THE INFECTIONS IN AIDS

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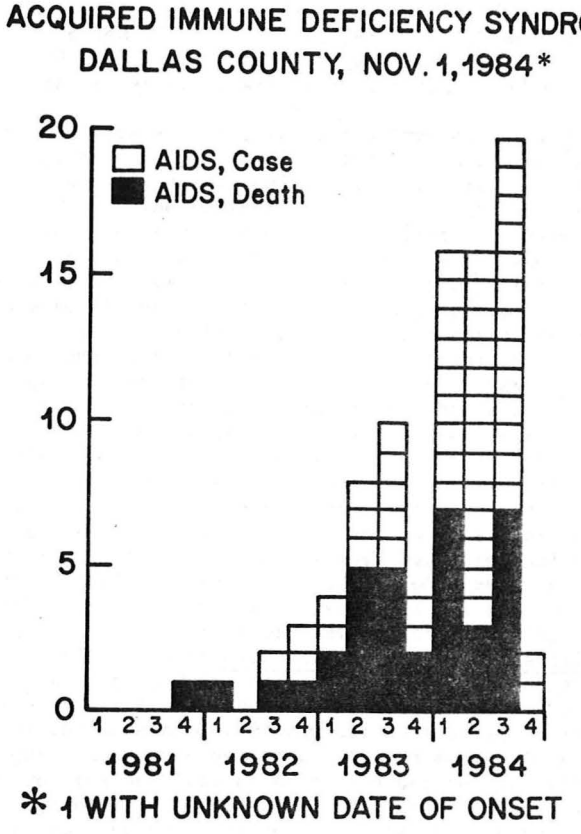
Since the beginning of the epidemic and through October 8, 1984, there have been 6330 cases of AIDS including 2966 deaths in the United States. The AIDS epidemic in Dallas began in 1981. Through November 1, 1984, there have been 88 cases including 35 deaths in Dallas County (Figure 1, data compiled by Dr. Charles Haley, Dallas County Epidemiologist).

Figure 1



It is the purpose of this discussion to concentrate attention on the infections in AIDS, emphasizing their clinical diagnosis and management. To accomplish this, four cases illustrating the most common infections seen in this disorder will be presented. The most common infections exclusive of the putative etiological agent, HTLV-III, are disseminated cytomegalovirus (CMV) infection, esophageal candidiasis, Pneumocystis carinii pneumonia (PCP), Mycobacterium avium-intracellulare (MAI) infection, Cryptococcus neoformans infection, extending mucocutaneous lesions due to herpes simplex virus, diarrhea due to cryptosporidium, Toxoplasma gondii infection and herpes zoster.

Patient A is a 46 year-old man who entered PMH with a 3 week history of fever, chills, headache and a 20 lb weight loss. He was seen by his personal physician while he was ill who noted oral thrush. The patient denied significant past illnesses, homosexuality, intravenous drug abuse or a history of prior blood transfusion. Physical examination upon entry into the hospital revealed a temperature of 39.3°, a blood pressure of 150/90 and a pulse rate of 100. Nuchal rigidity was noted but there were no other neurological signs. Admission laboratory revealed a white blood count of 3100 with 83% polymorphonuclear leukocytes, 10% lymphocytes, 6% monocytes and 1% eosinophiles. The hematocrit was 31 and the erythrocyte sedimentation was 133. The VDRL was positive at 1:1 dilution; the MHA-TP was positive. A lumbar puncture revealed 15 white cells, 74% of which were lymphocytes and 15% monocytes. The CSF glucose was 45 mg per deciliter. The CSF cryptococcal antigen titer was positive at a dilution of 1:256.

The patient was treated for cryptococcal meningitis with the combination of 5-fluorocytosine and amphotericin-B. The 5-fluorocytosine dose was 150 mg/kg divided into 4 daily dosages at six hour intervals. The amphotericin-B dose was 0.3 mg/kg/day. The patient was treated with benzathine penicillin x 3 weekly injections for syphilis of indeterminate duration. The patient became afebrile after about 2 weeks in the hospital. Two weeks later, however, he developed a fever to 39°. The 5-fluorocytosine had been discontinued because of the development of granulocytopenia and a total leukocyte count of 1300. Treatment of the cryptococcal meningitis then consisted of 30 mg amphotericin-B per day. The development of a new febrile state was ascribed at first to the amphotericin-B. The fever persisted and was associated with an increasing cardiac size. An echocardiogram revealed a large pericardial effusion. A pericardiocentesis was performed which revealed 110 white blood cells and 100 red blood cells. The white blood cell differential consisted of 87 inactive mesothelial cells with the remainder being mononuclear cells. There were no polymorphonuclear leukocytes. The protein was 6.1 gms per deciliter. An S3 and S4 were heard along with the murmur of mitral insufficiency. Chest x-rays suggested pulmonary vascular congestion. The patient had been salt loaded to attempt to diminish toxicity from the amphotericin. A buffy coat culture was positive for cytomegalovirus. A bone marrow biopsy was positive showing many organisms morphologically consistent with Mycobacterium avium-intracellulare. The patient was started on high-dose isoniazid, ethambutol, ansamycin, sulfisoxazole and amikacin. The dose of INH later had to be changed to 400 mg/day because of the development of confusion, disorientation and ataxia, symptoms and signs that were consistent with INH encephalopathy. The patient was discharged from the hospital after he had become afebrile on INH, ethambutol, ansamycin and sulfisoxazole. A repeat lumbar puncture taken before discharge from the hospital revealed one white blood cell with a cryptococcal antigen titer of 1:4. In the 6 months after discharge, the patient has resumed his former occupational duties. He continues to have recurrent oral thrush which has been managed on intermittent oral ketoconazole. Recurrent herpes simplex virus perianal lesions have been managed with topical acyclovir. A drug eruption necessitated withdrawal of the sulfisoxazole.

This patient has been categorized as belonging to no recognizable AIDS risk group. His initial disease was cryptococcal meningitis which was controlled with 10 weeks of amphotericin-B therapy. His most recent LP done

as an outpatient revealed a CSF cryptococcal antigen titer of 1:2. He has had persistent oral thrush and perianal herpetic lesions. His MAI infection has been controlled on INH, ethambutol and ansamycin. He represents an AIDS patient with a central nervous system infection. He also had the development of a fever of undetermined origin occurring in the course of AIDS. In this instance, the fever of undetermined origin was due to disseminated MAI infection.

