Adult Respiratory Distress Syndrome in a Previously Healthy Young Male*

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Infection with pneumocystis carinii and cytomegalovirus was found in a young male suspected of having miliary tuberculosis. Problems of diagnosis and predisposing factors for these infections in the patient are discussed. The patient's clinical course and management are reviewed. Autopsy findings are presented. Alternative modes of therapy are considered.

DR. LISA BABITZ (Resident in Medicine): The patient was a 43-year-old Chilean male in the U.S. for five years. He presented to the ER with a five-week history of fatigue, a twenty-pound weight loss, and a two-week history of productive cough, hemoptysis, night sweats, dyspnea, and headache. When he first presented with malaise, his doctor performed some blood tests and a chest X-ray. All were reportedly normal. He was seen by a second doctor who prescribed an antidepressant and subsequently IM penicillin for a positive VDRL and a weakly positive FTA. With the worsening of his cough and dyspnea, he saw a third physician. He was found to have a bilateral interstitial infiltrate on chest X-ray and was sent to the ER to rule out miliary TB.

Past medical history was remarkable for a history of a heart murmur in his childhood, a question of syphilis, which was treated in Chile, about 18 years prior to admission, and herpes zoster of the right side three years prior to admission. The patient admitted to drinking a beer a week, but denied any "recreational" drug use. His travel history was remarkable for 31 years spent in Chile, followed by travel in Europe and Great Britain, and a year aboard a cruise ship. He was a sexually active homosexual living for the past five years in a rural community with a weekend apartment in a large city.

Physical exam revealed a cachectic white male in moderate respiratory distress with a hacking cough. His pulse was 90/minute and regular, and his blood pressure was 120/80. His respiratory rate was 36/minute at rest, and his temperature was 99.6°F rectally. His sclerae were anicteric. His fundoscopic exam was unremarkable. The oropharynx was without erythema or exudate. The only adenopathy noted was a small 1 cm mobile, non-tender, left axillary lymph node. His lungs were resonant to percussion with clear breath sounds throughout. His cardiac exam was remarkable for a II/VI mid-systolic murmur at the left sternal border without radiation. Normal
heart sounds with a physiologic split were heard. The abdomen was non-tender, and there was no hepatosplenomegaly. Extremities showed no clubbing. Genital, rectal, and neurologic examinations were unremarkable.

Laboratory studies showed a hemoglobin concentration of 13.7 gm/dl and a hematocrit of 29.2 percent. The white blood cell count was 8100/mm³ with 76 percent segmented cells, 2 percent bands, 18 percent lymphocytes, 2 percent monocytes, and 1 percent eosinophils. His PT and PTT were within normal limits. Electrolytes were unremarkable, BUN was 27 mg/dl, and glucose was 128 mg/dl. His urine was clear yellow with a specific gravity of 1.030 and a pH of 5. The urine was positive for ketones and protein by dipstick. Microscopic examination showed several white blood cells and two red blood cells per high-powered field. His cardiogram showed normal sinus rhythm with normal wave forms. Sputum examination did not show any acid-fast bacilli. Spinal fluid was examined and revealed no white cells, 156 red cells/mm³, 25 mg/dl of protein, and 17 mg/dl glucose. No organisms could be seen on gram stain.

**DR. ALAN KLIGER (Associate Professor of Medicine):** This young man presented with fatigue, weight loss, malaise, headache, and symptoms suggesting pulmonary infection: night sweats, fever, dyspnea, hemoptysis, and a productive cough. Dr. Carter, what was his chest X-ray like on admission?

**DR. ANTHONY CARTER (Resident in Radiology):** The chest film from the date of the patient’s admission shows a fine reticular pattern throughout his lungs which obscures some of the pulmonary vasculature. He has no significant adenopathy or calcifications, and no pulmonary effusions can be seen. His heart is of normal size. This is a non-specific pattern, but, with the history in mind, it points away from tuberculosis. It suggests a diffuse pneumonia, such as is seen in viral respiratory infections. Fluid overload alone could appear this way, as could drug abuse. Heroin abuse certainly could produce a pattern like this one.

