormalities (Figures 5 and 6). He has continued to do well for two months after DFMO therapy was discontinued. The patient's helper-to-suppressor T-cell ratio was 0.3 (normal, 1.8 to 2.4) before DFMO therapy and did not change after eight weeks of therapy. Cultures of lung lavage and transbronchial biopsy both before and after DFMO therapy failed to grow cytomegalovirus. Finally, there were no side effects attributable to DFMO.

Patient 6

A 51-year-old white homosexual man was evaluated on July 5, 1984, for four months of daily temperature elevation to 40°C (104°F) associated with night sweats and progressive dyspnea. Physical findings included a temperature of 38.5°C and oral mucosal candidiasis. A chest roentgenogram showed bilateral interstitial infiltrates; there was grade 4 gallium uptake on a gallium lung scan (Figures 7 and 8). Arterial blood gas values (room air) were Pao_2 83 mm of mercury, $Paco_2$ 33 mm of mercury and pH 7.44. Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage showed *P carinii* pneumonia.

The patient had a history of severe cutaneous reaction to TMP-SMX and refused pentamidine therapy as well as admission to hospital. On July 7, 1984, he began DFMO therapy as an outpatient. After two days, he became and remained afebrile. After five days he was no longer dyspneic, and arterial blood gases (room air) were Pao_2 94 mm of mercury, $Paco_2$ 36 mm of mercury and pH 7.43; a chest roentgenogram showed significant improvement. The next chest roentgenogram done after 24 days of DFMO therapy showed no abnormalities (Figure 7). A repeat gallium lung scan at this time showed resolution to bibasilar focal grade 2 gallium uptake (Figure 8).

After six weeks of DFMO therapy the patient remained afebrile, with no dyspnea. In terms of other potential benefit from DFMO, the helper-to-suppressor T-cell ratio was 0.09 (normal, 1.8 to 2.4) before DFMO therapy and did not change after six weeks of therapy. Culture of the initial trans-