This first patient represents a case of cryptococcal meningitis in a patient with AIDS. The meningitis was characterized by a paucity of cells in the cerebrospinal fluid although the cryptococcal antigen titer was 1:256. The diagnosis of AIDS in this patient initially was not felt to be secure because cryptococcal meningitis can occur in normal persons. The subsequent clinical course established the diagnosis of AIDS. A helpful indication that he did in fact have AIDS on admission to the hospital is attested to by the fact that he had an absolute lymphopenia. Additional tests that would have been of interest in establishing diagnosis of AIDS would have been the ascertainment of the absolute number of T4 cells and a serum protein electrophoresis to determine whether or not a polyclonal gammopathy was present. He was placed on a conventional regimen for the treatment of cryptococcal meningitis, namely 5-fluorocytosine and amphotericin B. The dose of 5-fluorocytosine was 150 mg/kg/day given as a q 6 h dosage. The dose of amphotericin B was 0.3 mg/kg/day. The 5-fluorocytosine had to be stopped because of the development of severe leukopenia. When the total white blood cell count reached 1300, the medication was stopped. It is known that 5-fluorocytosine can induce neutropenia and thrombocytopenia. In AIDS patients pancytopenia in the presence of a hypercellular marrow has been noted. Myelodyspoiesis has been suggested as one mechanism underlying these marrow changes. Subsequent to the development of the leukopenia and the discontinuation of the 5-fluorocytosine the dose of amphotericin B was raised to 30 mg/day. Automatically this would entail a 10 week course of therapy instead of the 6 week course that can be accomplished with the combination of 5-fluorocytosine and amphotericin B.

At approximately the 28th day of hospitalization, he developed a fever of undetermined origin. Initially this fever was suspected to be due to the administration of amphotericin B. Patients with AIDS have an increased incidence of febrile side reactions to the drugs which they are receiving. The suspicion that this fever was related to amphotericin B delayed the necessary work-up for the fever. If a drug reaction actually had been the cause of the fever, discontinuance of the drug should have resulted in a prompt cessation of the fever. After the beginning of fever, the patient developed an enlarged cardiac silhouette and had clinical signs of congestive heart failure as well as echocardiographic demonstration of a large pericardial effusion. To diminish the potential toxicity of the amphotericin the patient had been intentionally loaded with infusions of NaCl. This probably precipitated the episode of volume overload. A pericardiocentesis was performed which revealed a exudative fluid having a protein concentration of 6.6 gm/dl. Subsequent to the determination of the characteristics of the pericardial fluid, a bone marrow biopsy was performed which revealed poorly formed granulomas and multiple acid-fast organisms consistent with Mycobacterium avium-intracellulare.

The episode of fever of undetermined origin in this patient represents one of the 5 common infectious disease syndromes seen in patients with AIDS. These 5 syndromes are: 1) The pulmonary infiltrate syndrome, 2) The central nervous system syndrome, 3) Fever of undetermined origin, 4) The gastrointestinal syndrome, and 5) The dermatologic disease syndrome. Although fever can complicate the course of the lymphadenopathy syndrome, when it occurs in a patient with diagnosed AIDS it usually connotes an opportunistic infection, a drug fever, or the presence of a malignancy such as non-Hodgkins lymphoma. The opportunistic infections which have been most commonly associated with fever of undetermined origin have been disseminated Mycobacterium avium-intracellulare infection, disseminated cytomegalovirus infection or other granulomatous diseases like typical tuberculosis, histoplasmosis or coccidioidomycosis.

The therapy of MAI infections is being worked out at the present time. In vitro these organisms are quite resistant to usually antituberculosis drugs. Some drugs and dosages to which these organisms have been susceptible in vitro are high dose isoniazid, the combination of isoniazid plus ethambutol, ansamycin, clofazamine, sulfa drugs such as sulfisoxazole, and amikacin. (Table 1)

Table 1

Minimal Inhibitory Concentrations of Selected Drugs in *Mycobacterium avium-intracellulare* Isolates*

Drug	Patient				
	1	2	3	4	5
	$\mu g/mL$				
amikacin	> 10.0	> 10.0	> 10.0	> 10.0	> 10.0
cefoperazone	> 10.0	> 10.0	> 10.0	> 10.0	> 10.0
clofazimine	2.0	2.0	2.0	2.0	5.0
ansamycin (LM-427)	2.0	< 1.0	< 1.0	1.0	2.0
thiacetazone	> 10.0	> 10.0	> 10.0	> 10.0	> 10.0

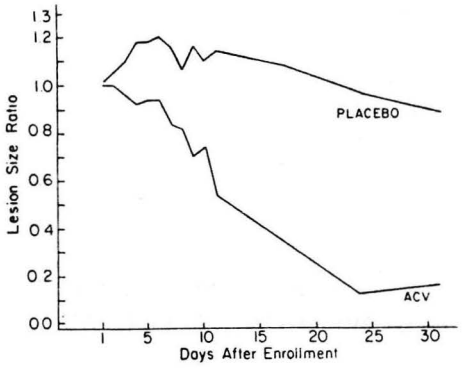
* Minimal inhibitory concentrations were determined by the agar dilution method on Middlebrook THIO agar (Gibco, Madison, Wisconsin)

JB Greene, et al. Ann Intern Med 1982; 97:539-546. American College of Physicians.

Certain third generation cephalosporins and new classes of antibiotic compounds, the carbapenems and the quinolones, also show promise in in vitro studies. The patient was started on high dose isoniazid, ethambutol, ansamycin, sulfisoxazole and amikacin. The amikacin had to be discontinued because the patient could not tolerate the intramuscular injection. The sulfisoxazole was discontinued because of the development of fever and rash. The initial dose of INH was 900 mg. However, that dose was too high and an encephalopathic state ensued. This state consisted of confusion with a disturbed sensorium and ataxia. The dose of INH had to be lowered and eventually the patient was maintained on 400 mg of INH, V_{B_6}, ethambutol and ansamycin at 150 mg/day. After beginning these drugs the patient became afebrile within about a 3 weeks period. The pericardial effusion disappeared and the 10 weeks course of amphotericin B was completed. At the end of 10 weeks of amphotericin the cryptococcal antigen titer in the cerebrospinal fluid was 1:4. A subsequent lumbar puncture approximately 2 months after this last one revealed a cryptococcal antigen titer of 1:2.

The patient has been maintained at a relatively symptom free state during his 6 months away from the hospital. He has been troubled with recurrent episodes of oral thrush which have been controlled on 200 mg ketoconazole bid and topical acyclovir for recurrent severe extending perianal herpes simplex virus infection. He has not required further amphotericin B although many physicians who have worked closely with these patients maintain that it is necessary to give them twice weekly or weekly injections of amphotericin B in order to maintain them free of significant cryptococcal disease. The MAI infection has been controlled on INH, ethambutol and ansamycin. All 3 forms of acyclovir, intravenous, oral and topical, have been shown to ameliorate the course of extending mucocutaneous herpetic infections in the immunosuppressed patient. Since oral acyclovir is presently not available except on a compassionate basis, the herpetic infection has been controlled successfully with the use of topical acyclovir (Figure 2). The patient has gained weight and has gone back to his former occupation.

