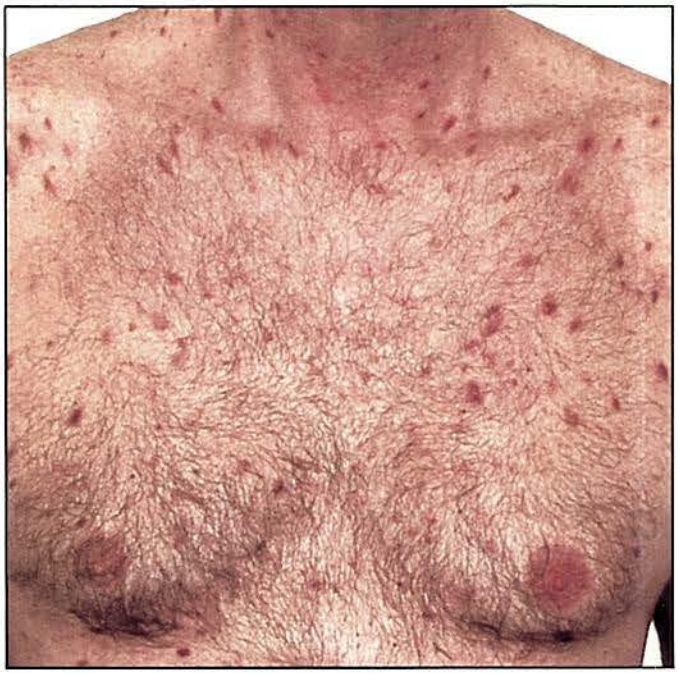
AIDS
DIAGNOSIS AND MANAGEMENT

Kaposi's sarcoma

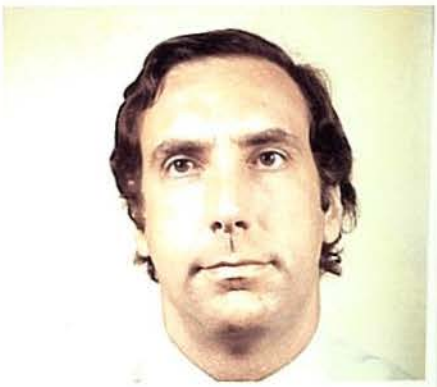


Acquired Immune Deficiency Syndrome

Abe M. Macher, M.D.
Henry Masur, M.D.
H. Clifford Lane, M.D.
Anthony S. Fauci, M.D.
National Cancer Institute and National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Abe M. Macher, M.D.
Staff Fellow
Laboratory of Pathology
National Cancer Institute
National Institutes of Health
Bethesda, Md.

Henry Masur, M.D.
Deputy Chief
Critical Care
Medicine Department
Clinical Center
National Institutes of Health
Bethesda, Md.



H. Clifford Lane, M.D.
Senior Investigator
Laboratory of Immunoregulation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Md.

Anthony S. Fauci, M.D.
Chief, Laboratory of Immunoregulation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Md.

Cover photo: Multiple erythematous cutaneous lesions of Kaposi's sarcoma.

AIDS: Recognition of the syndrome

IN JUNE 1979, a 32-year-old man appeared at a New York City hospital complaining of severe dyspnea and a persistent, non-productive cough. He had been in excellent health until two weeks earlier when he had gone to a hospital emergency room complaining of a cough and fever. At that time a chest radiograph was reported as negative and he was given a 10-day course of erythromycin; his symptoms became progressively worse.

Evaluation revealed that this young man was strikingly dyspneic with a few dry rales; physical examination was otherwise negative. There were diffuse interstitial infiltrates on chest radiograph. Laboratory analysis showed a white blood cell count of 3,100 cells/mm^3 with 75 percent polymorphonuclear cells, 16 percent bands, and 9 percent lymphocytes; a room air arterial blood gas revealed a pH of 7.51, pO_2 of 48 mm Hg, and pCO_2 of 22 mm Hg. When an open lung biopsy (*Figure 1*) was performed several hours later, the health care team was surprised to find interstitial mononuclear infiltrates with numerous *Pneumocystis carinii* and occasional cytomegalovirus inclusion bodies.

The patient was treated with intravenous trimethoprim-sulfamethoxazole* and had a stormy, prolonged course before he recovered. An extensive workup failed to reveal a malignant neoplasm, or any other underlying disease that might cause an immune dysfunction which might explain a predisposition to these opportunistic infections. Review of the literature identified only three cases in which an adult patient had Pneumocystis pneumonia without an accompanying immunosuppressive illness and no case of an adult presenting with Pneumocystis pneumonia as the first manifestation of immunosuppressive disease.

Thus, this case appeared at first to be an anomaly. But medical meetings in New York City over the next several months brought to light 15 additional cases of unusual opportunistic infections, particularly Pneumocystis pneumonia, in previously healthy persons. When features of these cases were compared, it became apparent that all involved young men were either homosexuals or drug abusers.

At about the same time, another group of physicians began seeing a substantial number of cases of Kaposi's sarcoma — a usually indolent skin tumor appearing in elderly males — in previously healthy young male homosexuals. Not only was the Kaposi's sarcoma rapidly progressive, but many of the patients also developed fatal opportunistic infections.

The Centers for Disease Control (CDC) quickly recognized that unusual opportunistic infections and cases of Kaposi's sarcoma were being seen in previously healthy persons in several large eastern and western cities, and that there was no precedent for these cases. The CDC began an active surveillance system, and by the end of June 1983, over 1,600 cases had been recognized, with a new case rate of two or three per day.

Clearly, these developments represented a new disease process with unprecedented immunologic, clinical, and epidemiologic features. The process became known as the Acquired Immune Deficiency Syndrome (AIDS). As the number of cases continued to increase daily and the syndrome spread to new population groups, it became clear that the medical community was being presented with a devastating disorder that required specialized expertise for clinical management and urgent scientific initiatives for discovering methods to prevent its spread and reverse its lethal consequences.

*Please see prescribing information, page 23.

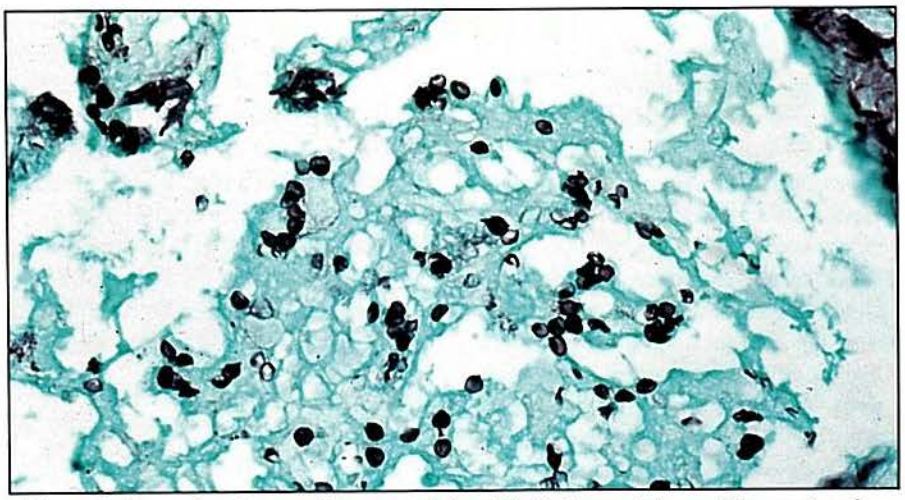


Figure 1. Intraalveolar exudate containing black silver stain positive cysts of Pneumocystis carinii (*methenamine silver stain*).

AIDS: The emergence of a new syndrome

SINCE THE late 1970s, a striking number of previously healthy male homosexuals have developed opportunistic infections or an aggressive form of Kaposi's sarcoma that had almost never been seen in the absence of clinically obvious immunosuppressive disease. These men and others with AIDS—drug abusers, recipients of blood products and Haitians—had impressive deficiencies in their immune response, yet careful clinical evaluations and autopsies failed to reveal a malignant neoplasm, or any other immunosuppressive entity that might explain their immunodeficiency.

From a clinical standpoint, the immunodeficiency had developed during adulthood since no patient had experienced any unusual infection or tumor during the first several decades of life. Thus, the immunodeficiency was acquired rather than congenital. Moreover, the variety of infectious processes being seen suggested that the immunodeficiency was in fact the primary event, and that the infectious processes were the result of the immunodeficiency rather than the cause.

The immunodeficiency that occurred in these homosexuals, drug abusers, Haitians, and recipients of blood products was both quantitatively and qualitatively different from immunologic disorders previously recognized in adults. Profound and irreversible, the immunodeficiency predisposed the patients to developing infections that have been unusually frequent and severe. The immunologic deficiency appeared to be qualitatively different from that seen in other immunosuppressive populations in that Kaposi's sarcoma (*Figure 2*), *Mycobacterium avium-intracellulare,* mucocutaneous *Herpes simplex,* and toxoplasmosis were all common, while opportunistic organisms such as *Listeria monocytogenes* or *Nocardia asteroides,* which are common in transplant recipients and Hodgkin's disease patients, were rarely seen.

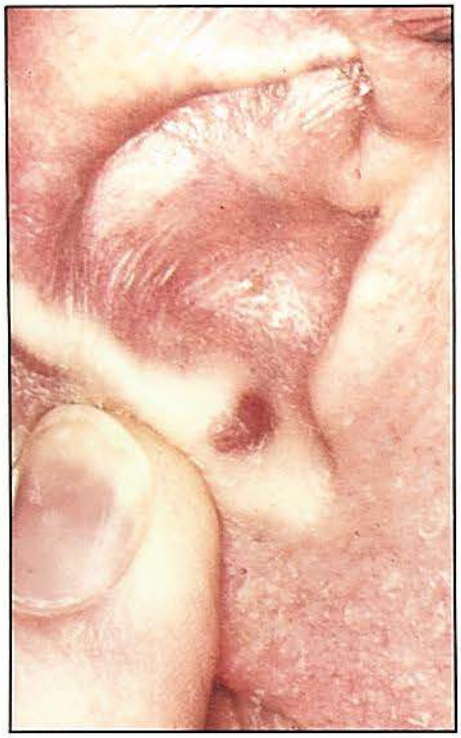


Figure 2. Erythematous cutaneous Kaposi's sarcoma lesion of the ear.

As clinicians became aware of these occurrences in previously healthy individuals, unusual clinical events of all types in homosexuals, drug abusers, Haitians, and recipients of blood products became the focus of considerable interest. Cases of Epstein-Barr virus-associated Burkitt's lymphoma, non-Hodgkin's lymphoma, colonic carcinomas, oropharyngeal carcinomas, immune complex nephropathies, generalized lymphadenopathy, and autoimmune phenomena were reported, often associated with opportunistic infections.

Since no laboratory marker of AIDS has been discovered, defining AIDS in a manner that distinguished the truly new clinical occurrences from the heightened awareness of unusual disease processes in populations at risk for AIDS became a real problem. For example, non-Hodgkin's lymphoma, Burkitt's lymphoma, and renal failure are seen in all segments of society and are often complicated by opportunistic infections or second malignancies. The occurrence of these processes in homosexuals could be a manifestation of AIDS, but it is also possible that these uncommon diseases have always occurred in all population groups, but are now being recognized and reported because of heightened awareness in the medical community.

To determine the magnitude of AIDS and its true epidemiologic pattern, the CDC has adopted a strict definition that is unlikely to be inflated by unrelated disease processes. As we learn more about AIDS, the definition may need to be expanded or to become more sophisticated. This definition (see page 4) is clinical rather than based on immunologic parameters since the latter do not yet clearly separate AIDS patients from those with other disease processes, or from individuals who are clinically well. There seems little doubt that

There is great variation in the clinical course leading up to the development of opportunistic infection or Kaposi's sarcoma.

generalized lymphadenopathy in homosexuals without identifiable infections or tumors is probably associated with AIDS. There are, however, no laboratory markers to separate AIDS-associated lymphadenopathy from lymphadenopathy of unknown etiology that has been recognized in all patient populations for many decades. Thus, homosexuals with lymphadenopathy are not currently included under the definition of AIDS, although this patient group is being intensively studied to determine how it is in fact AIDS-related.

Prodromal syndrome

There is great variation in the clinical course leading up to initial documentation of AIDS via development of an opportunistic infection or Kaposi's sarcoma. Some patients have no constitutional symptoms or specific complaints until they note the initial skin or mucous membrane lesions of Kaposi's sarcoma or until they develop specific symptoms of a life-threatening infection such as *Pneumocystis carinii* pneumonia or cryptococcal meningitis. Some patients have a short history (weeks or months) of non-specific weakness, malaise, weight loss, diarrhea or fever. This short history of non-specific complaints may be punctuated by the development of oral candidiasis (*Figure 3*) or localized dermatomal Herpes zoster. Oral candidiasis is so unusual in healthy individuals not receiving antibiotics or steroids that its occurrence in a homosexual or other individual at risk for AIDS should lead to consideration of an immunologic disorder and a search for potential causes. For some patients, the prodromal malaise, fever and weight loss may extend over several months or years before a specific opportunistic infection or Kaposi's sarcoma is documented.