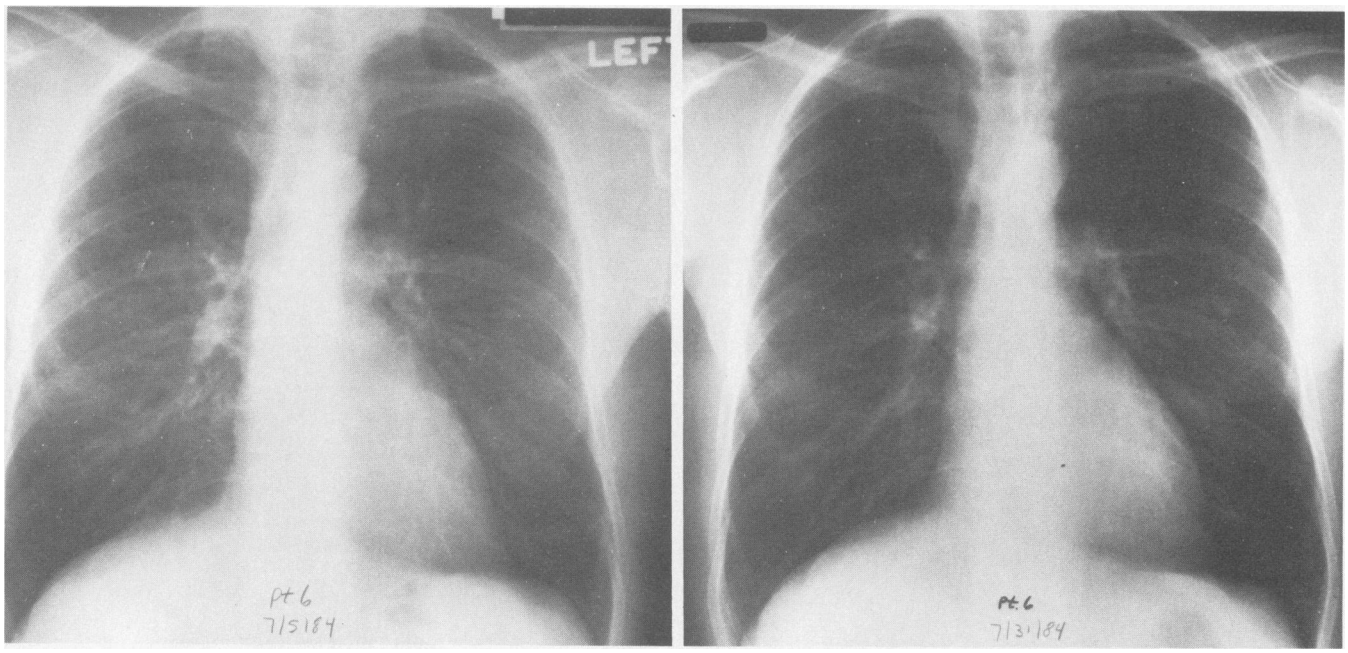

Figure 7.—Chest roentgenograms in patient 6, before **(left)** DFMO therapy showing bilateral infiltrates and after **(right)** 24 days of treatment with DFMO as first-line therapy showing a normal study.

bronchial biopsy and bronchoalveolar lavage was negative for cytomegalovirus; the patient refused a repeat bronchoscopy following DFMO therapy. The only apparent side effect was a decrease in the platelet count from 174,000 per μl before therapy to 83,000 per μl after five weeks of DFMO therapy. After another week of therapy, the platelet count spontaneously increased to 130,000 per μl.

Discussion

P carinii pneumonia, if untreated, is fatal in 90% to 100% of patients.[35] Pentamidine was the first effective drug to treat *P carinii* pneumonia, but it causes significant adverse effects in almost half of the patients.[11,12] Subsequently, TMP-SMX was used to treat this infection.[9,10] In patients who do not have AIDS, TMP-SMX is as effective as pentamidine against *P carinii* pneumonia and has few adverse effects.[13] In patients with AIDS, however, TMP-SMX has been associated with significant toxicity. Approximately half the AIDS patients given TMP-SMX for *P carinii* pneumonia have had severe drug reactions, including fever, cutaneous reactions and life-threatening cytopenia.[6-8] Clearly, a new medication is needed for *P carinii* pneumonia in patients with AIDS. The recently recognized antiprotozoan effect of DFMO made this compound a possible new treatment for *P carinii* pneumonia.[14]

Patient 1 could not tolerate TMP-SMX. After eight days of pentamidine therapy, he had increased dyspnea and temperature elevation, and more infiltration shown on chest roentgenograms, as well as increased hypoxia. A gallium lung scan showed diffuse grade 3 gallium uptake, and bronchoscopy showed persistent *P carinii* pneumonia. After four days of DFMO therapy, the patient's temperature was normal; after one week of therapy, the chest roentgenogram showed improvement and arterial blood gas values were normal. After 30 days of DFMO therapy, the gallium lung scan was normal, transbronchial biopsy failed to show *P carinii* pneumonia and bronchoalveolar lavage showed no *P carinii* cysts.

After six days of pentamidine therapy, patient 2 remained in a toxic-appearing condition, with elevated temperature, worsened findings on roentgenograms of the chest and arterial blood gas studies and diffuse grade 4 gallium uptake on a gallium lung scan. After six days of DFMO therapy, he became afebrile and the arterial blood gas values and chest roentgenogram were improved. In addition, serial gallium scans of the lung showed progressive improvement concomitant with improved serial chest roentgenographic findings and arterial blood gas analyses. Bronchoscopy after eight weeks of DFMO therapy showed only scattered cysts of *P carinii* on the transbronchial biopsy and no cysts in the bronchoalveolar lavage specimen. The patient did well for three months before recurrent *P carinii* pneumonia developed, which again was refractory to pentamidine therapy. Although the patient's course was complicated by severe diarrhea, he again responded to eight weeks of DFMO therapy. After this second course of DFMO repeat transbronchial biopsy and bronchoalveolar lavage were negative for both *P carinii* pneumonia and cysts.

Patient 3 had persistent *P carinii* pneumonia despite 17 days of TMP-SMX and two weeks of pentamidine therapy. He also had cryptococcal organisms in the bronchoalveolar lavage specimen and cryptococcemia. The simultaneous initiation of amphotericin B and DFMO complicates interpretation of the benefit of DFMO in this patient. However, the patient became afebrile on the fifth day of therapy, when he had received a total dose of only 60 mg of amphotericin B. The rapid clinical response more likely reflects effective treat-