Figure 2



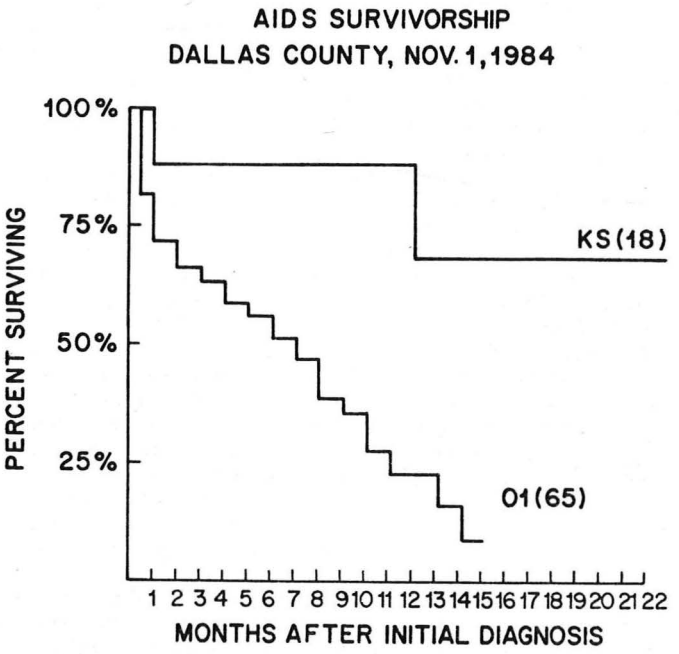
Influence of topical acyclovir therapy on lesion size ratio in immunocompromised patients with mucocutaneous HSV infections.

©RJ Whitley, et al. J Infect Dis 1984;150:323-329. University of Chicago.

The survival rate of AIDS patients with opportunistic infections clearly is signicantly less than in patients with Kaposi's sarcoma. In Dallas, 50% of the patients with opportunistic infections are dead at the end of 6 months. However, a percentage of the patients have been maintained in a relatively symptom free state and able to resume the normal functions of everyday living although their course is oftentimes complicated by the supraimposition of other infections. The natural history of patients with

AIDS in Dallas is virtually identical with the one recorded in patients seen in New York City (Figure 3, data compiled by Dr. Charles Haley, Dallas County Epidemiologist).

Figure 3



Patient B was a 29 year-old man, an admitted homosexual. Two weeks prior to admission to PMH he was seen in the Emergency Room where a diagnosis of mycoplasma pneumonia was made and he was treated with erythromycin. One week prior to admission, the patient had a normal mental status exam. Three days prior to admission, he had a decrease in mental acuity along with malaise, nausea and vomiting, ataxia and inability to communicate. On the day of admission he became lethargic, could not speak and was brought to the Emergency Room again. He was febrile, his blood pressure was 138/94, and the pulse rate was 120. His throat examination revealed oral candidiasis and there was pronounced nuchal rigidity. He was lethargic but responded to pain, to calling his name and to commands. However, he could not speak and had a left gaze preference. He was diffusely hyper-reflexic. Lumbar puncture revealed 47 white blood cells and 25 red blood cells with 75% lymphocytes, 23% monocytes, 1% basophiles and 1% eosinophiles. The glucose was 48. A CT Scan revealed a right hypodense area in the frontal parietal region which enhanced with contrast. There was a shift of midline structures to the left. The patient was admitted to the hospital and started on multiple antibiotics. A serum toxoplasmosis indirect fluorescent antibody determination was 1:2048. The titer on the CSF was 1:8. The Sabin-Feldman dye test titer was 1:1024 on serum; a toxoplasma agglutination test was 1:40,960. An IgM toxoplasma test on serum done by the ELISA method was negative. The CSF dye test titer was 1:2 and the CSF toxoplasmosis agglutination titer was 1:40. A brain biopsy was performed by the Neurosurgical Service. They noted morphological evidence of a pyogenic meningitis and cerebritis. No toxoplasma organisms were noted on stains of the brain specimen submitted to pathology. However, Toxoplasma gondii was grown in tissue culture after approximately 1 month of incubation. The patient was treated for central nervous toxoplasmosis with 1.5 gms sulfadiazine q 6 h, pyrimethamine 25 mg po q 12 h, and folinic acid, 10 mg daily. Clindamycin was also added at 600 mg q 6 h. The patient's mental status never improved. He was mute and quadriparetic. He had recurrent episodes of aspiration pneumonia and finally died of pulmonary complications after two months of hospitalization. Postmortem examination revealed continuing evidence of cerebritis and the presence of cyst forms of Toxoplasma gondii.

This patient represents an example of a central nervous system infection in a patient with AIDS. He had biopsy and cultural evidence of central nervous system infection due to Toxoplasma gondii. Despite two months of intensive antimicrobial therapy, toxoplasma cysts could still be seen in brain at autopsy.

The second patient represents an example of the central nervous system syndrome. The etiology of this syndrome consists of infections due to cryptococci, toxoplasmosis, typical tuberculosis, disseminated MAI, progressive multifocal leukoencephalopathy, candidal meningitis and a new disease state called subacute encephalitis. Malignant states including CNS lymphoma are also included. The clinical configuration of subacute encephalitis consists of a subacute course characterized by progressive dementia and alteration of motor functions. Patients lose interest in their work and play activities and gradually are reduced to a vegetative state. Cells can be seen in the cerebrospinal fluid at an increased number, although at times no alteration in cell number is noted. The etiology of subacute encephalitis is presently undergoing investigation. At postmortem about half

the cases are associated with typical intranuclear inclusion of cytomegalovirus infection. The remainder of the cases do not have a defined etiology. The therapy of progressive multifocal leukoencephalopathy in AIDS patients presently is non-existent although in one renal transplant recipient at Parkland Memorial Hospital, survival has exceeded 2 years due to intermittent treatment with cytosine arabinoside at approximately 6 week intervals. The therapy of candidal meningitis is with amphotericin B with or without 5-fluorocytosine. Mycobacterial infections with MAI have been managed with the drugs that have been mentioned. Typical tuberculosis can usually be managed with INH, rifampin and ethambutol.

This patient was first seen in the Emergency Room at Parkland with a pulmonary infiltrate that was diffuse and involved all sections of the lung. The diagnosis of atypical pneumonia was entertained and erythromycin was instituted. Knowledge of the patient's sexual activities and awareness of the necessity to determine the presence or absence of absolute lymphopenia might have resulted in earlier hospitalization for work-up. His mental acuity lessened 3 days prior to admission into the hospital. At the time of admission to the hospital his mental status clearly had deteriorated. He had cells in the spinal fluid. CT scan revealed evidence of cerebritis and a focal enhancing lesion. Toxoplasma IFA studies were sent. The critical point in the management of these patients with focal disease requires that a brain biopsy be performed as soon as possible. At brain biopsy, necrotic brain material and purulence were noted; toxoplasma organisms could not be seen at pathological exam although they were grown in tissue culture after about 1 month of incubation. The level of this patient's toxoplasma antibodies suggest that active disease due to this organism was operative but biopsy was essential to obtain definitive proof and to establish that another disease process was not operative. The ratio of CSF to serum antibodies can help to establish the diagnosis of CNS toxoplasmosis

$$\frac{\text{IgG CSF}}{\text{IgG serum}} \cdot \frac{\text{Toxoplasma IFA serum}}{\text{Toxoplasma IFA CSF}} \geq 8$$

but definitive proof of that diagnosis is best established by means of biopsy. Once the biopsy had been obtained, the multiple antibiotics upon which the patient had been started could be discontinued and primary emphasis given to antitoxoplasma therapy.