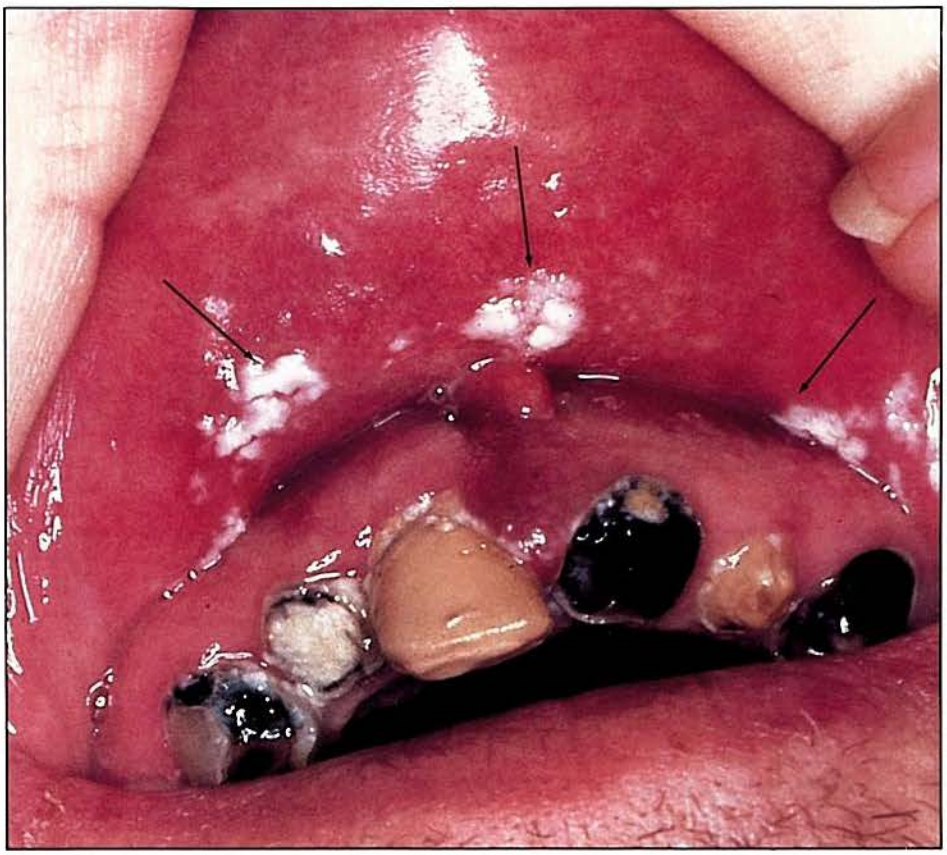


Figure 3. Cheesy white mucosal plaques of oral candidiasis (oral thrush).

Some patients with AIDS have a well-documented history of generalized lymphadenopathy that stretches over many months or several years. Patients with lymphadenopathy may or may not have had associated symptoms. Often they have had complete evaluations of their adenopathy, including biopsy, with no detectable cause.

Definition of AIDS

AIDS is currently defined by the CDC as a disease (such as Pneumocystis pneumonia or Kaposi's sarcoma) that is at least moderately predictive of a defect in cell-mediated immunity, and that occurs in the absence of a known cause for diminished resistance to that disease.

Diseases under the CDC definition include:

1) pneumonia, meningitis, or encephalitis due to aspergillosis, candidiasis, cryptococcosis, cytomegalovirus infection, *Herpes simplex* infection, nocardiosis, strongyloidiasis, toxoplasmosis, zygomycosis or atypical mycobacteriosis;

2) esophagitis due to *Candida, Herpes simplex,* cytomegalovirus;

3) unusually extensive mucocutaneous *Herpes simplex* of more than four weeks' duration;

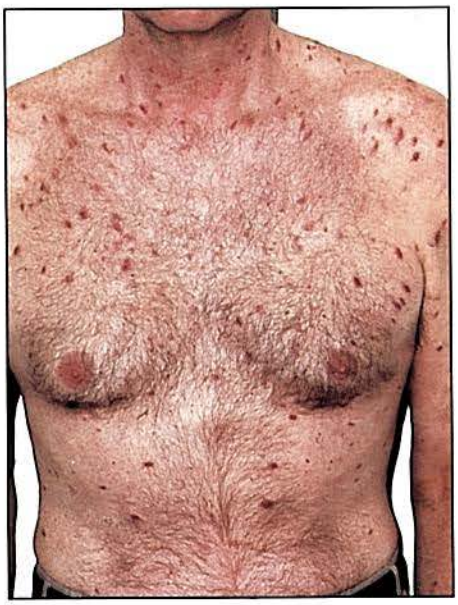
4) progressive multifocal leukoencephalopathy;

5) disseminated or central nervous system infection due to coccidiomycosis, cryptococcosis, histoplasmosis;

6) chronic enterocolitis (>four weeks) due to cryptosporidiosis;

7) Kaposi's sarcoma;

8) lymphoma limited to the brain.



The immunologic profile is not currently specific enough to be part of the definition of AIDS.

Individuals with one of the above infectious processes would be excluded from AIDS if they developed a malignant neoplasm other than Kaposi's sarcoma or lymphoma of the brain, had received corticosteroids close to the time of presentation, or were uremic at presentation, since these potentially immunosuppressive processes could themselves predispose to opportunistic infection.

The populations affected by AIDS have grown from male homosexuals to I.V. drug abusers, Haitians, and recipients of various blood products including concentrated Factor VIII, and then to sexual contacts of AIDS patients or of those at high risk. A few patients with unequivocal AIDS deny homosexuality, drug abuse, or receipt of blood products, although the reliability of their histories is never certain. Some neonates and older children of individuals at risk for AIDS have immunologic defects and opportunistic infections, but it has been difficult to establish whether these children have AIDS or some other type of unrelated immunodeficiency syndrome.

Why AIDS did not appear until the late 1970s, although homosexuality and blood product therapy had long existed, is a scientific mystery. The epidemiology suggests that AIDS is caused by an infectious agent that is transmitted by sexual contact, blood, or blood products. There seems little doubt, however, that AIDS is a new clinical and immunologic syndrome that did not exist before the late 1970s, and that extensive investigation will be needed to elucidate how it developed, how it causes immunosuppression, how it can be treated, and how its spread can be prevented.

Clinical manifestations of AIDS

THE initial manifestation of AIDS can be either an opportunistic infection or Kaposi's sarcoma. Many patients who present initially with Kaposi's sarcoma will ultimately develop opportunistic infections, but only a minority of patients who present with opportunistic infections later develop Kaposi's sarcoma.

There is a characteristic constellation of opportunistic infections in AIDS (see box, lower right). Some occur often in other immunosuppressed populations; but several are almost never seen in patients with other immunosuppressive illness: *Mycobacterium avium-intracellulare,* perirectal *Herpes simplex,* cerebral toxoplasmosis, persistent cryptosporidiosis. Moreover, certain common opportunistic infections in other patient groups (*Listeria monocytogenes, Nocardia asteroides*) are rare in AIDS patients.

The most common clinical complications in AIDS are described below, followed by a description of specific infectious complications most frequently seen.

Fever of unknown origin/ weight loss/malaise

Febrile episodes can occur before an opportunistic infection or tumor develops, and after Kaposi's sarcoma or treatment of a specific opportunistic infection. Persistent fever may be a debilitating problem, often associated with considerable malaise and weight loss; the fever may be either low grade and persistent, or episodic and spiking to 39.0°C or higher. The fever is often associated with considerable malaise and weight loss and some patients have associated rigors and diaphoresis. Although some tolerate their fever without problems, others are unable to work or actively care for themselves due to debility. Weight loss can amount to 20 to 30 percent of body weight.

Febrile episodes can occur before an opportunistic infection or tumor develops. The cause of the fever and associated symptoms is usually difficult to identify.

The cause of the fever and associated symptoms is usually difficult to identify with certainty. A sizable percentage of patients show cytomegalovirus in their blood, Epstein-Barr virus in their throats and peripheral blood lymphocytes, and *Mycobacterium avium-intracellulare* in their bone marrow, blood and other organs. At autopsy, many of the pathogens listed in the box are present. It is unclear whether these pathogens are mainly responsible for the fever and constitutional symptoms, or whether as yet unidentified pathogens (perhaps unnamed viruses) or pathologic processes (immunologic or metabolic) are responsible. The symptoms do not usually respond to empiric trials with antiviral or antimycobacterial chemotherapy; drug combinations tried to date have not been successful in eradicating cytomegalovirus or *Mycobacterium avium-intracellulare* infections.

A rigorous fever workup is appropriate and should include cultures for bacteria, fungi, mycobacteria, and viruses of blood, cerebrospinal fluid (CSF), bone marrow, and other body fluids or organs; radiologic evaluation of the head, chest, and abdomen; biopsy of lymph nodes and perhaps of the liver.

Common opportunistic infections in AIDS

- *Pneumocystis carinii* pneumonia
- Disseminated cytomegalovirus
- Disseminated *Mycobacterium avium-intracellulare*
- *Candida* esophagitis
- Mucocutaneous *Herpes simplex*
- Cryptococcal meningitis
- Cerebral toxoplasmosis
- Enteric cryptosporidiosis

Common clinical manifestations in AIDS

- Fevers of unknown origin/weight loss/fatigue
- Diffuse pneumonia
- Diarrhea
- Neurologic disorders and retinitis

Diffuse pneumonia

AIDS patients frequently develop dyspnea, shortness of breath and progressive hypoxemia. These symptoms can develop rapidly over several days or insidiously over many weeks or months. The chest radiograph may be clear initially. However, diffuse bilateral infiltrates, interstitial or alveolar, usually develop.

Pneumocystis carinii is the most common cause of diffuse infiltrates. Cytomegalovirus and *Cryptococcus neoformans* are also seen, and cases of Legionnaire's disease, other fungal processes, and occasional bacterial pneumonias are documented.

Prompt diagnostic evaluation via bronchial lavage, brushings, washings, or lung biopsy are appropriate. The precise technique depends on the patient's clinical condition and the technical expertise available. Careful studies are needed for bacteria (including mycobacteria and Legionella), fungi, viruses (especially cytomegalovirus) and protozoa (especially Pneumocystis). Empiric therapy without definitive diagnosis frequently leads to therapeutic uncertainty since Pneumocystis and Cryptococcus respond poorly to chemotherapy and the clinician is often uncertain if the patient's clinical deterioration is due to wrong choice of empiric drugs or slow response despite appropriate therapy. When a patient has had a definitive diagnosis but responds poorly, or deteriorates after improvement, repeat investigation via bronchoscopy and/or biopsy is usually quite helpful in determining whether the therapeutic regimen chosen has failed to treat the microorganism it was directed against or whether another disease process is responsible for the deteriorating clinical situation.

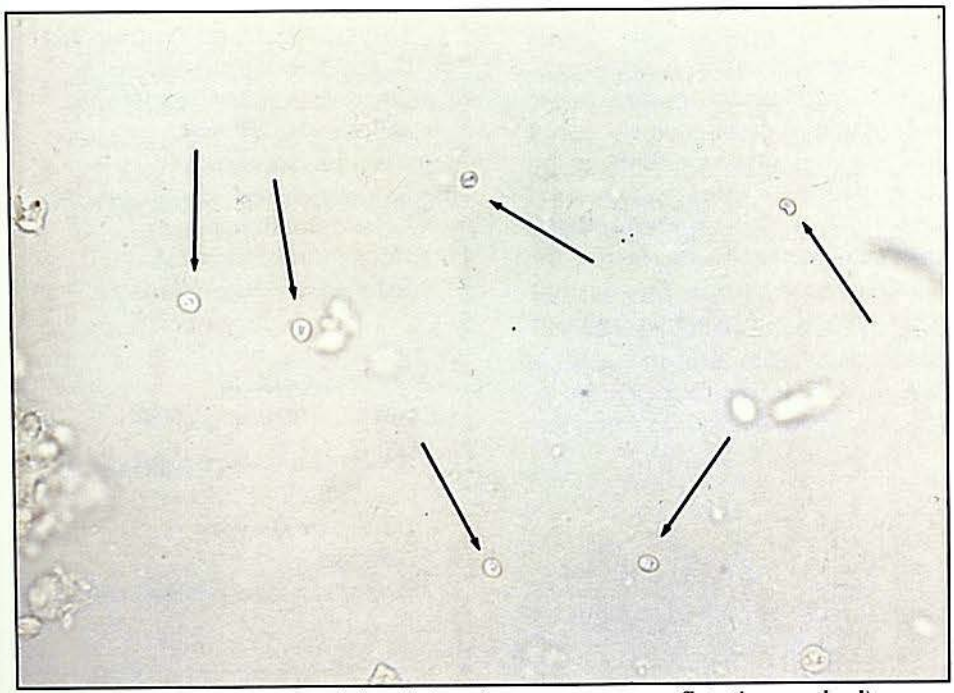


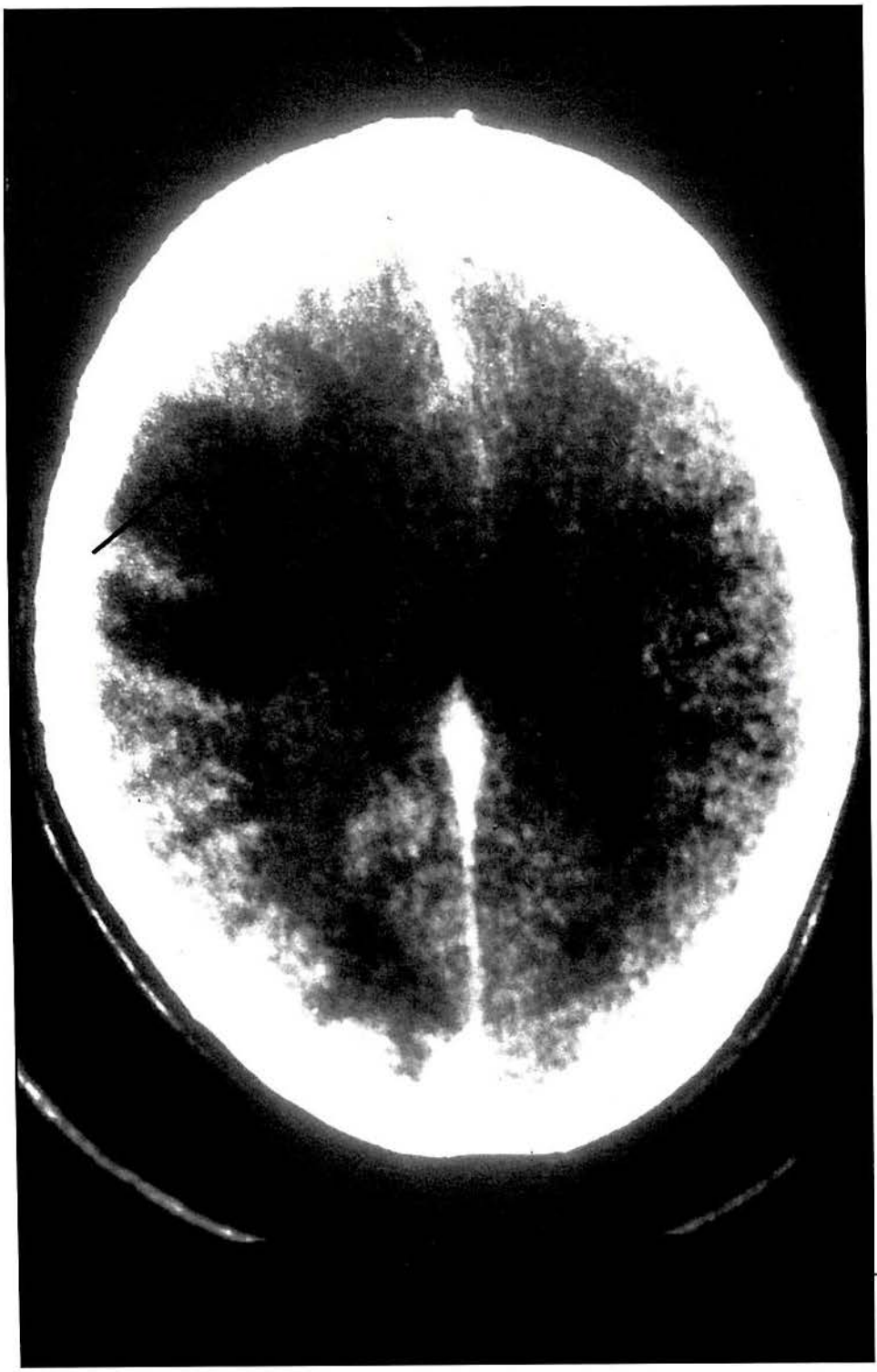
Figure 4. Cysts of Cryptosporidia *(light microscopy-sucrose flotation method).*