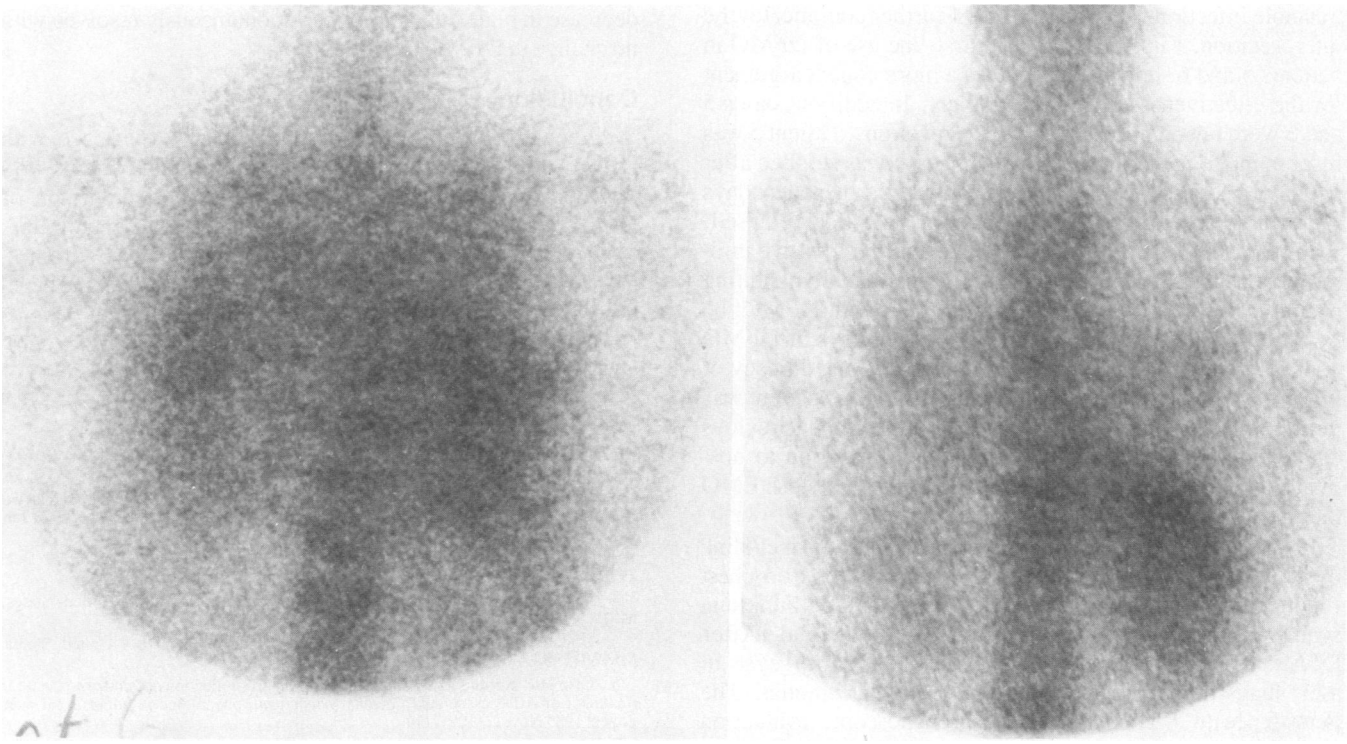

Figure 8.—Gallium lung scans, posterior view, in patient 6, before **(left)** DFMO therapy showing diffuse grade 4 gallium uptake and after **(right)** 24 days of treatment with DFMO as first-line therapy showing resolution to bibasilar focal grade 2 gallium uptake.

ment of *P carinii* pneumonia with DFMO than a response of pulmonary cryptococcosis to 60 mg of amphotericin B. After five weeks of DFMO and amphotericin therapy, the patient remained afebrile and felt well, and the abnormalities on chest roentgenograms and gallium lung scans had resolved. Finally, bronchoscopy near the completion of DFMO therapy showed no *P carinii* pneumonia on transbronchial biopsy and only a few cysts in the bronchoalveolar lavage specimen. The patient subsequently died of disseminated cytomegalovirus infection. At autopsy, six weeks after DFMO therapy was discontinued, neither *P carinii* pneumonia nor cysts were identified in the lung pathologic findings.

Interpreting the benefit of DFMO in patient 4 is complicated by concurrent treatment with erythromycin for *Streptococcus pneumoniae*. After discontinuing pentamidine administration, and while taking erythromycin but no therapy for *P carinii* pneumonia, the patient's clinical condition deteriorated. After two days of treatment with DFMO, he became afebrile and subsequent arterial blood gas analyses and chest roentgenograms showed improvement. There was no gallium uptake in his lungs (grade 1) after eight weeks of DFMO therapy. He remained well for an additional two months following cessation of DFMO therapy. Subsequently an acute undiagnosed illness developed and the patient died; no autopsy was carried out. The role of effective antibacterial therapy for *S pneumoniae* infection cannot be discounted in his initial clinical improvement. However, the sustained clinical improvement for four months after the diagnosis of *P carinii* pneumonia implies likely benefit from DFMO.