The therapy of CNS toxoplasmosis consisted of loading the patient with an oral dose of pyrimethamine (100 mg) and then continuing the patient on 25 mg bid of the drug. The patient was also started on sulfadiazine at 1.5 gm q 6 h. Folinic acid was also begun to prevent the development of leukopenia. Clindamycin can also be instituted. The dose is not well established but should approximate 2400-3200 mg/day. Another antibiotic of potential use in this situation is spiramycin. This drug, however, can only be obtained from a Canadian pharmaceutical firm and requires FDA approval before it can be used. Despite the institution of antitoxoplasma therapy upon admission into the hospital the patient did poorly. He was able to regain some consciousness and became able to respond to commands by movement of his right hand but he remained quadriparetic and developed multiple recurrent episodes of aspiration pneumonia. An evaluation of therapy approximately 3 weeks into the hospital course revealed an improvement of the CT Scan and a diminution of the number of cells in the cerebrospinal fluid but the patient died 2 months after admission into the hospital. At postmortem examination evidence of active inflammatory disease and toxoplasma

cysts were found on examination of the brain. Most authorities who have treated AIDS patients with toxoplasmosis of the central nervous system have recommended continuance of the antitoxoplasma therapy indefinitely.

Patient C was a 42 year-old man who had moved to Dallas from New York after 13 years of residence in that city. He was an admitted homosexual. He had had no sexual relations for a year and a half prior to his present admission into the hospital. Complaints on admission to the hospital were 3 weeks of fatigue, fever, cough and myalgias. He then developed dyspnea, night sweats, cough, substernal pain and weight loss. He had had three friends who had died of AIDS in the last year. Physical examination on admission revealed a temperature of 39.2°, a blood pressure of 110/70, a pulse rate of 140 and a respiratory rate of 40. Bibasilar rales were noted on the pulmonary examination. His white blood count was 11,500 with 81% polymorphonuclear leukocytes, 1 band, 3% lymphocytes, 4% monocytes and 1% atypical lymphocytes. The SGOT was 204 and the alkaline phosphatase was 131. Arterial blood gases revealed a pH of 7.46, a pCO_2 of 34, and a pO_2 of 54 on room air. Fiberoptic broncoscopy revealed many cysts consistent with a diagnosis of Pneumocystis carinii pneumonia. The patient was started on sulfa-trimethoprim, 4 ampules q 6 h. After one week of therapy with sulfa-trimethoprim with no improvement, he was switched to pentamidine isethionate. There was no improvement on that regimen. Subsequently he was placed on both sulfa-trimethoprim and pentamidine. Two bronchoscopies done during the course of hospitalization revealed continuing evidence of pneumocystis. The patient had to be intubated because of respiratory distress. Approximately 40 days after admission into the hospital, while receiving sulfa-trimethoprim and pentamidine in the MICU, he was noted to be agitated and less responsive. Progression to lethargy and coma ensued. A blood glucose was performed which was 23 mg/dl. The mental status deterioration had lasted approximately 5 hours before 50% dextrose was administered to the patient. Electrolyte determinations performed at the time of the hypoglycemic episode revealed a serum sodium of 122 and a potassium of 5.4. Because of the hyponatremia and hyperkalemia, a diagnosis of adrenal insufficiency was entertained but no plasma cortisol levels were performed. He subsequently died on the 47th hospital day without regaining consciousness. Postmortem exam revealed continuing focal residual pneumocysts in lung but the predominant pathogen seen on lung sections was cytomegalovirus. Cytomegalovirus infection associated with focal necrosis was present in the adrenal medulla and cortex.

The patient presented with a pulmonary infection, the most common infectious disease syndrome seen in AIDS patients. The pneumocystis pneumonia was not able to be controlled with sulfa-trimethoprim therapy and he had to be switched to pentamidine. While on pentamidine he had an episode of hypoglycemia. Hypoglycemia is a known complication of pentamidine therapy. No tests were done to assess the adequacy of the adrenal corticosteroid output but it is possible that some amount of adrenal insufficiency might have been present and contributed to the hypoglycemic episode.

The third patient represents an example of the pulmonary syndrome. This is the most common syndrome with which AIDS patients present when they have an opportunistic infection. Usually but not always the etiologic agent is Pneumocystis carinii. However, the differential diagnosis is broad and includes such entities as cytomegalovirus pneumonia, Kaposi's sarcoma of the lung, Legionella pneumonia and diffuse infections due to the cryptococcus and nocardia (Table 2). An increased incidence of pneumococcal infections has also been noted in patients with AIDS. Since the differential diagnosis is

Table 2

Types and Frequency of Pulmonary Disorders in 441 Patients with AIDS.

Pulmonary Disorder	No. of Patients
Pneumocystis carinii pneumonia	373
Without coexisting infection	255
With coexisting infection	118
Cytomegalovirus	50
Mycobacterium avium-intracellulare	37
Mycobacterium tuberculosis	15
Legionella	9
Cryptococcus	8
Other	3
Other pulmonary infections	93
M. avium-intracellulare	37
Cytomegalovirus	18
Cytomegalovirus/*M. avium-intracellulare*	5
Cytomegalovirus/cryptococcus	1
Pyogenic bacteria	11
Legionella	10
Fungi	6
M. tuberculosis	4
Herpes simplex	2
Toxoplasmosis	1
Kaposi's sarcoma	36

broad and there is effective therapy for most of the disease entities mentioned, it is the general concensus that the etiologic diagnosis be established by means of lung biopsy. Since the patient with AIDS and pneumocystis infection usually has large numbers of pneumocysts present, the diagnosis can easily be established by fiberoptic bronchscopy and transbronchial biopsy, lavage or brush biopsy (Table 3).

Table 3

Yield from Various Studies Carried Out during Fiberoptic Bronchoscopy in 368 Patients with *Pneumocystis carinii* Pneumonia.*

Study	Total Performed	Total Positive	Yield (%)
Fixed tissue †	305	284	93
Touch imprint †	166	157	95
Lavage/wash	178	141	79
Brush biopsy	146	57	39

P. carinii pneumonia was diagnosed during this procedure or during another performed soon afterward.

†Specimens for these preparations were obtained by transbronchial biopsy

If the patient is thrombocytopenic, an etiologic diagnosis can oftentimes be made by means of bronchial lavage. Specimens obtained at fiberoptic bronchoscopy should be processed to look for agents like pneumocystis, cytomegalovirus, legionella, cryptococci and nocardia. A stain that can be performed easily and in which many of these agents can be visualized is the modified methylene blue stain. The stain can be performed in approximately 15 minutes of time and is available at the Microbiology Laboratory at PMH.