Diarrhea

Copious watery diarrhea is a frequent problem among AIDS patients. Moderate nausea may be an associated complaint. Homosexuals with AIDS may have a range of bowel complaints due to the enteric organisms that cause symptomatic disease in the general gay population, including *Giardia lamblia, Entamoeba histolytica,* and Shigella and Salmonella species. Debilitating, copious watery stools often persist despite numerous diagnostic procedures, including multiple stool samples for bacteriologic and parasitologic examination, gastrointestinal contrast studies, endoscopy, and small bowel biopsy, and despite empiric therapeutic trials with metronidazole and/or trimethoprim-sulfamethoxazole.*

By using a sucrose flotation procedure (*Figure 4*) on stool samples or electron microscopy on small bowel biopsies, a few of these patients can be shown to have cryptosporidiosis, an animal protozoan disease which on rare occasions causes self-limiting diarrhea in healthy humans with animal exposure, but which can probably cause severe diarrhea in AIDS patients. In most cases, exhaustive diagnostic procedures during life and at autopsy fail to establish a cause. Symptomatic therapy using anti-motility drugs and dietary alteration may have limited success; total parenteral nutrition is needed in some patients who lose considerable weight.

**Please see prescribing information, page 23.*



Neurologic disorders and retinitis

Neurologic disorders are common occurrences in AIDS patients and can have devastating consequences on the quality and duration of life. A slowly progressive encephalopathy characterized by diminished cognitive function and social withdrawal has occurred in more than 10 percent of some large series of AIDS patients. Computerized tomography usually shows no focal lesions, but the lateral ventricles may be enlarged. Brain biopsies or autopsies usually reveal non-specific pathologic changes. A few viral inclusion bodies may be seen, and mycobacteria may be cultured from the brain. The true etiologic agent(s) of this syndrome, however, has not been clearly identified. Patients with encephalopathies require a prompt evaluation of the infectious, metabolic, and neoplastic processes that can cause such a syndrome. Brain biopsy is probably warranted in severe cases where non-invasive studies are non-diagnostic in establishing a reversible cause.

Neurologic findings associated with focal lesions on computerized tomography are also common. *Toxoplasma gondii* (*Figure 5*) has been seen in many lesions, particularly in Haitians; lymphomas and inflammatory lesions of unclear etiology have also been recognized. Brain biopsies are usually necessary to establish the cause of these focal lesions since serologies and CSF cultures are not usually diagnostic.

Figure 5. CT brain scan demonstrating large intracerebral lesion of Toxoplasma gondii.

Clinical manifestations of AIDS

Other neurologic disorders seen in AIDS include cryptococcal meningitis, cerebral hemorrhage, epidural lymphomas, peripheral neuropathies, aseptic meningitis, and progressive multifocal leukoencephalopathy.

The neurologic disorders in AIDS patients frequently result in repeated hospitalizations. The consequences of encephalopathy, cryptococcal meningitis and focal lesions may lead to a need for custodial care. This can be demoralizing, both to the patient and to those providing the care.

Retinitis (*Figures 6 and 7*) is also common in AIDS. Although many patients are asymptomatic, some have floaters, some suffer severe alterations in acuity and field of vision, and a few lose most of their vision. Diagnostic studies during life are difficult since serologies are rarely definitive. The clinical appearance of the lesions is usually consistent with cytomegalovirus retinitis. Autopsy studies have shown that cytomegalovirus is the most common cause of retinitis in this population; some cases of Toxoplasma retinitis have also been documented. In a few patients, vitreous biopsies to document Toxoplasma may be appropriate since this type of retinitis is potentially treatable. Empiric therapy could be attempted, but a definitive diagnosis is very useful in a population in which chemotherapy (sulfadiazine and pyrimethamine*) may be complicated by leukopenia and/or by hypersensitivity reactions.

(Photos courtesy of Dr. A. Palestine, National Eye Institute)

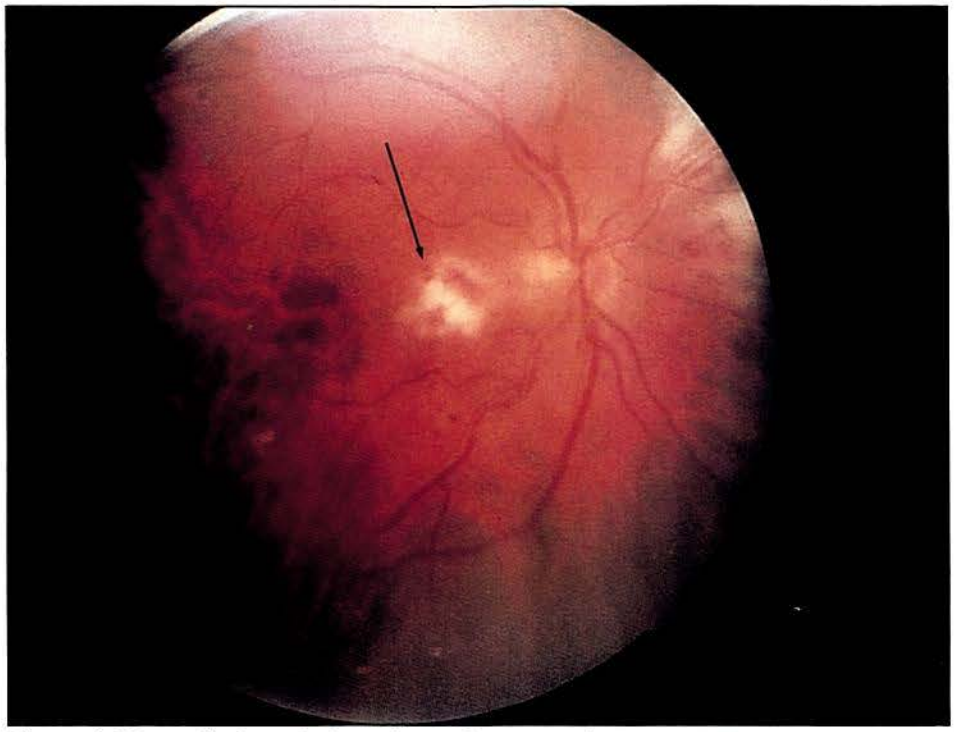


Figure 6. Hemorrhagic retinal exudates of cytomegalovirus retinitis.

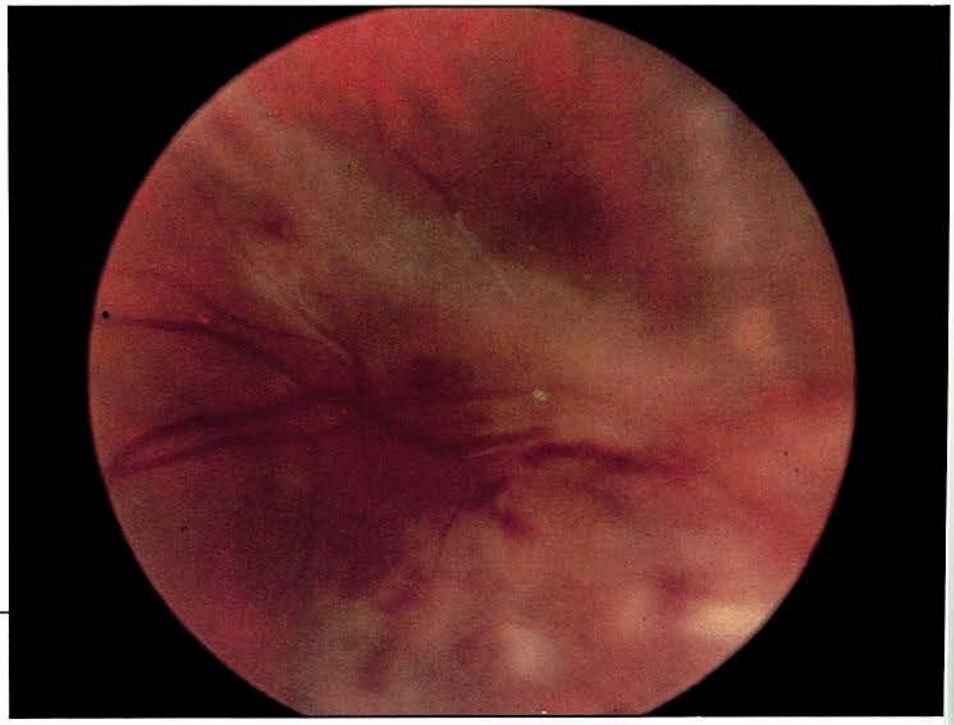


Figure 7. Posterior vitreous haze and hemorrhagic retinal exudates of cytomegalovirus retinitis.

*Please see prescribing information, page 27.

Specific infections commonly seen in AIDS

Pneumocystis carinii

Pneumocystis carinii pneumonia (PCP) is probably the most common opportunistic infection in AIDS. Over 55 percent of patients reported to the CDC and over 90 percent of those followed to autopsy in some series have had PCP. PCP is caused by a ubiquitous protozoan that is probably spread by a respiratory route. Pneumocystis only causes disease when there is a deficiency in the host's cell-mediated or humoral immune response. When disease does develop, it is confined to the lungs; it may present as a fulminant pneumonia that develops over a few days or as an insidious process characterized by dyspnea with or without a non-productive cough and fever. In AIDS, Pneumocystis pneumonia is characteristically an insidious process which develops over weeks or months. Physical examination is usually non-revealing and arterial blood gases can show either minimal or substantial hypoxemia. The chest radiograph (*Figure 8*) usually shows a diffuse and symmetrical interstitial pattern that progresses to alveolar consolidation. Atypical radiographic presentations occur with PCP, however, and the presence of asymmetry, lobar infiltration, pleural effusions, cavitation, or a normal examination should not exclude the diagnosis.

Pneumocystis carinii pneumonia may either present as a fulminant disease or, in some cases, as an insidious process.

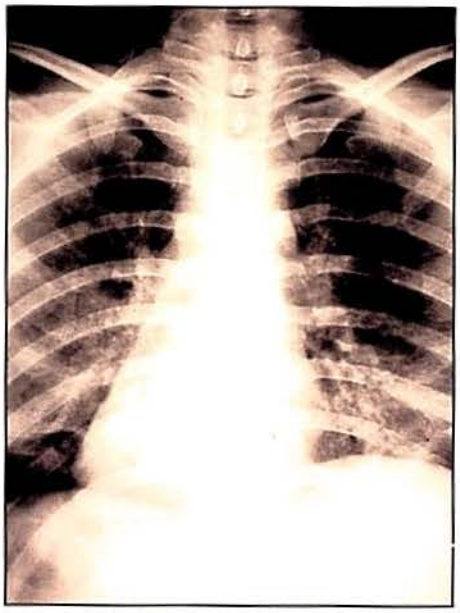


Figure 8. Chest x-ray demonstrating bilateral pulmonary infiltration.

Diagnosis. PCP can only be diagnosed by demonstration of the Pneumocystis organism in bronchial secretions or in lung tissue. Serologic tests assessing antigen or antibody levels do not have diagnostic significance. Hematoxylin and eosin stained sections of lung tissue show a characteristic interstitial cellular infiltrate and intraalveolar eosinophilic material, but unequivocal diagnosis requires use of a special stain such as methenamine silver, toluidine blue O, or Gram-Weigert to demonstrate the organism.

Recommended treatment. Trimethoprim-sulfamethoxazole* (20 mg/kg/day trimethoprim and 100 mg/kg/day sulfamethoxazole in 4 oral or intravenous daily doses) and pentamidine isethionate (4 mg/kg/day intramuscularly in one dose) for at least 10 days have demonstrated efficacy in treating PCP. In patients with malignant neoplasms, trimethoprim-sulfamethoxazole is as effective as pentamidine but less toxic. It is not known whether trimethoprim-sulfamethoxazole is as effective as pentamidine in AIDS patients with PCP, nor is it clear whether a combination of both drugs is better than either singly. The current recommendation is to institute trimethoprim-sulfamethoxazole therapy, and to add pentamidine if the patient has not improved by day 4 to 8 of therapy. The patient may respond very slowly and prolonged therapeutic courses (for more than two weeks) may be necessary. At least 10 percent of those who survive their first PCP infection may relapse or have recurrences.