Although DFMO appeared to be beneficial in treating *P carinii* pneumonia in patients 1 through 4, who were failing or intolerant to conventional therapy, these cases are somewhat difficult to interpret because of the prior use of TMP-SMX or pentamidine, or both. The presence of other treatable infections in patients 3 and 4 further complicates the interpretation. First-line and near-first-line use of DFMO in patients 5 and 6, however, provides a more cogent argument for the effectiveness of DFMO therapy. In addition, cases 5 and 6 were not complicated by other infections. Patient 5 was responding to pentamidine therapy when it was stopped after 14 days because of liver toxicity. Over the next ten days without therapy for *P carinii* pneumonia the patient relapsed, with recurrent dyspnea, fever, hypoxia and progressive infiltration on chest roentgenograms. Rather than reinstituting pentamidine therapy, we treated the patient with DFMO; he responded quickly, was discharged after ten days of DFMO administration and returned to work. Finally, the efficacy of DFMO is established most clearly in case 6. This patient was put directly on a regimen of DFMO alone without previous conventional therapy. He never required admission to hospital and had an unequivocally positive response to DFMO therapy for *P carinii* pneumonia.

In the six patients studied, clinical evaluation—including dyspnea and temperature, as well as the findings on chest roentgenograms, arterial blood gas studies and gallium lung scans—clearly implies that DFMO was beneficial. After DFMO therapy, patients 2, 3 and 4 still had *P carinii* cysts in their lungs despite resolution of *P carinii* pneumonia. The persistence of *P carinii* cysts on bronchoscopic evaluation with clinical and objective resolution of the pneumonia seems unique to AIDS patients, independent of the drug used for therapy. Such persistence is not seen in patients without AIDS, and its significance is unclear.[11,36]

The potential effects of DFMO on cytomegalovirus and helper and suppressor T-cell populations suggest that, in addition to its usefulness as an antiprotozoan agent, DFMO might have other benefits for patients with AIDS.[24,26] In this preliminary report, DFMO apparently did not affect either cytomegalovirus or immune incompetence. Patients 2 and 4 had cytomegalovirus cultured from the lung before and after DFMO therapy. Although patient 3 did not have cytomegalovirus on his post-DFMO therapy bronchoscopic evaluation, an autopsy six weeks after DFMO was discontinued showed he died of disseminated cytomegalovirus infection. Patients 1, 5 and 6 never had a diagnosis of pulmonary cytomegalovirus infection. Similarly, in four patients (patients 1, 2, 5 and 6) DFMO did not affect T-cell subset populations.

Previous experience has suggested that DFMO may cause reversible hearing defect, gastrointestinal disturbances or reversible hematologic abnormalities.[37] None of our six patients complained of hearing problems or had objective hearing defects ascribable to DFMO. No patient complained of gastrointestinal side effects referrable to DFMO. However, hematologic side effects did occur. Patient 1 incurred a low-grade neutropenia that did not require discontinuing the therapy. His persistently low leukocyte count five months after the cessation of DFMO is consistent with AIDS and was not necessarily a drug reaction. Patient 2 had pancytopenia that eventually required stopping DFMO therapy. The severe thrombocytopenia and neutropenia were reversed after one week, and hematologic toxicity did not recur when DFMO was reinstituted at a lower dose. Patient 3 had two reversible episodes of thrombocytopenia. Patient 4 had a reversible decrease in his leukocyte count, which did not recur when DFMO was reinstituted at a lower dose. Patient 6 had a decrease in platelet count, which spontaneously resolved with no change in DFMO therapy.

Conclusion

Although encouraging, our preliminary experience with DFMO therapy for *P carinii* pneumonia among patients with AIDS is insufficient to permit an overall comparison of DFMO efficacy with that of TMP-SMX and pentamidine. However, these six AIDS patients, all unresponsive or intolerant of conventional therapy for *P carinii* pneumonia, benefited from treatment with DFMO. If results in such patients continue to be favorable, future studies should include a comparison of DFMO and conventional therapy.

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