Once a diagnosis of pneumocystis pneumonia is established a conventional means of therapy is with sulfa-trimethoprim. The usual dose of the sulfa-trimethoprim is 20 mg/kg of the trimethoprim component given daily in a q 6 h dosing regimen. When patients with pneumocystis are treated early the case fatality rate approximates 20%. The more prompt recognition of the syndrome and earlier and more vigorous therapy has resulted in a lowering of the case fatality rate. If the patient does not respond to sulfa-trimethoprim in a 4 or 5 day period of time or shows increasing dyspnea and a worsening chest x-ray, most authorities advise switching to pentamidine isethionate. This drug has just become commercially available. Pentamidine is given as an intramuscular injection at 4 mg/kg/day. The minimal time required for therapy is at least 3 weeks. There is no evidence at present that combining the sulfa-trimethoprim with pentamidine enhances the survival of patients with pneumocystis. There is a suggestion that there might be a superimposition of the toxicities of the two drugs and the two drugs are not now given routinely together. If the patient's progress requires a switch to pentamidine or if he requires intubation and ventilatory support the case fatality rate rises to 90%. An experimental drug, difluoromethylornithine (DFMO), distributed by the Merrill-Dow Pharmaceutical Company has been used in patients who did not respond to sulfa-trimethoprim and/or pentamidine. This drug inhibits the action of ornithine decarboxylase which is important in the formation of polyamines such as putrescine and spermidine. This drug and its derivatives were originally intended to be anti-cancer agents because they have an inhibiting effect on the proliferation of rapidly dividing cells. They have not been successful for that purpose but, however, have been used successfully in African trypanosomiasis. This latter disease has been considered to have a fatal outcome once central nervous system involvement occurred. Patients who have been treated with large dosages of DFMO with African trypanosomiasis have showed clearing of trypanosomes from blood and spinal fluid and clinical improvement. Anecdotal reports now suggest that DFMO has been used successfully in instances where pneumocystis has failed to respond to sulfa-trimethoprim or to pentamidine. Parenthetically, DFMO is also effective <u>in vitro</u> in diminishing the replication of cytomegalovirus. Once the patient has completed the 3 weeks of therapy it has been debated as to whether the patient should be kept on sulfa-trimethoprim as prophylaxis against an ensuing relapse. Relapses are known to occur in about a third of patients who once have had pneumocystis pneumonia. Some authorities advise placing the patient on a double-strength tablet of sulfa-trimethoprim twice a day indefinitely. Fansidar, a fixed combination of pyrimethamine and sulfadoxime, a drug used for malaria prophylaxis, is presently being investigated to see whether or not it will prevent relapse of pneumocystis infection. Other authorities feel that the patient usually cannot tolerate treatment with sulfa-trimethoprim for any prolonged period of time because they will manifest reactions to the drugs, consisting of fever, rash or the development of neutropenia. Reactions to sulfa-trimethoprim and pentamidine have been common in patients treated with

these drugs (Table 4).

Table 4

Toxic Reactions Attributed to Antimicrobial Therapy in 36 Patients with the Acquired Immunodeficiency Syndrome

Reaction	Patients Receiving Trimethoprim-Sulfamethoxazole ($n=35$)		Patients Receiving Pentamidine ($n=30$)	
	Any Toxicity	Severe Toxicity	Any Toxicity	Severe Toxicity
	n			
Rash	18	12	1	1
Fever	14	13	1	1
Leukopenia	13	10	3	3
Thrombocytopenia	5	4	1	1
Azotemia	0	0	6	3
Hepatitis	7	4	9	0
Hypoglycemia	0	0	2	2
Any reaction	29	23	13	7

Pentamidine is known to induce neutropenia, sterile abscesses, azotemia, hypoglycemia, hepatic dysfunction, and diabetes mellitus. The most dangerous complication of pentamidine is the induction of hypoglycemia. Instances have been reported in which hypoglycemia has developed after each injection of pentamidine. Pentamidine can induce the elaboration of insulin from the beta cells of the pancreas. As a result, hypoglycemia can occur along with encephalopathy. In several patients, the use of pentamidine has been associated with the development of diabetes mellitus. In our patient, the pneumocystis infection was getting better but the actual mechanism of his death with probably a prolonged episode of hypoglycemic encephalopathy. This patient also had cytomegalovirus infection of the lung and disseminated cytomegalovirus infection. The patient had focal necrosis of the adrenal glands with both the adrenal medulla and cortex being involved. Adrenal gland involvement is not uncommon in AIDS patients (Table 5). It is possible that the development of relative adrenal insufficiency in this patient was sufficient so that effective counter-regulatory mechanisms could not be called into effect when the hypoglycemia induced by pentamidine occurred. Since plasma cortisol levels were not obtained in this patient it is impossible to say whether or not he had function adrenal insufficiency, but hyponatremia and hyperkalemia were noted and there was pathologic evidence of adrenal involvement with cytomegalovirus.

The therapy of other pulmonary infections encountered in the pulmonary syndrome of AIDS requires the use of erythromycin in an adult dose of 3-4 gms/day for at least a 3 week period of time for legionella infections. Cryptococcal lung disease requires the concomitant use of 5-fluorocytosine and amphotericin B. Pneumococcal disease is treated with penicillin. Nocardial infection is usually treated with a sulfa preparation such as sulfisoxazole. The dose of sulfisoxazole for the adult generally is 10 gm/day or enough of drug to reach a peak concentration in serum of 10 mg/dl. In the event of sulfa hypersensitivity, drugs that work in vitro against nocardia are cycloserine, the combination of ampicillin and erythromycin, and minocycline. This latter drug has been used successfully to treat 5 patients who had undergone cardiac or renal transplantation. The dose of minocycline

in these cases was 300 mg twice a day for a protracted period of time, that is at least 6 months. Mycobacterium tuberulosis infections are treated in the usual manner and the therapy of MAI infections have been discussed.

Table 5

Adrenal Gland Findings at Autopsy in Ten Patients with the Acquired Immunodeficiency Syndrome

Patient	Risk Factor for the Syndrome	Adrenal Gland Findings	Other Pathologic Findings
1	Homosexual	Lipid depletion	Kaposi's sarcoma of duodenum; CMV and pneumocystis infection of lungs
2	Homosexual	CMV adrenalitis	CMV infection of lungs, colon, spleen, liver, thymus, lymph nodes, and retina; *Mycobacterium avium-intracellulare* infection of spleen and lymph nodes
3	Intravenous drug user	Lipid depletion	Pneumocystis infection of lungs
4	Homosexual	CMV adrenalitis	CMV infection of lungs and colon; prior pneumocystis infection of lungs
5	Homosexual	CMV adrenalitis	Kaposi's sarcoma of abdominal lymph nodes; renal cell carcinoma; CMV infection of duodenum
6	Homosexual	CMV adrenalitis	Toxoplasmosis of brain and heart; Kaposi's sarcoma of skin and duodenum; CMV infection of lungs
7	Homosexual	CMV adrenalitis	Toxoplasmosis of brain; CMV infection of lungs, heart, esophagus, stomach, colon, thyroid, brain, and pancreas; *M. avium-intracellulare* infection of lymph nodes, bone marrow, lung, liver, and spleen; Kaposi's sarcoma of skin and lymph nodes; prior pneumocystis infection of lungs
8	Intravenous drug user	Lipid depletion	Pneumocystis infection of lungs; mycobacteriosis (? type) of liver
9	Homosexual	CMV, *M. avium-intracellulare,* and cryptococcus adrenalitis	CMV infection of lungs; cryptococcosis of brain, lungs, mesenteric nodes, spleen, and kidneys; disseminated *M. avium-intracellulare* infection of small intestine, mesenteric nodes, bone marrow, and spleen; pneumocystis infection of lungs
10	Homosexual	CMV adrenalitis	Pneumocystis infection of lungs; mycobacteriosis (? type) of mediastinal and paraortic lymph nodes

[ML Tapper, et al. Ann Intern Med 1984;100:239-241. American College of Physicians.