Mycobacterium avium-intracellulare

Mycobacterium avium-intracellulare is a common environmental contaminant found in dust, water, poultry, and livestock in the southeastern U.S. The organism is a pulmonary saprophyte that can cause invasive lung

*Please see prescribing information, page 23.

disease in immunocompetent patients. However, the organism has low pathogenic potential even in the immunosuppressed. Only about 14 cases of disseminated disease have been documented in adults and, even among cancer patients, *Mycobacterium avium-intracellulare* is responsible for fewer than a third of atypical mycobacterial disease processes. However, *Mycobacterium avium-intracellulare* has been strikingly common in AIDS patients, suggesting that they have an unusual immunologic process that selectively predisposes to this mycobacterial infection. Over 40 AIDS patients, including homosexuals, drug addicts, and hemophiliacs, have had *Mycobacterium avium-intracellulare* documented in their bone marrow, blood, lymph nodes, and/or other tissues. Disseminated disease is not uncommonly found at autopsy. The role this organism plays in causing prolonged fever, fatigue, or weight loss is unclear.

Other atypical mycobacteria have not commonly caused disease in AIDS patients. Mycobacterium tuberculosis has been a common infection only in Haitians with AIDS.

Diagnosis. *Mycobacterium avium-intracellulare* disease is documented by cultivating the organism from non-pulmonary tissue or from normally sterile body fluid; it can be cultivated from blood. Histopathology of biopsy specimens (*Figure 9*) may reveal masses of acid-fast organisms on special stains. Granulomas are often poorly formed or absent, so tissues should be specifically stained for mycobacteria even in the absence of granulomas.

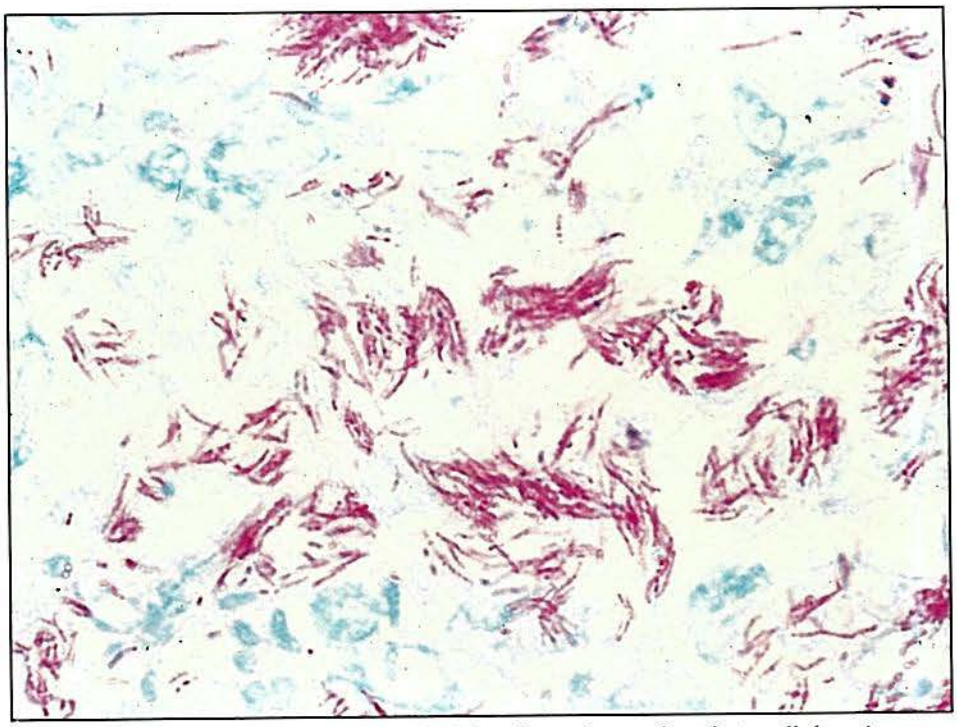


Figure 9. Acid-fast stain demonstrating Mycobacterium avium-intracellulare *in lymph node biopsy (Fite stain).*

Treatment. Management of disseminated *Mycobacterium avium-intracellulare* in AIDS has been uniformly unsuccessful, clinically and microbiologically. The organism is usually resistant to most conventional antimycobacterials. Investigational compounds such as ansamycin (Mont Edison Pharmaceuticals, New York City) and clofazamine (National Hansen's Disease Center, Carrville, Louisiana) often show good *in vitro* activity, but their safety or efficacy in chemotherapeutic regimens is unclear.

Herpes simplex virus

In immunocompetent patients, both primary and recurrent *Herpes simplex* virus (HSV) infections manifest themselves as vesicular lesions on an erythematous base in oral or genital areas. Almost all AIDS patients have had a primary HSV infection. They are at unusually high risk for recurrences as compared with other immunosuppressed populations. Most commonly, these recurrences present as extensive genital or perirectal ulcerations. There have also been reports of herpetic esophagitis and tracheobronchitis.

Diagnosis. Identification of multinucleated giant cells on scrapings from the lesion and isolation of HSV is diagnostic.

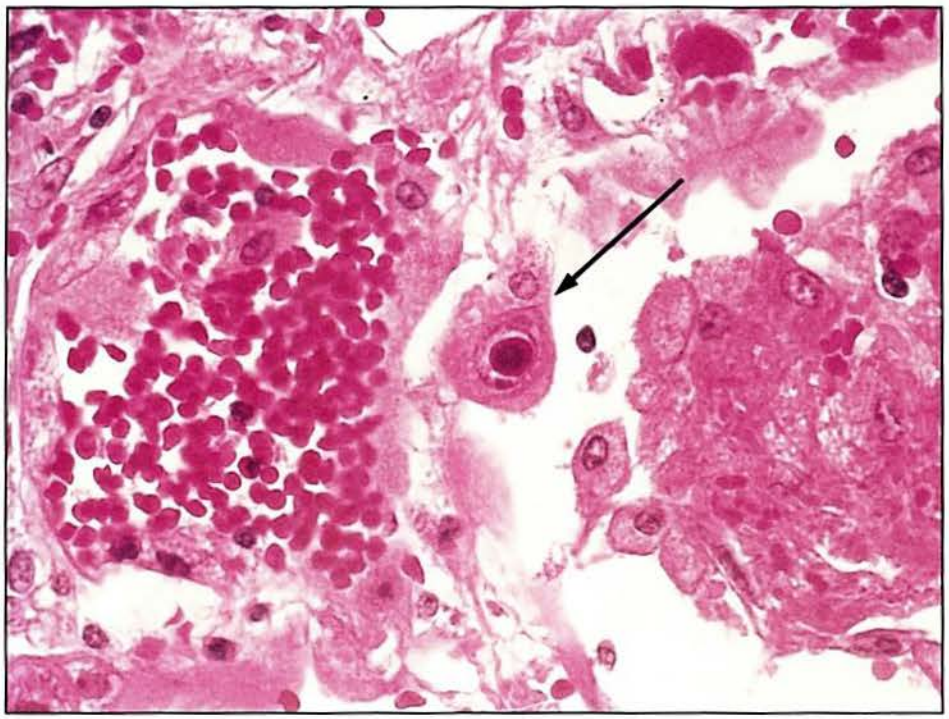


Figure 10. Lung biopsy demonstrating large inclusion cell of cytomegalovirus pneumonia (hematoxylin-eosin stain).

Recommended treatment. I.V. acyclovir* (5 mg/kg q8h for 7 days) reduces the duration of viral shedding and the time to crusting or epithelialization in many AIDS patients. The disease often recurs after therapy is stopped.

Disseminated cytomegalovirus infection

Cytomegalovirus (CMV), a member of the Herpes virus family, infects virtually all AIDS patients. CMV has been isolated from throat washings, urine, and/or blood of almost all patients followed at the Clinical Center of the National Institutes of Health, and all have anti-CMV IgG antibody.

Cytomegalovirus is a large, enveloped DNA virus found in saliva, blood, semen, cervical secretions, feces, and lymphocytes of a wide variety of patients. It is transmitted congenitally, through intimate contact, or via blood products. In the U.S., between 25 and 50 percent of apparently healthy heterosexuals, and over 90 percent of healthy homosexuals and bisexuals are seropositive. However, cytomegalovirus can virtually never be isolated from the heterosexual group; it is occasionally found in throat isolates, urine, or ejaculates of the homosexuals and bisexuals. After infection, the virus remains dormant in the leukocytes. When the immune response is suppressed, the virus may be reactivated and cause clinical symptoms. Fever, marked neutropenia, and lymphopenia, as well as various combinations of diffuse interstitial pneumonia, ulcerative gastrointestinal lesions, retinitis, hepatitis, maculopapular rash, thrombocytopenic purpura, and encephalitis may all be manifestations of CMV infection in AIDS patients.

Diagnosis. The presence of cytomegalovirus in the blood or of rising serologic titers does not prove that constitutional symptoms or specific disease processes are causally related. A characteristic histologic response in conjunction with viral isolation, immunofluorescence or other documentation of compatible viral particles in a biopsy specimen support a diagnosis of CMV disease (*Figure 10*).

Recommended treatment. No antiviral therapy is known to be effective.

Candida species

Patients commonly develop oral thrush prior to the documentation of Kaposi's sarcoma or of a life-threatening opportunistic infection. Thrush may also persist after AIDS is documented. Oral candidiasis is characterized by patches of gray or white pseudomembranes or by ulcers that can be painful or debilitating, interfering with nutritional intake.

Candida esophagitis is also common in AIDS and is often its presenting manifestation. Patients complain of dysphagia or retrosternal pain in the presence or absence of oral candidiasis. Endoscopy or an esophagram demonstrate mucosal erosions.

*Please see prescribing information, page 25.

Other candidal lesions of the skin, candidal cystitis, and disseminated *Candida* disease are uncommon in AIDS.

Diagnosis. The diagnosis of oral *Candida* is based on the presence of typical plaques or ulcers on the oral mucosal surfaces, and substantiated by demonstration of yeasts and pseudohyphae on smear. *Candida* esophagitis (*Figure 11*) is documented by demonstrating mucosal erosions by endoscopy or barium swallow and confirmed by demonstrating invasive *Candida* on esophageal biopsy.

Recommended treatment. Oral nystatin (5 x 10^5 units q4h), clotrimazole lozenges (1 q4h) or oral ketoconazole (100-200 mg q12h) are usually adequate to control oral thrush. *Candida* esophagitis should be treated with amphotericin B (100-150 mg I.V. over 7 to 10 days) since this disease process can cause life-threatening complications such as perforation or hemorrhage if not adequately treated.

Cryptococcus neoformans

Cryptococcus neoformans is a common airborne fungus that can cause disease in both immunocompetent and incompetent patients. Disseminated Cryptococcus can present as a chronic debilitating process characterized by various combinations of fever, pulmonary infiltrates, malaise, and weight loss. Meningitis can occur as an aspect of disseminated cryptococcosis or as a specific entity. The meningitis may present as an insidious personality change, an alteration of consciousness, a debilitating illness, or an acute form of the disease.

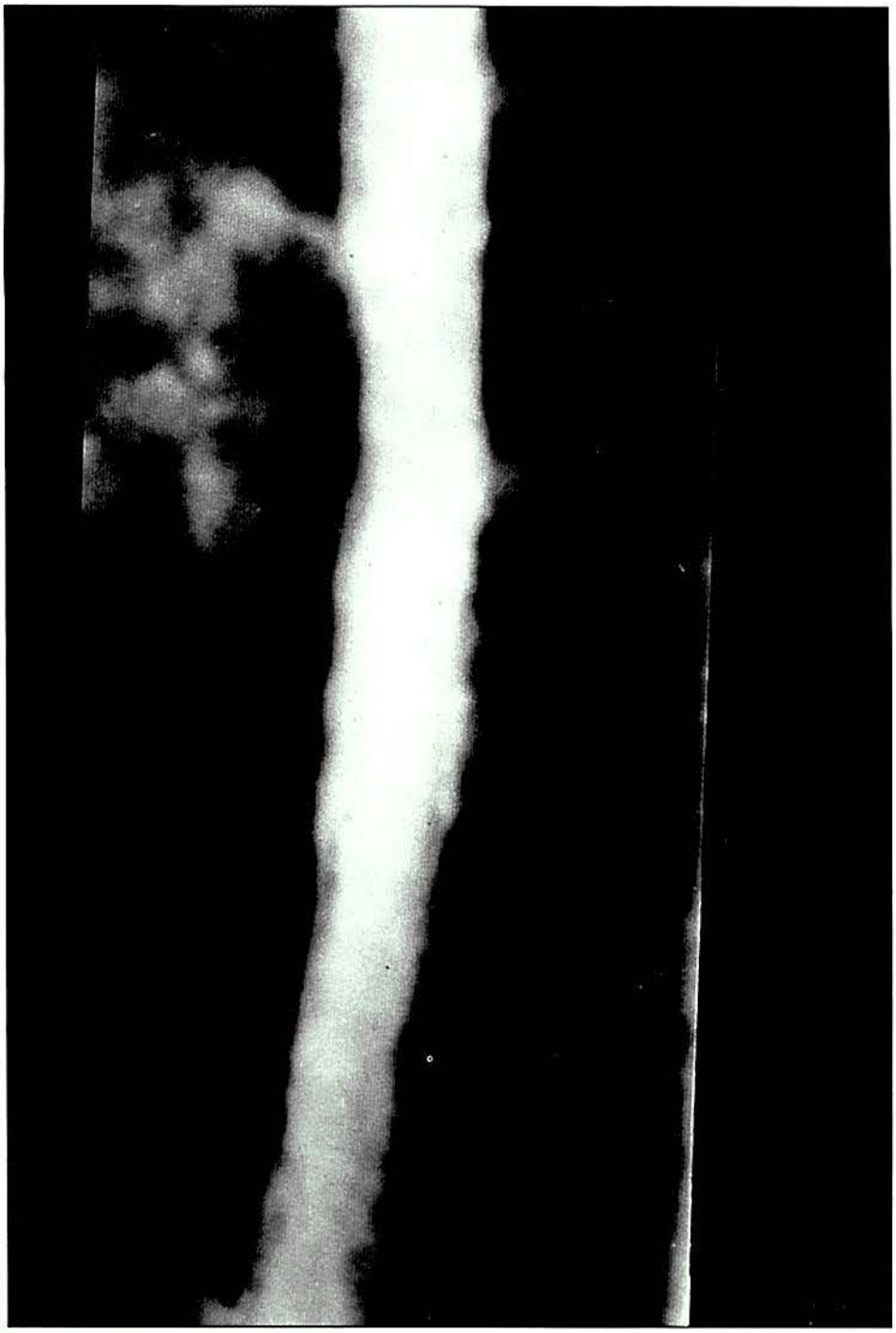


Figure 11. Barium swallow (esophagram) demonstrating esophageal mucosal ulcers secondary to Candida *esophagitis.*

In patients with AIDS, the CSF findings in untreated patients are usually not subtle. Yeast can be seen on India ink stain, the cryptococcal antigen is high, and the CSF protein is elevated, while glucose is severely depressed. White blood cells may or may not be present.