**DR. KLIGER:** When this patient first presented, both the medical house staff and the radiology department felt strongly that the leading diagnosis was pulmonary tuberculosis. The day after admission the case was presented to Dr. Richard Root of the Infectious Disease Section, who did not agree with the diagnosis. Dr. Root, please tell us what your thoughts were, and how you proceeded in your evaluation.

**DR. RICHARD ROOT (Professor of Medicine):** My approach to this patient was aided by my having had three similar cases presented to me two months earlier at UCLA. Focusing on some things about the epidemiologic history in this patient, I think we can move rapidly to a specific diagnosis. To do so I will follow my traditional approach to infectious disease cases. Namely, we must ask the following questions. What are the epidemiologic factors in which a disease develops? What are the major clinical manifestations? What are the host factors that one has to consider? And how does that lead to a specific diagnostic or therapeutic measure? The host factors that were of interest in this patient were that he really had no known underlying disease or major disorder previously. Of interest in a relatively young person is that he apparently had a spontaneous herpes zoster infection. This raised the question of a possible decrease in his cellular immune function. From the epidemiologic standpoint, he was from Chile, where tuberculosis is endemic, and he had traveled all over the world. Perhaps more importantly, he had a positive VDRL and FTA, indicating a contact with venereal pathogens in the past, and his life style was that of a practicing homosexual. This last information had been elicited on the initial history and was presented to me somewhat as an afterthought by the fellow or resident who saw the case with me on the ID service. The patients that had been presented to me at
UCLA were male homosexuals with combined pneumocystis and cytomegalovirus pneumonia. The nature of this patient’s pulmonary infiltrates was somewhat atypical for tuberculosis, with a much finer pattern, and being more reticulonodular than truly miliary. One of the physical findings that was striking to me when I saw the patient was that his fingers were clubbed. An old clinical saw, which follows my personal experience, is that despite the hypoxemia that may be induced by pulmonary tuberculosis, it is not a disease that is regularly associated with clubbing. If a patient with tuberculosis shows clubbing of the fingers, one should consider other diagnoses to explain it. Such a patient either does not have tuberculosis, which, as we'll find out, was the case in this patient, or he has a complication, such as a pulmonary carcinoma or bronchiectasis, which might lead to clubbing in the setting of a previous or active tuberculosis. It is also important in the presentation of this patient that, while the sputum was “negative for AFB,” there was very little sputum that was worth examining.

Given the range of diagnostic possibilities, the nature of the interstitial pneumonia, and the host factors present, the possibility was very strong in my mind that he had a pneumocystis or a cytomegalovirus infection. With these possible diagnoses and the fact that the patient was already suffering from severe hypoxemia, it was important to establish a diagnosis rapidly. At that point the pulmonary service became involved in the care of the patient.

**DR. KLiGER:** Dr. Merrill, you saw the patient for the pulmonary service. Dr. Root and the other consultants felt that it was important to make a diagnosis rapidly. You have at your disposal a series of tools, including the sputum examination, endotracheal aspiration, bronchoscopy with brushings and lavage, bronchial biopsy, and open lung biopsy. In a patient who has a diffuse process such as this, what is the best approach for a rapid diagnosis?

**DR. BILL MERRILL (Assistant Professor of Medicine):** In general, the test that I choose depends on the patient’s clinical stability at the time that he is first seen. If the patient has a room air pO₂ of 40 or 50 mm Hg, and has little response to the administered oxygen, then I think it’s wise and most expeditious to go directly to an open lung biopsy. The time delay caused by ordering other tests and analyzing them may mean that the patient will be on a ventilator requiring a high FIO₂ and high positive end expiratory pressures (PEEP) at the time that one would like to do a further diagnostic procedure, such as an open biopsy. This patient had a pO₂ of 60 mm Hg on room air, although he did have a tremendous A-a gradient. His pCO₂ was somewhere in the 20s. He was working tremendously at breathing to maintain his pO₂, and he had a big gradient. Since he was relatively comfortable on Friday night, we elected to do a semi-elective bronchoscopy the following Monday. On Monday morning, after he had been treated for tuberculosis for about three days, we did a bronchoscopy with a lavage and biopsy.