The therapy of cytomegalovirus infection is presently undergoing active investigation. Adenine arabinoside, acyclovir and interferon have been used both singly and in combination in treating CMV pneumonia but without success. In the bone marrow transplant recipient, the case fatality rate from cytomegalovirus pneumonia is 90%. Recently a new drug, 2'-nordeoxyguanosine (NDG, DHPG), has been shown in vitro to inhibit the replication of CMV. DHPG is a derivative of acyclovir and the active triphosphorylated form accumulates in cells despite the fact that CMV does not code for its own thymidine kinase. DHPG, however, is a toxic drug and in rats given large doses of the drug testicular atrophy has been noted. In patients with progressive CMV retinopathy, DHPG has been used in single cases, both in Boston and in San Francisco, to reverse the course of the retinopathy. It is ordinarily expected that retinopathy in the AIDS patient will be progressive disease that will lead to blindness. In the cases in which it has been successful, there has been a reversal of the disease process with the maintenance of useful vision. DHPG is presently being developed by Burroughs-Wellcome Company and Syntex Pharmaceuticals Company.

Patient D was a 29 year-old homosexual man who had diarrhea for a two year period of time. The diarrhea had been worked up at Baylor University Medical Center and at Parkland Hospital. At the onset of illness he had 10-15 watery stools per day. Initial work-up revealed negative stool cultures for salmonella, shigella, campylobacter, campylobacter-like organisms, gonorrhea and negative studies for ova and parasites, including cryptosporidium. A barium enema, an upper gastrointestinal tract series with a small bowel follow-through were within normal limits. A duodenal aspirate was negative for giardiasis and a small bowel biopsy was within normal limits. During that hospitalization he was found to have a positive VDRL and was treated with benzathine penicillin. Approximately 4 months after the first hospitalization he presented at Parkland Memorial Hospital with a 40 lb weight loss. He complained of 10-15 watery stools per day. Endoscopy revealed esophageal candidiasis which was treated with 200 mg of ketoconazole twice a day. Proctoscopy revealed a friable rectal mucosa and herpes simplex virus was grown from the area. He was treated with intravenous acyclovir. Stool cultures were positive for Edwardsiella tarda. A 72 hour stool revealed 12 gms fat. A sputum culture was positive for Mycobacterium avium-intracellulare. When the cultures became positive, he was readmitted into the hospital to evaluate the possibility of disseminated MAI infection. Bone marrow and liver biopsies revealed granulomas but no morphological or cultural evidence of MAI. He was started on isoniazid, ethambutol, rifampin, amakicin and cycloserine. Because of central nervous system side effects, the cycloserine was discontinued. Later, he again was readmitted to Parkland Hospital for a work-up of continuing diarrhea. A 72 hour stool fat revealed 51 grams of fat. A small bowel biopsy revealed villus blunting and chronic inflammation; a rectal biopsy revealed acute and chronic inflammation. Studies for ova and parasites were negative. Specific studies for cryptosporidium were negative. Because Edwardsiella tarda has been associated with a diarrheal state, a trial of sulfa-trimethoprim therapy was instituted. However, this had to be discontinued because of drug fever. Later, a private physician noted cryptosporidium in stool and tried the patient on spiramycin. This therapy transiently improved his diarrheal state. However, when the spiramycin was discontinued, the diarrhea returned and was no longer responsive to the drug. About two years after the onset of his symptoms, he was admitted to Parkland Hospital for the last time to attempt hyperalimentation. At the time of admission his weight was 87 lbs, the blood pressure was 80/60, the pulse rate was 120 and his oral temperature was 38.1°. A left retinal exam showed cotton wool spots and areas of hemorrhage. The white blood count was 3000 with 57% polymorphonuclear leukocytes, 5% bands, 29% lymphocytes, 5% monocytes, and 4% atypical lymphocytes. The sodium was 132, potassium 2.6, CO_2 19 and the chloride was 101. An alkaline phosphatase was 194 and the SGOT was 15. He had a guiac positive stool. A conference was held with his Ward Physicians and subspecialists from the Infectious Disease Service, the Nutritional Support Team and the Gastroenterology Service. It was elected to try the patient on hyperalimentation. A repeat small biopsy was attempted but had to be discontinued since the patient could not tolerate the procedure. A repeat bone marrow examination revealed multiple acid fast bacilli. He was restarted on INH, ansamycin, clofazamine, and amakacin. During the hospital course he developed a urinary tract infection due to E. coli. He continued to have Edwardsiella tarda in stool but cryptosporidium examinations x 4 were negative, as were ova and parasite examination x 6 and 10 routine stool cultures for pathogenic bacteria. His alkaline phosphatase climbed to 1105.

He developed bilateral chest infiltrates. Fiberoptic bronchoscopy was performed. A modified methylene blue stain revealed organisms consistent with Nocardia asteroides. Cytomegalovirus was also grown from the pulmonary secretions. To control the nocardial infection, an attempt was made to desensitize the patient to sulfisoxazole. This was only transiently successful and subsequently he was placed on ampicillin and erythromycin. His pulmonary infection progressed and he lost vision in both eyes from progressive CMV retinopathy. He died from necrotizing pneumonia and empyema due to nocardia. Blood and lung cultures were positive for nocardia. Evidence of cytomegalovirus was found disseminated in lungs, esophagus, stomach, colon, rectum, spleen, adrenal glands, and both eyes. In the gastrointestinal tract, CMV was associated with ulcers in the esophagus, stomach and throughout the entire colon. The colonic ulcerative disease was extensive and associated with typical CMV cells at the base of the ulcers. The adrenal glands showed evidence of necrosis due to CMV. There was no residual evidence of MAI infection.

This patient had AIDS and the diarrheal syndrome. Extensive efforts to implicate a specific etiologic agent for the diarrhea were unsuccessful. Postmortem examination revealed extensive involvement of the gastrointestinal tract with cytomegalovirus. The extent to which this contributed to his long term process with diarrhea cannot be ascertained. He had adrenal necrosis due to CMV. The possibility of adrenal insufficiency, however, was never entertained as a diagnosis so that plasma cortisol levels were never determined.