Diagnosis. Cryptococci must be demonstrated by culture or India ink preparation in cerebrospinal fluid, blood, sputum, urine, or biopsy specimen (*Figure 12*). An elevated CSF cryptococcal antigen titer is also diagnostic.

Recommended treatment. Amphotericin B (0.6 mg/kg/day) or amphotericin B (0.3 mg/kg/day) with flucytosine (125 mg/kg/day P.O. divided into four doses) for a total of at least 42 days is the standard therapy. In many AIDS patients, leukopenia makes administration of flucytosine difficult because of the drug's myelosuppressive effects. Response to therapy is often poor and relapses are common. Flucytosine should be used with caution in patients with impaired renal function.

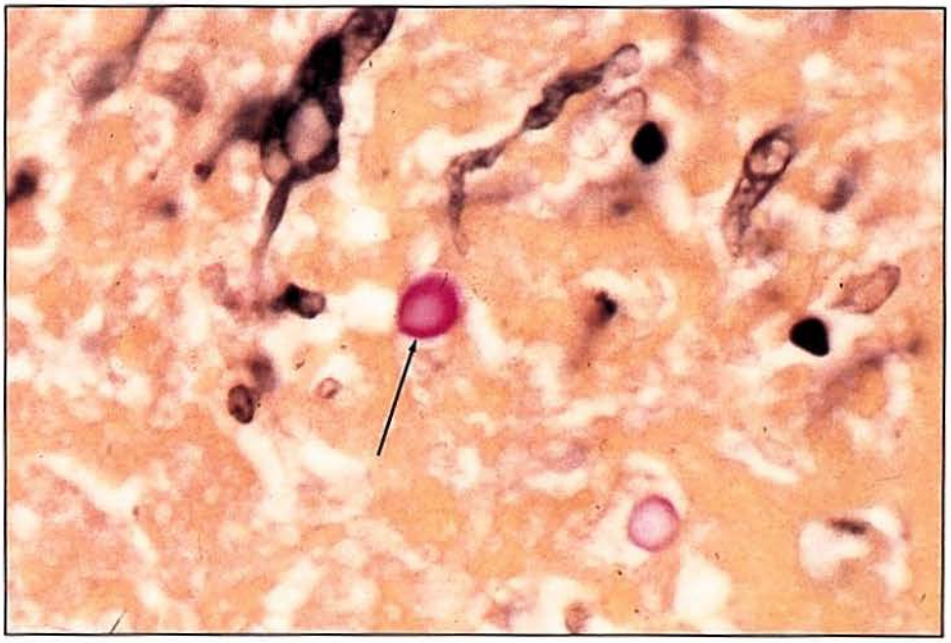


Figure 12. Lung biopsy demonstrating mucicarmine positive encapsulated yeast of Cryptococcus neoformans (*mucicarmine stain*).

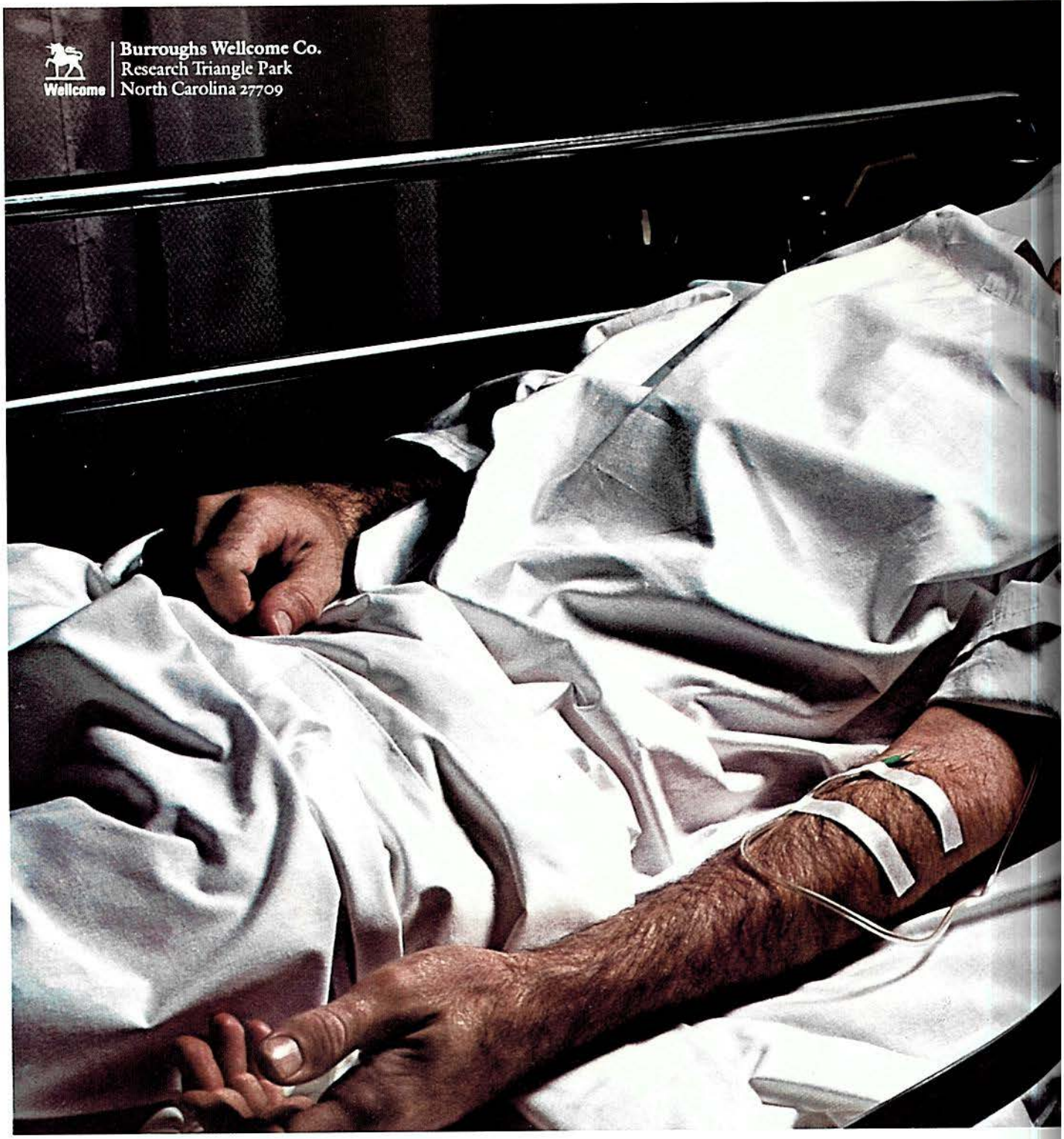
Toxoplasma gondii

Toxoplasma gondii is a protozoan that infects 20 to 40 percent of the adult population in the U.S. After initial infection via raw meat or cat feces, the Toxoplasma cysts lie dormant in the brain or muscle, contained by cell-mediated immune response. With severe immunosuppression, the cysts become metabolically active, tachyzoites invade surrounding tissue, and significant disease occurs.

Presenting signs and symptoms include fever, local neurologic signs, and often obtundation. Toxoplasmosis most commonly presents in AIDS patients as a cerebral mass lesion which is contrast-enhancing on computerized tomography. Dissemination to other organs has also been demonstrated.

Diagnosis. Serology has not been useful for diagnosing toxoplasmosis in AIDS. Diagnosis depends on demonstrating the tachyzoite in tissue sections, or on isolating the organism via intraperitoneal mouse injections from a tissue that does not ordinarily contain the dormant cyst.

Recommended treatment. Sulfadiazine (1g q6h P.O.) and pyrimethamine (25 mgqd P.O. after 75 mg P.O. initial dose). This combination should be given for a prolonged period the duration of which should be determined by the patient's clinical response. The efficacy of this treatment for AIDS patients is uncertain.



SEPTRA I.V. Infusion works decisively *in vitro*† SEPTRA I.V. is effective against a wide range of susceptible organisms: *Pneumocystis carinii*,‡ *E. coli*, *Klebsiella* sp, *Enterobacter* sp, *H. influenzae*,§ *S. pneumoniae*,§ *P. mirabilis*, indole-positive *Proteus* sp (*P. rettgeri* and *P. vulgaris*), *Morganella morganii*, and *Shigella* sp (*S. flexneri*, *S. sonnei*). SEPTRA complements the *in vitro* activity of other antimicrobials for expanded spectrum.

SEPTRA I.V. Infusion works decisively *in vivo*

URINARY TRACT INFECTION—clinically useful in severe or complicated infections of the urinary tract due to susceptible organisms.

†*In vitro* data do not necessarily correlate with clinical results.

‡Data from animal studies only.

§There are little clinical data on the use of SEPTRA I.V. in serious systemic infections due to *H. influenzae* and *S. pneumoniae*.

PNEUMOCYSTIS CARINII PNEUMONITIS—clinically effective in both children and adults with this life-threatening infection.

SHIGELLOSIS—clinically useful for enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* in both children and adults.

Serious infections* demand decisive action

SEPTRA® I.V.
(trimethoprim-sulfamethoxazole)
INFUSION

delivers decisive therapy

SEPTRA I.V. Infusion works decisively in body fluids
SEPTRA provides *high serum levels* which surpass the MICs of susceptible organisms.[1] Renal excretion of SEPTRA assures *high urine concentrations.*

**Pneumocystis carinii* pneumonitis, severe or complicated urinary tract infections and shigellosis.

Please see prescribing information, page 23.

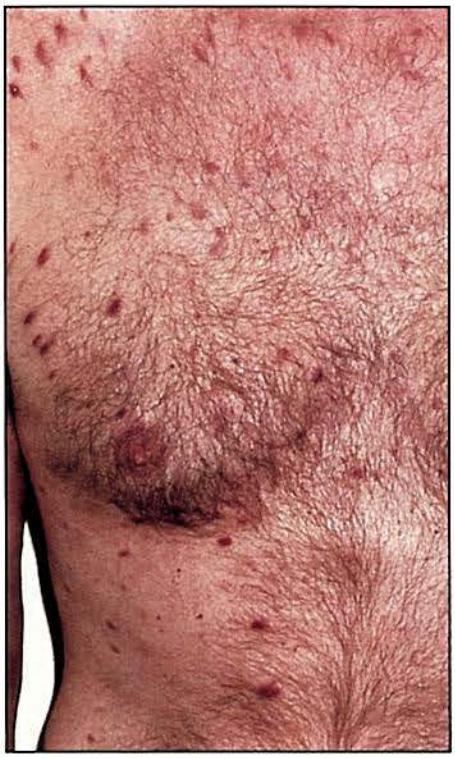
Neoplasms common in AIDS

Kaposi's sarcoma

Kaposi's sarcoma has been recognized since 1872 as an indolent tumor of endothelial cell origin which occurs in older men of Mediterranean descent. In North America, until the late 1970s, this malignant neoplasm was an uncommon tumor that rarely became disseminated or adversely affected longevity. A few cases of aggressive Kaposi's sarcoma were recognized in immunodeficient patients and in individuals with other malignant neoplasms, particularly Hodgkin's disease. Of interest was the observation that kidney transplant recipients who developed Kaposi's sarcoma often experienced tumor regression if their immunosuppressive chemotherapy was terminated. This suggested that immunosuppression might play a permissive role in allowing this tumor to develop.

In Africa, Kaposi's sarcoma has had a different clinical presentation. It is common in young men living in areas where Burkitt's lymphoma is endemic. In contrast to the North American form of the tumor, African Kaposi's sarcoma is rapidly progressive, with a very poor prognosis.

In the late 1970s, clinicians in New York and California noted a sudden increase in the frequency of Kaposi's sarcoma. An alarming number of cases were seen in younger men, almost all of whom were homosexual. This "new" Kaposi's sarcoma was a rapidly progressive process which was multifocal. The skin, mucous membranes, and gastrointestinal tract were frequent sites of involvement. A small fraction of patients developed life-threatening visceral involvement due to massive tumor infiltration of the lung, brain, or gastrointestinal tract. To date, most cases of Kaposi's sarcoma in AIDS have occurred in male homosexuals, though a few cases have been documented in male drug abusers and in Haitians of both sexes. The majority of patients develop life-threatening opportunistic infections if followed long enough.



Kaposi's sarcoma in AIDS can progress rapidly, involving the skin, mucous membranes and viscera.

Patients who present with Kaposi's sarcoma alone appear to be less severely immunosuppressed than are patients who initially present with opportunistic infection. They often do not develop severe opportunistic infections until many months after recognition or after the initial opportunistic infection.

Why Kaposi's sarcoma is so common in AIDS is unclear. There is considerable evidence associating the disease with cytomegalovirus. One hypothesis is that Kaposi's sarcoma is a multicentric process caused by CMV transformation of endothelial cells, permitted by the immunosuppression associated with AIDS.

Diagnosis. Kaposi's sarcoma is diagnosed on the basis of characteristic histopathology. Skin and mucous membrane lesions are often, but not invariably, firm nodules. They usually are of a characteristic purple hue (*Figures 13 and 14*).