**DR. KLiGER:** During those initial three days the patient did not remain clinically stable. He had high spiking fevers, and the partial pressure of oxygen in his arterial blood declined. Anti-tuberculous therapy was begun, and, in light of Dr. Root’s thoughts, he was also treated for pneumocystis carinii with intravenous Septra before the biopsy was performed. Dr. Root, in your opinion, was bronchoscopy required before initiation of specific therapy?

**DR. ROOT:** We felt strongly that one should have moved expeditiously to pursue either bronchoscopy or open lung biopsy on this patient. We felt if there was to be a delay, we certainly would start treatment for both tuberculosis and pneumocystis.

**DR. KLiGER:** Can we see the results of that lung biopsy?
DR. G.J. WALKER SMITH (Associate Professor of Pathology): The clinicians felt they had a rather specific clinical diagnosis and Dr. Warren, our senior resident, felt that she had found a specific pathogen in the tissue and asked for our confirmation. This is the low-power view of the transbronchial lung biopsy, which, for some of you, may be virtually unrecognizable as lung (Fig. 1). Indeed, it is a very cellular tissue, and we'll come back to that in just a moment. Certainly, alveolar architecture is very difficult to recognize. There is a little biopsy-induced hemorrhage which is common to such specimens. In the proper clinical setting I would characterize this lesion as an interstitial pneumonitis. There is epithelial proliferation and a great deal of interstitial collagen proliferation, which is of extreme interest considering the course that this patient ultimately follows. This delicate interface between acute alveolar injury and organizing interstitial pneumonia in which collagen is beginning to be laid down is something that we know very little about, either in human or experimental models. Looking ahead, this process of organization continued unrelentingly in this patient. Next, looking over a high-power field we see an alveolar exudate (Fig. 2). Those of you who remember the classic textbook pictures of pneumocystis carinii pneumonia know that this morphology is characteristic of that disorder. The definitive diagnosis, however, depends upon selective staining, either of intracystic sporozoites or of the intact capsule. We chose the latter course because of its utility and our experience with it. A silver methenomine stain shows multiple pneumocysts, with some actually filling many of the alveolar structures despite the 24-hour history of therapy (Fig. 3).

Apropos of the earlier question of whether the patient's sputum had been examined for pneumocystis, bronchioles in the open biopsy showed masses of pneumocystis organisms present in the small airways. Although this is not always the case with pneumocystis, one might guess that had we examined the sputum, we might have

FIG. 1. Radiograph with bilateral diffuse infiltrates.
seen the organisms in this particular case. The organisms in such a case are so numerous that they will be seen regardless of the approach one uses to the lung, whether by open lung biopsy, transthoracic aspirate, or a transbronchial approach. In other cases of pneumocystis infection, however, the picture may resemble a desquamative interstitial pneumonitis. In that form of pneumocystis carinii pneumonitis, the organisms are relatively scarce, and I am less optimistic about transbronchial or aspirate procedures yielding the diagnosis. As with most infectious processes in the lung, a negative study will not necessarily exclude the diagnosis. Overall, the open lung biopsy will probably continue to be the best approach for highest yield.

DR. ROOT: Did you see any inclusion bodies on the biopsy?

DR. SMITH: No other pathogens were suspected or recognized in the transbronchial biopsy.

DR. FRED SCHIFFMAN (Assistant Professor of Medicine): How many days of therapy are required to obscure or to eliminate these organisms in the lung tissue?

DR. MERRILL: There have been some clinical studies on that specific point. Pneumocysts have been seen in lung tissue five days after therapy is started. Exactly how long they continue to appear following the onset of therapy is unknown.
DR. MARGARET BIA (Assistant Professor of Medicine): Were any of the lung specimens sent for CMV culture?

DR. KLIGER: Cytomegalovirus pneumonia was considered in the differential diagnosis, and cultures were obtained. Let's hear the rest of the clinical course.