This fourth patient presented with the gastrointestinal syndrome. The gastrointestinal syndrome has been subdivided by workers in Seattle into the syndromes of enteritis, proctocolitis, and proctitis (Table 6). The syndrome of enteritis is accompanied by a profuse watery diarrhea without the presence of inflammatory cells in stool. The syndrome of proctocolitis consists of the frequent painful passage of mucous and blood accompanied by inflammatory cells. The syndrome of proctitis implies that the inflammatory lesion does not extend beyond the rectum. These patients are usually constipated and the process of defecation is painful. From an operational standpoint, proctitis is distinguished from proctocolitis both by symptomatology and by the fact that in proctocolitis, inflammatory lesions and ulcerative disease extend into the colon 15 or more cm above the anal verge. The etiological organisms causing enteritis are generally agents like giardiasis, salmonellosis, and cryptosporidium. Agents causing protocolitis include shigellosis, campylobacter, campylobacter-like organisms, lymphogranuloma venereum and Entamoeba histolytica. Agents causing proctitis include herpes simplex virus, Treponema pallidum, gonorrhea, and Chlamydia trachomatis of non-LGV serotypes. This patient presented with the enteritis syndrome and also had proctitis. The proctitis was caused by herpes simplex virus and was successfully treated with intravenous acyclovir. The proctitis has recurred but each time whem it was symptomatic, it could be treated with intravenous acyclovir. In the future, after FDA approval, oral acyclovir can be utilized to treat such patients. An extensive investigation was made into his enteritis syndrome. Multiple stool cultures for pathogenic bacteria, examinations for ova and parasites and specific examinations for cryptosporidium were made. These were never positive except in one private laboratory where cryptosporidia were found in a stool sample. The therapy of cryptosporidium is presently undergoing investigation. The only drug which

Table 6

Microbiologic and Symptomatic Correlates of Proctitis, Proctocolitis, and Enteritis among 65 Homosexual Men with Intestinal Symptoms Who Underwent Sigmoidoscopy to a Distance above 15 cm.

	PROCTITIS	PROCTOCOLITIS	ENTERITIS
	SIGMOIDOSCOPIC FINDINGS ABNORMAL ONLY BELOW 15 CM (N = 41)	SIGMOIDOSCOPIC FINDINGS ABNORMAL BEYOND 15 CM (N = 15)	SIGMOIDOSCOPIC FINDINGS NORMAL (N = 9)
Sexually transmitted rectal pathogens			
Neisseria gonorrhoeae	12	0	2
Herpes simplex virus	13	1	0
Chlamydia trachomatis (non-LGV) *	8	1	0
Treponema pallidum	6	0	0
Total with any rectal pathogen	*33* †	*2*	*2*
Infectious causes of colitis			
Campylobacter jejuni/C. fetus fetus	3	4	0
Shigella flexneri	0	2	0
Chlamydia trachomatis (LGV) *	0	3	0
Entamoeba histolytica ‡	5 (26)	4 (11)	1 (8)
Clostridium difficile cytotoxin	1	1	0
Total with any colitis pathogen	*8*	*9* †	*1*
Infectious causes of inflammation limited to small intestine			
Giardia lamblia ‡	2 (26)	2 (11)	4 (8)
Any three of four symptoms present: diarrhea, abdominal pain, bloating, nausea	3	8	9 †
Any three of four symptoms present: constipation, rectal discharge, anorectal pain, tenesmus	38 †	7	0

*LGV denotes lymphogranuloma venereum. †P<0.05, by multiple logistic regression analysis

‡Figures in parentheses indicate the number of patients who submitted stools for examination for ova and parasites

has been found to have at least a slight effect even though it may be transient in some patients is spiramycin (Table 7).

Table 7

Outcome of Treatment with Spiramycin for Cryptosporidium Infection in Ten Patients

Patient	Age/Sex	Category	Gastrointestinal Findings				Spiramycin	
			Stools per Day	Duration	Weight Loss	Proof of Malabsorption	Dose	Period of Treatment
	yr		*n*	*wks*	*kg*		*g/d*	*wks*
1	41/M	Homosexual	10-12	12	30	Yes	3	3
2	52/M	Homosexual	10-15	3	40	Yes	3	1
3	30/M	Homosexual	20	4	20	Yes	3	2
4	30/M	Homosexual	15-20	6	30	Yes	3	3
5	31/M	Haitian	10-12	24	20	Not done	3	3.5
6	2/M	Haitian	6-8	6	...	Not done	1	4
7	36/M	Homosexual	15-20	12	35	Yes	3	5
8	33/M	Homosexual	6-12	10	17	Not done	3	1
9	33/M	Homosexual	8-12	12	30	Not done	3	16
10	26/F	Bone marrow transplant	8-10	6	15	Not done	3	3

* Evidence of infection with *Cryptosporidium* seen in stool examination or small bowel biopsy sample before and after treatments with spiramycin.
† Residual diarrhea in number of bowel movements per day, and duration of time to change of diarrhea.

	Evidence of *Cryptosporidium**				Diarrhea Response Time		Status
	In Stool		In Biopsy Sample		Residual Diarrhea†	Time to Change	
	Before	After	Before	After			
					d	*d*	
1	+	−	+	−	3-4	7	Dead
2	+	−	not done	+	Resolved	4	Dead
3	+	−	+	−	Resolved	2	Dead
4	+	−	+	−	6-8	4	Alive
5	+	+	Not done	Not done	6-8	4	Dead
6	+	+	Not done	Not done	Resolved	30	Dead
7	+	+	+	−	Resolved	6	Alive
8	+	+	Not done	+	3-4	3	Dead
9	+	−	Not done	Not done	Resolved	3	Alive
10	+	−	Not done	Not done	Resolved	3	Alive

D Portnoy, et al. Ann Intern Med 1984;101:202-204. American College of Physicians.

This drug is available only from a Canadian pharmaceutical firm and must be obtained with FDA approval. Edwardsiella tarda was found on a consistent basis in this patient's stool cultures. This agent has been known to cause a salmonella-like diarrhea. The organism was susceptible to sulfa-trimethoprim and the patient was tried on this drug for a period of time but had to be discontinued because of the development of drug fever. The patient also was tried on spiramycin for a short period of time but after its cessation the diarrhea recurred and was no longer influenced by spiramycin. Profuse watery diarrhea is known to occur in the lymphadenopathy syndrome and at times its etiology cannot be ascertained. In our patient there were no specific clues

as to the etiology of his diarrhea despite two small bowel biopsies, multiple radiologic examinations of the entire gastrointestinal tract, colonoscopy and sigmoidoscopy.

There are a subset of patients with AIDS who have an enteritis syndrome in which an etiology cannot be ascertained. Such patients have been grouped under the category of an enteropathy associated with AIDS for which no etiology can be determined (Table 8).