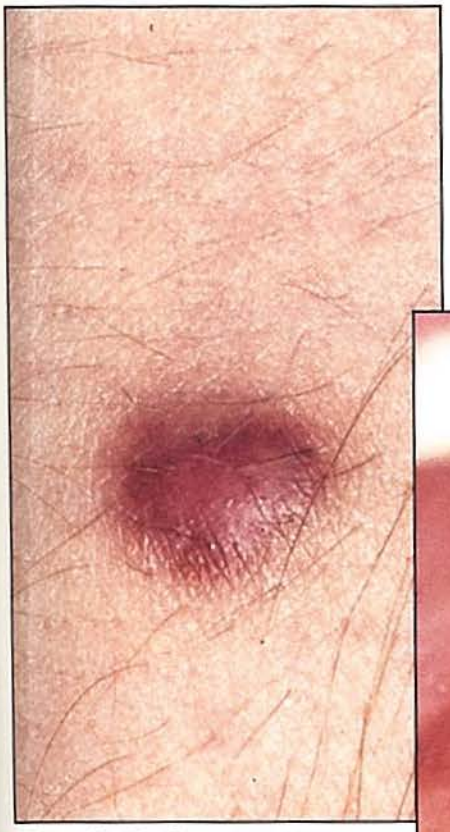


Figure 13. Erythematous cutaneous nodule of Kaposi's sarcoma.

Recommended treatment. Kaposi's sarcoma associated with AIDS is currently being treated with cytotoxic chemotherapeutic regimens and various immunostimulants, including alpha-interferon, gamma-interferon, and interleukin-2. The cytotoxic therapy has frequently been complicated by life-threatening opportunistic infection. Efficacy of the chemotherapy and the immunostimulants has not yet been adequately assessed.

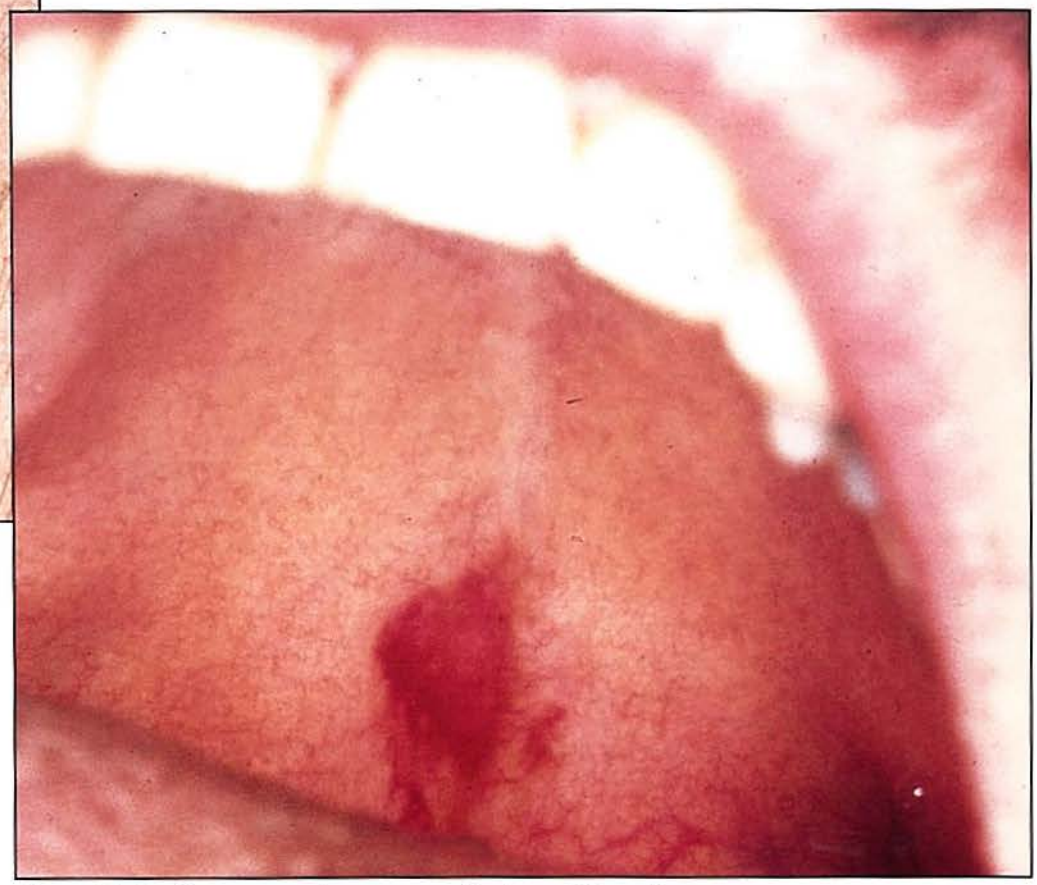


Figure 14. Erythematous palatal mucosal lesion of Kaposi's sarcoma.

Other tumors

Over a dozen cases of Burkitt's lymphoma (*Figure 15*) have been reported in young homosexual men. This appears to be an unusually high number for this age group, although accurate statistics are unavailable. An unusually high proportion of these cases has been associated with Epstein-Barr virus, either by isolation techniques or through nuclear antigen staining. The association of Kaposi's sarcoma with another herpes virus, CMV, has stimulated speculation about the potential role immunosuppression might play in permitting these viruses to cause tumors.

Colonic carcinoma, oropharyngeal carcinomas, and non-Hodgkin's lymphomas have been reported in homosexual patients who appear to have the same immunologic and clinical profile as those with AIDS. Non-Hodgkin's lymphoma confined to the central nervous system has the strongest association with AIDS. Awareness of these various malignancies may be due to improved reporting by physicians, but it seems likely that some tumors other than Kaposi's sarcoma and central nervous system lymphoma do occur with heightened frequency in AIDS patients.

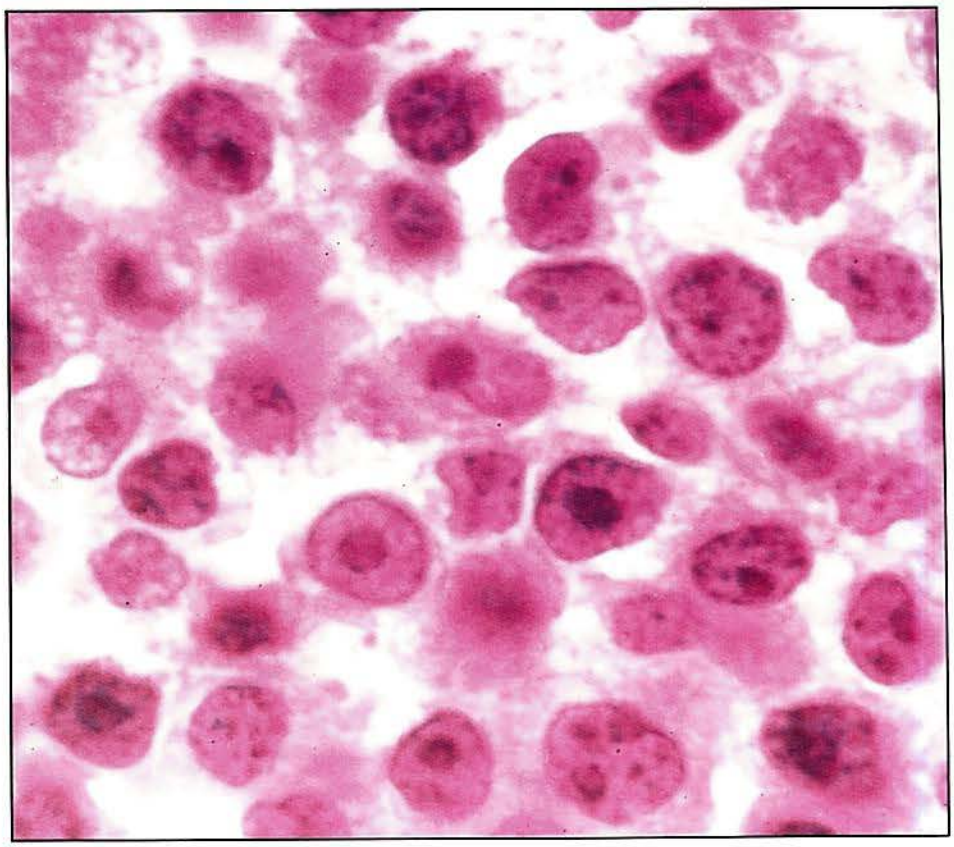


Figure 15. Lymph node biopsy demonstrating Burkitt's lymphoma (hematoxylin stain).

Over a dozen cases of Burkitt's lymphoma have been reported in young homosexual men.

Laboratory findings and immunologic profile

There is neither a serologic marker nor a diagnostic immunologic profile for AIDS. However, a characteristic pattern shows a modest anemia, leukopenia, and a normal or depressed platelet count. The differential count may reveal a severe lymphopenia. Bone marrow biopsy shows mild hypoplasia in some patients. Coagulation studies are usually normal.

Chemistry profiles in AIDS patients usually show mild transaminasemia, mild to severe hypoalbuminemia, and elevated triglyceride levels. Studies of adrenal and thyroid function are usually normal.

There are no characteristic radiographic findings. Routine abdominal CT scans may show modest splenomegaly and retroperitoneal lymphadenopathy in a few patients.

Immunologically, AIDS is characterized by a decrease in the number and function of helper/inducer ($T4^+$) T-lymphocytes.

Almost all AIDS patients shed cytomegalovirus in their throats and urine and almost all of those who have had a documented opportunistic infection show cytomegalovirus in their blood. Epstein-Barr virus can be recovered from the throat and peripheral leukocytes of most patients. A high proportion is ultimately found to harbor *Mycobacterium avium-intracellulare* in their bone marrow. Most have antibody to one or more hepatitis viruses.

Humoral immune function is not as markedly abnormal as cellular immune function. Circulating immunoglobulin levels (IgG, IgA, IgM) are usually normal or elevated and complement levels are normal. Antigenic challenges to assess humoral response show variable responses to recall antigens and decreased responses to primary challenges.

Immunologic features of patients with AIDS

1. Lymphopenia—predominantly due to a selective defect in the helper/inducer subset (OKT4, Leu-3) of T lymphocytes
2. Decreased *in vivo* T cell function
   - A. Susceptibility to neoplasms
   - B. Susceptibility to opportunistic infections
   - C. Decreased delayed-type hypersensitivity
3. Altered *in vitro* T cell function
   - A. Decreased blast transformation
   - B. Decreased alloreactivity
   - C. Decreased specific and non-specific cytotoxicity
   - D. Decreased ability to provide help to B lymphocytes
4. Polyclonal B cell activation
   - A. Elevated levels of total serum immunoglobulins and circulating immune complexes
   - B. Inability to mount a *de novo* serologic response to a new antigen
   - C. Increased numbers of spontaneous Ig secreting cells
   - D. Refractoriness to the normal *in vitro* signals for B cell activation

Typical immunologic profile of patients with AIDS

	Patients	Controls
Total lymphocyte count	<1,000/mm^3	1,500/mm^3
Total T lymphocytes	<1,000/mm^3	1,200/mm^3
Total helper/inducer T lymphocytes (T4+, Leu-3+)	<400/mm^3	800/mm^3
Total suppressor/cytotoxic T lymphocytes (T8+, Leu-2+)	400/mm^3	400/mm^3
Helper/suppressor ratio (T4/T8, Leu-3/Leu-2)	<1.0	>1.0
Skin test reactivity	Absent	Present
In vitro lymphocyte function		
Blast transformation to Phytohemagglutinin A	<25,000cpm	50,000cpm
Natural killer cell activity	<20% lysis	40% lysis
Immunoglobulin levels		
IgG	2,000mg/dl	1,200mg/dl
IgA	350mg/dl	240mg/dl
IgM	190mg/dl	190mg/dl
Other serologic abnormalities		
Circulating alpha-interferon	Present	Absent
Alpha$_1$-thymosin	>1,000pg/ml	<500pg/ml
B_2-microglobulin	>5.0mg/dl	<2.5mg/dl

Immunologically, patients with AIDS demonstrate lymphopenia due to a selective depletion in the helper/inducer (T4+ or Leu-3+) subset of T lymphocytes (see chart at left). This depletion of T4+ lymphocytes leads to a decrease in the ratio of helper to suppressor cells, the so-called T4/T8 or Leu-3/Leu-2 ratio. These T cell subsets are generally enumerated by measuring the binding of fluoresceinated monoclonal antibodies by the technique of fluorescence activated cell sorting (FACS). FACS patterns for an AIDS patient and a healthy control are shown in Figure 16. This decrease in the number of the T4+ lymphocytes is accompanied by profound abnormalities of both *in vivo* and *in vitro* T cell function.

While initially thought to be normal, the B lymphocytes or antibody-producing cells of patients have been found to be characterized by intense *in vivo* polyclonal activation. This polyclonal B cell activation, which is presumably due to viral transformation in the absence of normal regulatory T cells, influences results in normal or slightly elevated immunoglobulin levels, circulating immune complexes, and at times autoimmune phenomena.

In addition to these abnormalities of lymphocyte function, AIDS patients exhibit other serologic evidence of immunopathology including elevated levels of alpha$_1$-thymosin, B_2-microglobulin and acid-labile alpha-interferon.

As has been pointed out earlier, however, these immunologic abnormalities are not specific for AIDS and have been described not only in other disease states (predominantly viral infections) but in healthy homosexual men as well. There is currently no reliable blood test for AIDS.