DR. BABITZ: On the sixth hospital day, two days after bronchoscopy and the initiation of IV Septra, the patient's pulmonary status worsened, with an FIO2 of 0.5, and a tidal volume of 850 ml. Endotracheal intubation and assisted ventilation were begun with a positive end expiratory pressure (PEEP) of 10 mm Hg. A blood gas determination showed a pH of 7.7, pCO2 of 43 mm Hg, and pO2 of 60 mm Hg. Mechanical ventilation continued until his death two months later, and his course was marked by multiple respiratory complications, a variety of infections, malnutrition, and chronic gastrointestinal bleeding.

Shortly after intubation it became apparent that the patient required high levels of PEEP to maintain adequate oxygenation. During the first two weeks of ventilation the PEEP requirements increased from 10 to 16 mm Hg. Attempts were made to optimize his respiratory status by diuresis, and blood transfusions were given to maintain the oxygen-carrying capacity. However, despite these measures, the PEEP requirement remained at 16 mm Hg. Eight days after intubation the patient developed subcutaneous emphysema extending bilaterally through the chest and neck. A chest X-ray taken at that time revealed pneumomediastinum, as well as bilateral apical pneumothoraces which did not appear to be under tension. That evening the patient became agitated, diaphoretic, and cyanotic, and was noted to have absent breath sounds on the right side as well as marked hypoxia. A chest X-ray revealed a tension pneumothorax of the right lung, which was relieved immediately by the placement of a chest tube. His hypoxia also improved. Another chest tube was placed in one of the left apical pneumothoraces. Two days later, peak airway pressures continued to reach 80 mm Hg, and the patient began to have episodes of agitation and tachycardia. A 50 percent right pneumothorax was seen, despite the presence of a functioning right-sided chest tube. A second right-sided chest tube was placed, and the patient was treated with Pavulon to decrease the peak airway pressures. He developed multiple new pneumothoraces despite success in lowering his PEEP to 8 mm Hg. About 13 days after intubation a tracheostomy was performed. The third and fourth weeks of ventilation required continual manipulations of his tidal volume, respiratory rate, FIO2, and PEEP in order to maintain adequate oxygenation and to keep his pCO2 within the physiologic range. It became apparent that simply increasing the respiratory rate to 24/minute did not decrease his pCO2, but did decrease his pO2. Therefore, it became necessary to tolerate pCO2's in the 50's and 60's. One month after intubation the patient developed a tracheo-esophageal fistula. Two months after intubation PEEP was discontinued entirely for about 24 hours, before oxygenation necessitated its reinstitution. Two months and ten days after intubation the patient expired, following a week of progressive hypoxia.

Several infections complicated the patient's clinical course. Bronchoscopy cultures were obtained four days after admission, and an atypical mycobacterium was cultured from the specimen. It was our opinion that the mycobacterium was not a pathogen, because it was not seen invading the tissue samples obtained on biopsy. The patient received a two-week course of intravenous Septra, followed by two weeks of treatment with pentamidine. On admission, the patient's CMV antibody titer was 1:64. Three weeks after admission the CMV antibody titer was 1:128. His sputum and urine both contained large numbers of CMV. The patient also had frequent episodes of fevers and elevations of his white blood cell count. With each
episode, all of his indwelling venous and arterial catheters were removed and cultured, as were his blood, sputum, and urine. Four days after intubation the patient experienced a rigor and an increasing white blood cell count, and tobramycin and mandol were administered in addition to the intravenous Septra. The fever quickly abated, and the antibiotic therapy was changed to cefoxitin when cultures of his sputum grew staphylococcus aureus. Two weeks after intubation, the patient again experienced an episode of fever and leukocytosis, and budding yeast were found in his urine and sputum. No hyphal forms were seen, but no apparent bacterial source for the fever was found. He was treated with Amphotericin B. One month after intubation, two blood cultures grew enterococcus, and the patient was treated for four weeks with ampicillin and gentamicin. Five and one-half weeks after intubation the patient became leukopenic. His white blood cell count was 1700/mm³ with 29 percent segmented cells, 54 percent bands, 4 percent lymphocytes, 3 percent monocytes, and 1 percent eosinophils. His platelet count was 150,000 mm³. Antibiotic-induced bone marrow suppression was suspected, and his white blood cell count rose when vancomycin was substituted for ampicillin. Finally, about two months after intubation he developed a herpes zoster rash on his left flank. When the zoster spread to his chest and arms he was treated with Ara-A.