Table 8

Histologic Studies in Patients with the Acquired Immunodeficiency Syndrome

	Patients with		Controls	
	Diarrhea	No Diarrhea	Homosexual	Heterosexual
Jejunal biopsy samples				
Abnormal	5/5	3/5	2/7	. . .
Intraepithelial lymphocytes	40 ± 4	28 ± 4	28 ± 2	16 ± 3 (n = 8)
Epithelial cell heights, μm	29 ± 5	28 ± 4	35 ± 3	35 ± 2 (n = 9)
Rectal biopsy samples				
Abnormal	7/7	0/5	3/11	. . .
Crypt cell degeneration	6/7	1/4	0/11	. . .
Viral inclusions	5/7	1/4	0/11	. . .
Cytologic changes	7/7	0/4	3/11	. . .
'Immature' plasma cells	7/7	0/4	2/11	. . .
Intraepithelial lymphocytes	10.5 ± 1.5	9.3 ± 1.0	9.4 ± 0.6	11.2 ± 2.6 (n = 7)
Cells per crypt, n	4320 ± 544	3668 ± 991	4044 ± 211	3962 ± 1025 (n = 6)
Epithelial cell height, μm	31 ± 3	30 ± 2	29 ± 1	28 ± 2 (n = 9)

In pathological and at postmortem examinations, the only changes seen in such patients are alterations suggestive of host versus graft disease as seen in bone marrow transplant recipients and the presence of cytomegalovirus cells through the gastrointestinal tract. Sometimes the cytomegalic cells can be seen at the base of large ulcers. In our patient, pathologic examination of the gastrointestinal tract revealed ulcerative disease in the esophagus, stomach, and throughout the colon. Multiple ulcers were found in the colon. Cytomegalic cells were easily seen at the base of these ulcers. Their usual anatomic location at the base of the ulcers represent involvement of endothelial cells and/or epithelial cells of the gastrointestinal mucosa. Cytomegalovirus induced ulcerative disease of the gastrointestinal tract can lead to profuse bleeding and/or perforation. The enteritis syndrome with profuse diarrhea and protein losing enteropathy has also been observed. In this patient, small bowel biopsy during life revealed villous atrophy and increased inflammatory cells within the small intestine. These changes may, in part, have been induced by severe malnutrition. An alternative explanation is that the small bowel changes resulted from the action of some agent or agents not known at the present time. One report has determined that viral particles have been seen in such patients. The electron microscopic appearance of these particles is unlike that of other known viruses. In simian acquired immunedeficiency syndrome (SAIDS), diarrheal-like states have also been observed. In these monkeys, cryptosporidium can be responsible for the diarrhea but at other times an

exact etiologic diagnosis has not been found. The SAIDS retrovirus can multiply within many cells prepared from the tissues of macaque monkeys but there is no evidence at present that HTLV III can replicate in cells other than T4 cells. In this patient, the debilitating nature of the protracted diarrhea resulted in intense malnutrition with a weight loss to 87 lbs. Significantly, he did not have maladsorption of fat during the early portion of his illness but during the later stages of his illness he had significant fat maladsorption. Inflammatory cells were never seen in stool preparations prepared from the patient. Hyperalimentation was tried in this patient with a lessening of stool volume associated with reduced oral intake. In certain AIDS patients, hyperalimentation has been the only modality by which they could be maintained. Terminally, our patient developed nocardial disease of the lung associated with disseminated cytomegalovirus infection. Attempts to treat the nocardial infection with sulfisoxazole were unsuccessful because of his allergy to the drug. Ampicillin and erythromycin were tried but without success. It is conceivable that minocycline might have been successful and may have been tried at an earlier stage in his disease process. This patient also had patchy necrosis of both the adrenal medulla and cortex and it is possible that part of the wasting seen was related to adrenal insufficiency. This patient also had CMV retinopathy. It first affected the left eye with a reduction in the field of vision. Cotton wool patches were noted initially but later extensive necrosis due to CMV was found in both eyes. In the cardiac transplant recipient and in renal transplant recipients who have CMV retinopathy, therapy usually consisted of the withdrawal of the immunosuppression. Occasionally, therapy with adenine arabinoside in association with the withdrawal of the immunosuppressive drugs has resulted in saving vision. As mentioned previously the new drug, DHPG, has reversed the retinopathy seen in several patients with this disease. It remains to be seen whether or not DHPG will prove to be a valuable drug in the therapy of patients with disseminated CMV infection.

The therapy of other agents inducing gastrointestinal tract syndromes in patients with AIDS includes sulfa-trimethoprim for shigellosis, metronidazole or atabrine for giardiasis, metronidazole, with or without iodoquinol or diloxanide furoate for amebiasis, spiramycin for cryptosporidium, aqueous protein penicillin G with for gonococcal disease, tetracycline for lymphagranuloma venereum and Chlamydia trachomatis of other serotypes, erythromycin for campylobacter and campylobacter-like organisms, and acyclovir for herpetic proctitis. Therapy of salmonellosis or other organisms such as Edwardsiella tarda might require protracted use of sulfa-trimethoprim. The diagnosis of lymphagranuloma venereum or Chlamydia trachomatis infections of other serotypes requires the use of serologic tests or of actual identification of the organism by culture or by new methods using monoclonal antibodies for the direct demonstration of elementary bodies. To diagnose lymphogranuloma venereum, a compliment fixation test titer equal to or greater than 1:128 is usually required. Therapy of this disease has necessitated at 2-3 weeks of tetracycline at 2 gms/day. The diagnosis of giardiasis or cryptospordium may require small bowel biopsy. However, in the patient with AIDS the organisms are usually in a sufficient number to be detected in stool.

This patient also had oral thrush and candidal esophagitis. Therapy in candidal esophagitis usually necessitates the use of ketoconazole at 200 mg twice a day. Therapy oftentimes has to be prolonged or maintained

intermittently in order to insure that the patient remains asymptomatic. Ketoconazole has the problem that it can induce hepatitis and if continued in the presence of hepatitis can lead to fatal hepatic disease. Adrenal corticosteroid output by the adrenal glands has been affected by the administration of ketoconazole and this must be kept in mind particularly since there is a substratum of patients with AIDS that have adrenal cortical involvement with CMV or MAI. Ketoconazole can also produce gynecomastia.

In a large series of patients studied at the National Institutes of Health, the most common opportunistic infection seen in patients with AIDS included candidal esophagitis, pneumocystis pneumonia, disseminated cytomegalovirus infections, toxoplasmosis, cryptococcal meningitis, disseminated Mycobacterium avium-intracellulare infections, extending mucocutaneous herpes simplex virus infections, and herpes zoster with or without dissemination. Therapy of herpes zoster requires intravenous adenine arabinoside or acyclovir. These entities with the exception of herpes zoster are represented in the four patients discussed in the protocol. In securing baseline studies in patients with AIDS for optimal management, it would seem wise to obtain serological studies for toxoplasmosis, for cytomegalovirus, herpes simplex virus and lymphogranuloma venereum. If disease ensues from these particular organisms, a rise in titer or a change might be helpful in the diagnosis of these diseases. For example, a rise in IFA titers to toxoplasmosis may signal the beginning of disease due to this particular agent and could be of utility in further management.

Most authorities feel that patients with AIDS can be managed at the present time in a much more sophisticated way than they were when the disease spectrum of opportunistic infections was not fully appreciated. Successful management of the opportunistic infection will be critical in maintaining patients with AIDS in a relatively asymptomatic state until there can be further progress in restoring their immune deficits or developing actual chemotherapeutic agents against HTLV-III. It is of interest to note at the present time that the NIH has actually instituted studies with Suramin an anti-trypanosomal drug because this compound has been found to inhibit the action of the enzyme, reverse transcriptase. Other anti-HTLV-III drug therapies can also be contemplated, since the replication of this agent involves the formation of a DNA provirus and it has been found in vitro that anti-DNA viral agents such as Idoxuridine can inhibit retrovirus replication.

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