Fluorescence activated cell sorting profile (FACS)

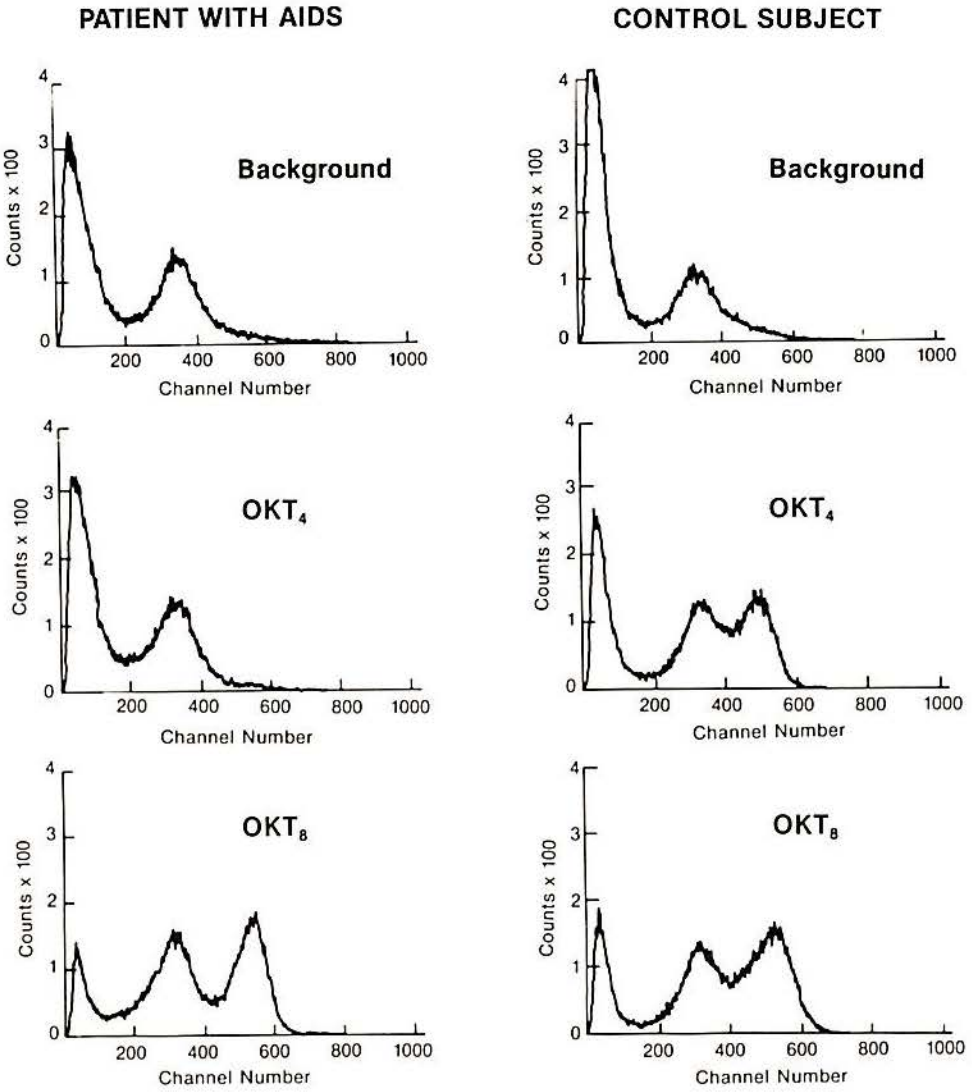


Figure 16. Fluorescence activated cell sorter analysis of peripheral blood mononuclear cells from an AIDS patient and a control. Non-specific binding of monoclonal antibody by monocytes is represented by the peak in the top two graphs. As can be seen, the peripheral blood mononuclear cells from AIDS patients are deficient in cells which bind the T4 mononuclear monoclonal antibody while T8+ cells are present.

Channel number refers to the fluorescence intensity while counts × 100 correspond to the number of cells exhibiting a given amount of fluorescence.

AIDS: A spectrum of disorders

Successful treatment of AIDS would logically be based on reconstitution of immunologic function.

ALTHOUGH AIDS is currently defined on the basis of documented opportunistic infection or Kaposi's sarcoma, the inescapable conclusion of clinical and immunologic studies in wider population groups suggests that there is a broad spectrum of related disorders. The recent appearance of large numbers of homosexual men with unexplained generalized lymphadenopathy and immunologic profiles similar to AIDS patients suggests that these symptoms may be part of the same syndrome. They may represent an early form of AIDS or a different host response to the AIDS agent. Studies of asymptomatic homosexuals and hemophiliacs have also demonstrated a striking frequency of immunologic defects similar to those found in patients with AIDS. Whether the patients with lymphadenopathy or the asymptomatic subjects with abnormal immunologic profiles will eventually develop AIDS is uncertain. Prospective studies are needed to determine this important issue.

AIDS can be transmitted by blood products and probably through sexual contact with individuals who are developing AIDS but have not yet manifested symptoms, opportunistic infection, or tumor lesions. This potential transmission by asymptomatic persons raises substantial public health problems for blood banks and for sexually active individuals of both sexes. There is no serologic or immunologic method for identifying AIDS patients or pre-AIDS patients, so it is extraordinarily difficult to prevent transmission. A serologic marker for AIDS is desperately needed.

Successful treatment of AIDS would logically be based on reconstitution of immunologic function in addition to the treatment of specific infections and tumors, which will continue to develop as long as the patient is immunosuppressed. Current investigations involve the use of interferon, interleukin-2, cell transfers, bone marrow transplantation and plasmapheresis, often in combination with antiviral drugs. None of these therapies has yet shown success in reversing immunologic dysfunction and altering the clinical course. This leaves the clinician in the uncomfortable position of treating infections and tumors as they occur, with the knowledge that ultimately an untreatable viral, mycobacterial, protozoal, or other microbial pathogen will eventually kill the patient, usually within 18 to 24 months after the initial opportunistic infection is documented, or within 24 to 48 months after documentation of an initial Kaposi's sarcoma lesion.

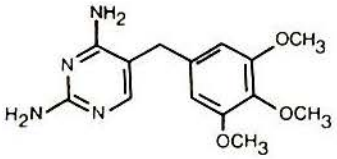
Further understanding of the immunoregulatory defects in AIDS and the cause of this defect are needed if a successful therapeutic regimen is to be developed that would reverse the grim prognosis currently facing AIDS patients.

SEPTRA®
I.V. INFUSION
(TRIMETHOPRIM-SULFAMETHOXAZOLE)

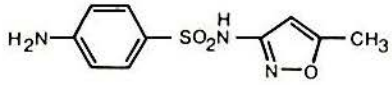
Wellcome

DESCRIPTION: Septra I.V. Infusion (trimethoprim-sulfamethoxazole), a sterile solution for intravenous infusion only, is a synthetic antibacterial combination product. Each 5 ml contains 80 mg trimethoprim* (16 mg/ml) and 400 mg sulfamethoxazole (80 mg/ml) compounded with 40% propylene glycol, 10% ethyl alcohol and 0.3% diethanolamine, 1% benzyl alcohol and 0.1% sodium metabisulfite added as preservatives, water for injection, and pH adjusted to approximately 10 with sodium hydroxide.

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3 and the following structural formula:



Sulfamethoxazole is *N*¹-(5-methyl-3-isoxazolyl)sulfanilamide. It is an almost white in color, odorless, tasteless compound with a molecular weight of 253.28 and the following structural formula:



CLINICAL PHARMACOLOGY: Following a one-hour intravenous infusion of a single dose of 160 mg trimethoprim plus 800 mg sulfamethoxazole to 11 patients whose weight ranged from 105 lbs. to 165 lbs. (mean, 143 lbs.), the mean peak plasma concentrations of trimethoprim and sulfamethoxazole were 3.4 ± 0.3 μg/ml and 46.3 ± 2.7 μg/ml, respectively. Following repeated intravenous administration of the same dose at eight-hour intervals, the mean plasma concentrations just prior to and immediately after each infusion at steady state were 5.6 ± 0.6 μg/ml and 8.8 ± 0.9 μg/ml for trimethoprim and 70.6 ± 7.3 μg/ml and 105.6 ± 10.9 μg/ml for sulfamethoxazole. The mean plasma half-life was 11.3 ± 0.7 hours for trimethoprim and 12.8 ± 1.8 hours for sulfamethoxazole. All of these 11 patients had normal renal function and their age ranged from 17 to 78 years (median, 60 years)[1].

Pharmacokinetic studies in children and adults suggest an age dependent half-life of trimethoprim as indicated in the following table.[2]

Age (yrs.)	No. of Patients	Mean TMP Half-life (hours)
< 1	2	7.67
1-10	9	5.49
10-20	5	8.19
20-63	6	12.82

Sulfamethoxazole exists in the blood as free, conjugated and protein-bound forms; trimethoprim is present as free and protein-bound and metabolized forms. The free forms are considered to be the therapeutically active forms. Approximately 44 percent of trimethoprim and 70 percent of sulfamethoxazole are protein-bound in blood. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim to an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Excretion of Septra is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. When administered together as in Septra, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Septra blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with Septra than with trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Septra includes common bacterial pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis*, indole-positive *Proteus* species, *Haemophilus influenzae (including ampicillin-resistant strains), Streptococcus pneumoniae, Shigella flexneri* and *Shigella sonnei*. It should be noted, however, that there are little clinical data on the use of Septra I.V. Infusion in serious systemic infections due to *Haemophilus influenzae* and *Streptococcus pneumoniae*.

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATION VALUES FOR SEPTRA SUSCEPTIBLE ORGANISMS (MIC-mcg/ml)

Bacteria	TMP Alone	SMX Alone	TMP/SMX (1:19)	
			TMP	SMX
Escherichia coli	0.05-1.5	1.0-245	0.05-0.5	0.95-9.5
Proteus species (indole positive)	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
Proteus mirabilis	0.5-1.5	7.35-30	0.05-0.15	0.95-2.85
Klebsiella-Enterobacter	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
Haemophilus influenzae	0.15-1.5	2.85-95	0.015-0.15	0.285-2.85
Streptococcus pneumoniae	0.15-1.5	7.35-24.5	0.05-0.15	0.95-2.85
Shigella flexneri†	< 0.01-0.04	< 0.16-> 320	< 0.002-0.03	0.04-0.625
Shigella sonnei†	0.02-0.08	0.625-> 320	0.004-0.06	0.08-1.25

TMP = Trimethoprim SMX = Sulfamethoxazole
†Rudoy, R.C., Nelson, J.D., Haltalin, K.C. Antimicrobial Agents and Chemotherapy 5:439-43, 1974.

The recommended quantitative disc susceptibility method may be used for estimating the susceptibility of bacteria to Septra.[3,4] With this procedure, a report from the laboratory of "Susceptible to trimethoprim-sulfamethoxazole" indicates that the infection is likely to respond to therapy with Septra. If the infection is confined to the urine, a report of "Intermediate susceptibility to trimethoprim-sulfamethoxazole" also indicates that the infection is likely to respond. A report of "Resistant to trimethoprim-sulfamethoxazole" indicates that the infection is unlikely to respond to therapy with Septra.

INDICATIONS AND USAGE:

PNEUMOCYSTIS CARINII PNEUMONITIS: Septra I.V. Infusion is indicated in the treatment of *Pneumocystis carinii* pneumonitis in children and adults.

SHIGELLOSIS: Septra I.V. Infusion is indicated in the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* in children and adults.

URINARY TRACT INFECTIONS: Septra I.V. Infusion is indicated in the treatment of severe or complicated urinary tract infections due to susceptible strains of *Escherichia coli, Klebsiella-Enterobacter* and *Proteus* sp. when oral administration of Septra is not feasible and when the organism is not susceptible to single agent antibacterials effective in the urinary tract.

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to Septra. Therapy may be initiated prior to obtaining the results of these tests.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Patients with documented megaloblastic anemia due to folate deficiency. Pregnancy at term and during the nursing period, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

Infants less than two months of age.

WARNINGS: SEPTRA I.V. INFUSION SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies have documented that patients with Group A, β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders.

PRECAUTIONS:

General: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Local irritation and inflammation due to extravascular infiltration of the infusion has been observed with Septra I.V. Infusion. If this occurs the infusion should be discontinued and restarted at another site.

Laboratory Tests: Appropriate culture and susceptibility studies should be performed before and throughout treatment. Complete blood counts should be done frequently in patients receiving Septra; if a significant reduction in the count of any formed blood element is noted, Septra should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: It has been reported that Septra may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with Septra I.V. Infusion.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with Septra. Observations of leukocytes obtained from patients treated with Septra revealed no chromosomal abnormalities.

Impairment of Fertility: Septra I.V. Infusion has not been studied in animals for evidence of impairment of fertility. However, studies in rats at oral dosages as high as 70 mg/kg trimethoprim plus 350 mg/kg sulfamethoxazole daily showed no adverse effects on fertility or general reproductive performance.

Pregnancy: Teratogenic Effects: Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim plus sulfamethoxazole in pregnant women, Brumfitt and Pursell[5] reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim plus sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim plus sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim plus sulfamethoxazole may interfere with folic acid metabolism, Septra I.V. Infusion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: See "CONTRAINDICATIONS" section.

Nursing Mothers: See "CONTRAINDICATIONS" section.

ADVERSE REACTIONS: The most frequent adverse reactions reported for Septra I.V. Infusion are nausea and vomiting, thrombocytopenia, and rash. These occurred in less than one in twenty patients. Local reaction, pain and slight irritation on I.V. administration are infrequent. Thrombophlebitis has rarely been observed. For completeness, all major reactions to sulfonamides and to trimethoprim are included below, even though they may not have been reported with Septra I.V. Infusion.

Allergic Reactions: Generalized skin eruptions, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, serum sickness, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Blood Dyscrasias: Megaloblastic anemia, hemolytic anemia, purpura, thrombopenia, leukopenia, agranulocytosis, aplastic anemia, hypoprothrombinemia and methemoglobinemia.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea, pseudomembranous colitis and pancreatitis.

C.N.S. Reactions: Headache, peripheral neuritis, mental depression, ataxia, convulsions, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

OVERDOSAGE: Since there has been no extensive experience in humans with single doses of Septra I.V. Infusion in excess of 25 ml (400 mg trimethoprim and 2000 mg sulfamethoxazole), the maximum tolerated dose in humans is unknown.

Use of Septra I.V. Infusion at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin 3 to 6 mg intramuscularly daily for three days, or as required to restore normal hematopoiesis.

Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating trimethoprim and sulfamethoxazole.