Dr. John Dwyer (Associate Professor of Medicine): Elizabeth, was he treated with steroids at any point during this?

Dr. Babitz: He received no steroids other than low doses of Solu-Cortef with each dose of Amphotericin B.

Dr. Kliger: May we review the chest radiographs taken during the hospitalization?

Dr. Carter: A chest film taken three days after admission reveals homogenous opacities in the left upper lobe, in the left lower lobe, and in the right upper lobe. The previous interstitial pattern had progressed to an alveolar phase. About a week after this he had pneumomediastinum, and developed subcutaneous emphysema and small pneumothoraces. Another film taken a night later shows a large tension pneumothorax on the right, with the mediastinum pushed to the left, and the right lung compressed into a small mass. That was in early November. A chest film in early December shows a diffuse, coarse, reticular pattern with some alveolar filling which remained essentially unchanged over the next two months of hospitalization until the day of his death. I might add that the initial course is fairly typical for pneumocystis pneumonia, with the appearance of an interstitial pattern first, followed by rapid development of an alveolar phase.

Dr. Kliger: Turning to the pulmonary management, I note that 560 arterial blood gas determinations were made in the course of the less-than-100-day hospitalization. These studies alone required a liter and a half of blood.

Bill, the patient died with multiple pulmonary complications. There were two major issues in the pulmonary management. First is the problem of oxygen toxicity, because this patient required increasing concentrations of inspired oxygen. Second is the problem of baro-trauma, because this patient suffered from pneumothoraces, eventually requiring five chest tubes. What can we do in the future to prevent ourselves from backing into this buzz saw?

Dr. Merrill: I think some of the problems that this patient had were unavoidable, in that the initial biopsy showed fibrosis, and a variety of factors resulted in what I imagine would be an end-stage lung. It is really unclear what role pneumocystis played, what role viruses played, and what role oxygen toxicity played as problems. For the first four to five days that he was in the hospital his FIO₂ was never much higher than 0.6–0.7. But there was really never any dramatic improvement, and, in
fact, he continued to require relatively high levels of positive end expiratory pressure, and, finally, increasing levels of FIO₂ to maintain oxygen delivery. Terminally he had many problems with both baro-trauma and a tracheo-esophageal fistula which were recognized by the physicians caring for him. There are some experimental ventilatory techniques that might have prevented these things and made subsequent management, once complications developed, a little easier, such as high-frequency ventilation [1,2]. None of them were available in this hospital, and, therefore, I think that, practically, there was not much that we could have done to prevent it.

DR. KLAGER: Can we see the pathology now?

DR. SMITH: Perhaps someone might comment on the efficacy of steroids early on in this particular patient. He did have evidence of early organization in the biopsy. As Dr. Merrill has suggested, the lungs did progress to end-stage, and they were extraordinary at autopsy.

The autopsy was performed by Dr. Nolan Core, who described the lungs as weighing 2,060 and 1,330 grams, right and left, respectively. The lung, radiographically, was a "white out"; pathologically it is a "white out" as well, with fibrous tissue seen everywhere (Fig. 4). In the upper lobe are abscesses which relate best to the tracheo-esophageal fistula. I can summarize the microscopy of this lung with very few words, because fibrous tissue is proliferating throughout and filling alveoli and bronchioles. In some fields epithelial proliferation and metaplasia were predominate. While Dr. Merrill has suggested that this fibrosis could be attributed to a number of factors, with which I would agree, the feature of bronchiolitis in this case suggests that perhaps oxygen toxicity did play a major role. Two pathogens were found that may have helped produce the fibrosis. Inclusions diagnostic for cytomegalovirus were seen in virtually all microscopic fields of the lung. There was residual pneumocystis infection, although in sections stained with silver methenomine, the organisms were less numerous than in the biopsy.

Last, but not least, this patient developed an esophageo-tracheal fistula in the final weeks of his life. The fistula, as seen from the esophageal side, measured 4 x 2 cm in greatest dimension. While widespread necrotizing pneumonia and gross abscesses resulted from the fistula, it was present long enough to contribute to the diffuse lung fibrosis.

In summary, we see an end-stage lung due to multiple factors. Possibly, the

FIG. 4. Silver stain with large numbers of pneumocystis organisms in two alveoli. 250 x.
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FIG. 5. Fibrotic lung from autopsy.

pneumocystis, as suggested by the original biopsy, and, certainly, cytomegalovirus infection contributed to an organizing interstitial pneumonitis. Therapy may have significantly accentuated the process. Oxygen toxicity and respiratory care which led to the complication of a tracheo-esophageal fistula were additional insults leading to lung fibrosis.

DR. ROOT: Did the patient have endocarditis?
DR. SMITH: No, there was no evidence of endocarditis.
DR. KLIGER: This patient had pneumocystic pneumonia, CMV infection, and several bacterial infections as well. Dick, what was the light that went on in your head, and why did you come to this diagnosis so quickly?

DR. ROOT: The cases that were presented to me at UCLA were later published along with a series from other institutions [3-6]. In these papers a syndrome was described which occurs in either homosexual males or in addicts, particularly those who use amyl nitrate as one of their “recreational” drugs. The number and type of infections in these cases have been striking. The common denominator has been CMV, but pneumocystis has been very common in these patients. Some of them had atypical mycobacterial infections, often recognized as a postmortem finding. Infection by candida species has been prominent as the cause of either mucous membrane lesions or disseminated disease in these patients. Bacterial infections have also been prominent. As in this patient, it is difficult to know whether these are simply a manifestation of the “nosocomial state,” in which the body is invaded by a series of tubes and catheters, or whether they represent a specific example of an immunologically induced defect in host resistance. The admitting leukocyte count in this patient was 8,000/mm³. The differential included 18 percent lymphocytes, giving him about 1,400 lymphocytes/mm³. That is just on the borderline low side of normal. The common feature seen in all of these patients is a severe immunologic defect, presumably induced by the cytomegalovirus infection. The other infectious complications, namely that of intracellular-type organisms, occur as a consequence of
the immunosuppressive effects of this infection. Because of the inability of these patients to eradicate the cytomegalovirus, immunosuppression persists, and the number and type of infections multiply. Ultimately, in the 160 cases reported to the CDC, there has been a mortality rate of 60-70 percent.

The first key to the early management of these patients is to recognize that the appropriate conditions exist for these infectious complications to occur. Second, one must rapidly attempt to establish the cause of diffuse pulmonary infiltrates. With respect to the profound nature of the immunosuppression, I would emphasize that 60 days after stopping appropriate treatment for pneumocystis in this patient, there was still evidence of at least the cyst forms of the organisms persisting in his lungs. Findings of this type, and relapses with active infections, lead to the recommendation that following a therapeutic course of trimethaprim and sulfamethoxasole, or of pentamidine, one should continue with prophylactic treatment against these organisms in such patients. Retrospectively, it would have been appropriate to have actually initiated therapy for pneumocystis pneumonia the night that we first saw him, rather than waiting for a 48-hour period. Such treatment would not have altered the possibility of establishing the diagnosis within that time. Whether this would have made a major difference in his outcome, given the fact that he already had evidence of chronic lung injury at the time he had a lung biopsy, is conjectural, I think, at best.

Finally, I think there are two critical questions that could be answered by members of the audience. Frank Bia, is there anything specifically available at the present time to eradicate CMV or to reduce its clinical manifestations?

DR. FRANK BIA (Assistant Professor of Medicine and Lab Medicine): There are antiviral agents, such as Ara A (adenine arabinoside), which are available. Some of the house officers have treated other herpes infections with it. Of all the herpes viruses, CMV seems to respond the least to Ara A, and, therefore, it is not indicated for treatment of CMV infections. A new agent, Acyclovir (acycloguanosine), has excellent activity against herpes viruses. However, groups which have evaluated that drug against CMV do not see that it has efficacy.

This association of CMV interstitial pneumonia and pneumocystis infection is not new. It is new, it seems, in this particular population. Bone-marrow transplantation patients have been developing interstitial pneumonia over the past five years. CMV was the causative agent in many of these patients, and often it was associated with pneumocystis.

We have not come up with any other treatments yet, but there are two possibilities. One, is the use of interferon. Interferon, of course, is not a viral-specific drug. It works on the host, producing effects on many different viruses. There is some evidence that interferon will be of use in patients who have CMV infections. There is currently a patient from the Philippines in the hospital now who has CMV retinitis. He lost one eye, and is on an interferon therapy protocol. The other possibility, which I believe you mentioned was tried in this patient, is the use of transfer factor. I have no experience with it.

Given this particular situation, I'd say that none of the available antiviral agents would have a beneficial effect on CMV, except perhaps interferon.

DR. ROOT: So, currently available therapy directed specifically against the organism that we believe to be responsible for the immunologic deficiency syndrome is either untried or not efficacious. This leaves us to consider the other factors that might require management in such patients. What is the nature of the immunosuppression produced in these patients, and how can one approach this therapeutically? Could
we, perhaps, have helped to produce a different outcome? For that John Dwyer will have the final word.

DR. DWYER: We studied the lymphocytes from this patient's blood in November, by which time his cell-mediated immunity was severely suppressed. We measured the response of his lymphocytes to phytohemagglutinin (PHA) and his ability to respond to both candida, as an antigen, and allogeneic cells. There was virtually no response to either of these antigenic stimuli. As we were not aware at the time of the clinical details of the case, we did not look at his suppressor cell function, which we would normally do in such a case. Similarly, it would have been appropriate to have studied his immune capacity, if any, to antigens associated with the various herpes viruses, as well as to tuberculin. I can only guess, therefore, at the likely sequence of events in this patient.

The active homosexual life of this patient obviously holds some clue to the etiology of his immunosuppression, but it is difficult to be certain of the mechanism involved. The literature appearing on this subject would suggest that there is some relationship between the number of sexual partners taken and the degree of immunosuppression that is induced. It is intriguing to try to speculate on the immunological mechanisms that may be responsible. Clearly both sperm and seminal fluid are antigenic, and it is possible that a form of immunosuppression known as antigenic competition is set up when numerous different sperm or seminal fluid antigens enter the lower part of the intestinal tract. Antigenic competition is a well-known phenomenon in which exposure to one antigen, either simultaneously with, or prior to exposure to another antigen, may lead to an inadequate, and, in fact, almost absent humoral and/or cell-mediated immune response to the second antigen. A number of animal models have been studied which show that it is particularly easy to produce tolerance to certain antigens that are first encountered through the intestinal tract. Both specific and non-specific immunosuppression can be achieved in this manner. The tolerance that develops may well have to do with processing of antigens absorbed in the intestinal tract by the Kupffer cells in the liver, which may present antigens to lymphocytes in a tolerogenic fashion. Alternatively, or perhaps compounding the problem, cytomegalovirus entering the intestinal tract may play a major role in extending the degree of immunosuppression already present. CMV can be isolated from many biological fluids in an infected patient, and it is certainly conceivable that it may enter the lower intestinal tract in seminal fluid. This virus, like EB virus, is able to produce gross disturbances of immune function in humans, and it appears to exert its major influence by causing a polyclonal B-cell expansion that triggers off immunosuppressive mechanisms that exert a non-specific effect on inflammation-producing T cells. Consequently, already weakened defenses to the microorganisms normally handled by effector T cells will become even less efficient. Certainly the infectious disease problems illustrated in this case read like a textbook list of problems likely to occur in somebody who is grossly T-cell deficient. As we have seen many patients with this syndrome, the above hypotheses should be testable in the near future.

We have just seen, in fact, a very similar case to the one under discussion, in which, before the results of open lung biopsy were known, his leading differential diagnosis was that of hypersensitivity pneumonitis. Because of the severe nature of his pulmonary infiltrate, he was started on steroids after the lung biopsy and improved in a dramatic fashion. Pulmonary function studies, his chest X-ray, and his well-being all responded promptly. When the biopsy was read, it was discovered that he had a pneumocystis carinii infection, and it seems very likely that some of the in-
tense inflammatory response that may have been so damaging to the lungs of the patient under discussion, were blocked in this earlier patient by the administration of steroids. I feel that we should seriously consider using steroids together with anti-pneumocystis therapy at an early stage in a number of cases. The beneficial effects of steroids may in fact be more than simply anti-inflammatory, as certain suppressor-cell mechanisms are selectively sensitive to steroids and so, inappropriate activity in this area may be dampered down by the administration of these agents. In the future, it may not seem surprising to be using low doses of drugs, such as cyclophosphamide, which selectively interferes with suppressor cells, to treat immunodeficient states.

DR. KLIGER: Would treatment with transfer factor have been helpful here?

DR. DWYER: We would have advised treatment with transfer factor for this patient. We have been administering transfer factor for the management of a number of infectious disease problems for the last ten years and have had some very encouraging experiences. In general, however, transfer factor has not been regarded too favorably in the literature until the recent past. Now it is experiencing a rebirth of respectability because of the clear-cut demonstration that antigen-specific transfer factor is indeed able to transfer immunity to a number of microorganisms and that this appears to apply to the herpes virus group, as well as a number of fungal and mycobacterial antigens. A control study has been reported in which the administration of transfer factor, obtained from donors immune to varicella, to children with acute lymphocytic leukemia prior to chemotherapy almost totally blocked the normally high incidence of opportunistic varicella infection that develops in these children. There is evidence that one can modify the course of an established infection with herpes virus by the administration of transfer factor. As this material induces reactivity amongst the recipient lymphocytes and is not directly immunologically active, it is obviously necessary to give the drug before there has been a gross reduction in the number of circulating lymphocytes.

DR. KLIGER: The published cases of male homosexuals, drug abusers, or patients with Kaposi's sarcoma who have complicating CMV or pneumocystis infections describe the presence of skin anergy and profoundly low levels of circulating lymphocytes. In particular, T lymphocytes are depleted, and their function is impaired. While our patient's count was decreased, it was not in the profoundly low range of the reported cases. In addition, the initial PPD was negative, but the control skin test was positive. The patient apparently did not have skin anergy. Do you have any thoughts to explain how a patient who seemed to have intact cell-mediated immunity could go on to this devastating disease?

DR. DWYER: I did not see the delayed hypersensitivity skin testing at the time it was done, nor am I sure of the antigen that was used in association with the tuberculin. If it was candida albicans, a positive result would certainly be puzzling, given this patient's total lack of ability to respond to this antigen in tissue culture. On the other hand, if he remained sensitive to other ubiquitous antigens, but was unresponsive to antigen that he had only recently experienced (for example, tuberculin), this would not be all that unusual. We know that if one has been previously sensitized to an antigen and is developing severe immunosuppression to the point of becoming anergic, he will lose the capacity to respond at the T-cell level to an antigen which he has not yet experienced before he loses the ability to respond to an antigen to which he has been previously sensitized. The fact that this patient's lymphocyte count was respectable at the time of his initial presentation and that it rapidly fell, indicates the need for some urgency in the work-up and immunological manipulation of patients with
this form of problem. There are always some dangers in extrapolating from lymphocyte count in the peripheral blood, as it is possible that gross alterations in the migratory patterns of T lymphocytes may result in a gross deficiency of T cells in the peripheral blood, while normal numbers may be present in the lymph nodes and spleen, etc. Probably, therefore, it is reasonable in most of these patients, even if they are severely lymphopenic, to try therapy with an agent such as transfer factor. Unfortunately, in this particular case, I cannot be any more specific as to the reasons for the apparent anomalies you mention.

PHYSICIAN: I have a question prompted by Dr. Root's mention of amyl nitrate. What is known about "recreational" drugs that are widely used in the homosexual populations, such as amyl, butyl, and propyl nitrates, in terms of their effects on the immune system?

DR. ROOT: The immunosuppressive effect of amyl nitrate has been proposed as a possible factor in these infections in recent months [7,8].

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