The LD_{50} of Septra I.V. Infusion in mice is 700 mg/kg or 7.3 ml/kg; in rats and rabbits the LD_{50} is > 500 mg/kg or > 5.2 ml/kg. The vehicle produced the same LD_{50} in each of these species as the active drug.

The signs and symptoms noted in mice, rats and rabbits with Septra I.V. Infusion or its vehicle at the high I.V. doses used in acute toxicity studies included ataxia, decreased motor activity, loss of righting reflex, tremors or convulsions, and/or respiratory depression.

DOSAGE AND ADMINISTRATION: (CONTRAINDICATED IN INFANTS LESS THAN TWO MONTHS OF AGE.) CAUTION—SEPTRA I.V. INFUSION MUST BE DILUTED IN 5% DEXTROSE IN WATER SOLUTION PRIOR TO ADMINISTRATION. DO NOT MIX SEPTRA I.V. INFUSION WITH OTHER DRUGS OR SOLUTIONS. RAPID OR BOLUS INJECTION MUST BE AVOIDED.

Children and Adults:

PNEUMOCYSTIS CARINII PNEUMONITIS: Total daily dose is 15 to 20 mg/kg (based on the trimethoprim component) given in three to four equally divided doses every 6 or 8 hours for up to 14 days. One investigator noted that a total daily dose of 10 to 15 mg/kg was sufficient in 10 adult patients with normal renal function.[6]

SEVERE URINARY TRACT INFECTIONS AND SHIGELLOSIS: Total daily dose is 8 to 10 mg/kg (based on the trimethoprim component) given in two to four equally divided doses every 6, 8 or 12 hours for up to 14 days for severe urinary tract infections and 5 days for shigellosis.

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Use Standard Regimen
15-30	½ the Usual Regimen
Below 15	Use Not Recommended

Method of Preparation: Septra I.V. Infusion must be diluted. EACH 5 ml SHOULD BE ADDED TO 125 ml OF 5% DEXTROSE IN WATER. After diluting with 5% dextrose in water the solution should not be refrigerated and should be used within 6 hours. If upon visual inspection there is cloudiness or evidence of crystallization after mixing, the solution should be discarded and a fresh solution prepared.

The following infusion sets have been tested and found satisfactory: unit-dose glass containers (McGaw Laboratories, Cutter Laboratories, Inc., and Abbott Laboratories); unit-dose plastic containers (Viaflex™ from Travenol Laboratories and Accumed™ from McGaw Laboratories). No other systems have been tested and therefore no others can be recommended.

NOTE: In those instances where fluid restriction is desirable, each 5 ml may be added to 75 ml of 5% dextrose in water. Under these circumstances the solution should be mixed just prior to use and should be administered within two (2) hours. If upon visual inspection there is cloudiness or evidence of crystallization after mixing, the solution should be discarded and a fresh solution prepared.

Administration: The solution should be given by intravenous infusion over a period of 60 to 90 minutes. Rapid infusion or bolus injections must be avoided. Septra I.V. Infusion should not be given intramuscularly.

HOW SUPPLIED: 5 ml ampuls, containing 80 mg trimethoprim (16 mg/ml) and 400 mg sulfamethoxazole (80 mg/ml) for infusion with 5% dextrose in water. Box of 10. (NDC-0081-0856-10)

10 ml vials, containing 160 mg trimethoprim (16 mg/ml) and 800 mg sulfamethoxazole (80 mg/ml) for infusion with 5% dextrose in water. Box of 10 (NDC-0081-0856-95)

STORE AT ROOM TEMPERATURE 15°-30°C (59°-86°F). DO NOT REFRIGERATE.

Also available in tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole (bottles of 100, 500 and 1000 tablets; unit dose pack of 100), oral suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each 5 ml (bottle of 473 ml; Unit of Use: bottle of 100 ml with child-resistant cap) and double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole (bottles of 100 and 250, unit dose pack of 100, and COMPLIANCE™ Pak of 20).

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BURROUGHS WELLCOME CO.
Research Triangle Park, N.C. 27709
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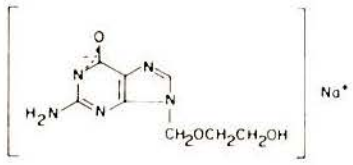
ZOVIRAX® Sterile Powder
(ACYCLOVIR SODIUM)
FOR INTRAVENOUS INFUSION ONLY

Wellcome

DESCRIPTION: Zovirax is the brand name for acyclovir, an antiviral drug active against herpesviruses. Zovirax Sterile Powder is a formulation for intravenous administration. Each vial of Zovirax Sterile Powder contains 549 mg of sterile lyophilized acyclovir sodium equivalent to 500 mg of acyclovir.

The chemical name of acyclovir sodium is 9-[(2-hydroxyethoxy)methyl] guanine sodium; it has the following structural formula:



Acyclovir sodium is a white, crystalline powder with a molecular weight of 247 daltons, and a solubility in water exceeding 100 mg/ml. Recommended reconstitution with 10 ml diluent per vial yields 50 mg/ml acyclovir (pH approximately 11). Further dilution in any appropriate intravenous solution must be performed before infusion (see Method of Preparation). At physiologic pH, acyclovir exists as the un-ionized form with a molecular weight of 225 daltons and a maximum solubility of 2.5 mg/ml at 37°C.

CLINICAL PHARMACOLOGY: Acyclovir is a synthetic, acyclic, purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against Herpes simplex, varicella-zoster, Epstein-Barr and cytomegalovirus. In cell cultures, the inhibitory activity of acyclovir for Herpes simplex virus is highly selective. Cellular thymidine kinase does not effectively utilize acyclovir as a substrate. Herpes simplex virus-coded thymidine kinase, however, converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase, and into triphosphate by a number of cellular enzymes.[1] Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[2] When incorporation occurs, the DNA chain is terminated.[3] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form.

The relationship between *in vitro* susceptibility of Herpes simplex virus to antiviral drugs and clinical response has not been established. The techniques and cell types used for determining *in vitro* susceptibility may influence the results obtained. With a quantitative assay to determine the acyclovir concentration producing 50% inhibition of viral cytopathic effect (ID_{50}), 28 HSV-1 clinical isolates had a mean ID_{50} of 0.17 μg/ml and 32 HSV-2 clinical isolates had a mean ID_{50} of 0.46 μg/ml. Results from other studies using different assays have yielded mean ID_{50} values for clinical HSV-1 isolates of 0.018, 0.03 and 0.043 μg/ml and for clinical HSV-2 isolates of 0.027, 0.36 and 0.03 μg/ml, respectively.[4,5,6]

Pharmacokinetics: The pharmacokinetics of acyclovir has been evaluated in 95 patients (9 studies). Results were obtained in adult patients with normal renal function during Phase I/II studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/M² or 500 mg/M² every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing.[7] When Zovirax was administered to adults at 5 mg/kg (approximately 250 mg/M²) by 1-hr infusions every 8 hours, mean steady-state peak and trough concentrations of 9.8 μg/ml (5.5 to 13.8 μg/ml) and 0.7 μg/ml (0.2 to 1.0 μg/ml), respectively, were achieved. Similar concentrations are achieved in children over 1 year of age when doses of 250 mg/M² are given every 8 hours. Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.[7]

Renal excretion of unchanged drug by glomerular filtration and tubular secretion is the major route of acyclovir elimination accounting for 62 to 91% of the dose as determined by ^{14}C labelled drug. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine. This may account for up to 14.1% of the dose in patients with normal renal function. An insignificant amount of drug is recovered in feces and expired CO_2, and there is no evidence to suggest tissue retention.[7] However, postmortem examinations have shown that acyclovir is widely distributed in tissues and body fluids including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

In a Phase I study in 3 adult volunteers, 1 g of probenecid was administered orally prior to a single 1-hour 5 mg/kg intravenous infusion of acyclovir. The acyclovir half-life and area under the plasma concentration-time curve increased by 18 and 40%, respectively, compared to a control infusion of acyclovir without probenecid. The mean urinary excretion of acyclovir decreased from 79% to 69% of the dose indicating that probenecid can influence the renal excretion of acyclovir.[8]

The half-life and total body clearance of acyclovir is dependent on renal function as shown below:[7]

Creatinine Clearance (ml/min/1.73M²)	Half-Life (hr)	Total Body Clearance (ml/min/1.73M²)
>80	2.5	327
50-80	3.0	248
15-50	3.5	190
0 (Anuric)	19.5	29

Zovirax was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 μg/ml and 0.7 μg/ml, respectively.

Consult DOSAGE AND ADMINISTRATION section for recommended adjustments in dosing based upon creatinine clearance.

The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE: Zovirax Sterile Powder is indicated for the treatment of initial and recurrent mucosal and cutaneous Herpes simplex (HSV-1 and HSV-2) infections in immunocompromised adults and children. It is also indicated for severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.

These indications are based on the results of several double-blind, placebo-controlled studies which evaluated the drug's effect on virus excretion, complete healing of lesions, and relief of pain.

Herpes Simplex Infections in Immunocompromised Patients
A multicenter trial of Zovirax Sterile Powder at a dose of 250 mg/M² every 8 hours (750 mg/M²/day) for 7 days was conducted in 97 immunocompromised patients with oro-facial, esophageal, genital and other localized infections (50 treated with Zovirax and 47 with placebo). Zovirax significantly decreased virus excretion, reduced pain, and promoted scabbing and rapid healing of lesions.[9,10,11]

Initial Episodes of Herpes Genitalis
A controlled trial was conducted in 28 patients with severe initial episodes of herpes genitalis with a Zovirax dosage of 5 mg/kg every 8 hours for 5 days (12 patients treated with Zovirax and 16 with placebo). Significant treatment effects were seen in elimination of virus from lesions and in reduction of healing times.[12]

In a similar study, 15 patients with initial episodes of genital herpes were treated with Zovirax 5 mg/kg every 8 hours for 5 days and 15 with placebo. Zovirax decreased the duration of viral excretion, new lesion formation, duration of vesicles and promoted more rapid healing of all lesions.[13]

Diagnosis
The use of appropriate laboratory diagnostic procedures will help to establish the etiologic diagnosis. Positive cultures for Herpes simplex virus offer a reliable means for confirmation of the diagnosis. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions associated with Herpes simplex infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[14]

CONTRAINDICATIONS: Zovirax Sterile Powder is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS: Zovirax Sterile Powder is intended for intravenous infusion only and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 (one) hour to prevent renal tubular damage (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

PRECAUTIONS:
General: The recommended dosage, frequency and length of treatment should not be exceeded (See DOSAGE AND ADMINISTRATION).

Although the aqueous solubility of acyclovir sodium (for infusion) is >100 mg/ml, precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/ml at 37°C in water) is exceeded or if the drug is administered by bolus injection. This complication causes a rise in serum creatinine and blood urea nitrogen (BUN), and a decrease in renal creatinine clearance. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Bolus administration of the drug leads to a 10% incidence of renal dysfunction, while in controlled studies, infusion of 5 mg/kg (250 mg/M²) over an hour was associated with a lower frequency—4.6%. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely. In most instances, alterations of renal function were transient and resolved spontaneously or with improvement of water and electrolyte balance, drug dosage adjustment or discontinuation of drug administration. However, in some instances, these changes may progress to acute renal failure.

ZOVIRAX® Sterile Powder (ACYCLOVIR SODIUM)

Administration of Zovirax by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in renal tubules.

When dosage adjustments are required they should be based on estimated creatinine clearance (See DOSAGE AND ADMINISTRATION).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma. Zovirax should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

Exposure of HSV isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in 6 severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered Zovirax. These occurred in patients with congenital severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness and, in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be borne in mind when treating such patients. The relationship between the *in vitro* sensitivity of herpesviruses to acyclovir and clinical response to therapy has yet to be established.

Drug Interactions: Co-administration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. Clinical experience has identified no other significant interactions resulting from administration of other drugs concomitantly with Zovirax Sterile Powder.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir appear to shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive lifetime bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system.

No chromosome damage was observed at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats or Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found in a dominant lethal study in mice. In 9 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 25 times the acyclovir plasma levels achieved in man.

Acyclovir does not impair fertility or reproduction in mice at oral doses up to 450 mg/kg/day. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c.) or rat (50 mg/kg/day, s.c.).

Although maximum tolerated doses were tested in the teratology studies, the plasma levels obtained did not exaggerate maximum plasma levels that might occur with clinical use of intravenous acyclovir.

There have been no adequate and well-controlled studies in pregnant women. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman.

ADVERSE REACTIONS: The most frequent adverse reactions reported during controlled clinical trials of Zovirax in 64 patients were inflammation or phlebitis at the injection site following infiltration of the I.V. fluid in 9 (14.0%); transient elevations of serum creatinine in 3 (4.7%); and rash or hives in 3 (4.7%). Less frequent adverse reactions were diaphoresis, hematuria, hypotension, headache and nausea, each of which occurred in 1 patient (1.6%). Of the 63 patients receiving placebo, 3 (4.8%) experienced inflammation/phlebitis and 3 (4.8%) experienced rash or itching. Hematuria and nausea were experienced by placebo recipients at the same frequency.

Among 51 immunocompromised patients, one, a bone marrow transplant recipient with pneumonitis, developed seizures, cerebral edema, coma and expired with changes consistent with cerebral anoxia on postmortem biopsy; another immunocompromised patient exhibited coarse tremor and clonus.

Additional adverse reactions were reported in uncontrolled trials. The most frequent adverse reaction was elevated serum creatinine. This occurred in 9.8 percent of patients, usually following rapid (less than 10 minutes) intravenous infusion. Less frequent adverse experiences were thrombocytosis and jitters, each in 0.4% of patients.

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma (see PRECAUTIONS).

OVERDOSAGE: No acute massive overdosage of the intravenous form has been reported.

Doses administered to humans have been as high as 1200 mg/M² (28 mg/kg) three times daily for up to two weeks. Peak plasma concentrations have reached 80 μg/ml. Precipitation of free acyclovir in renal tubules may occur when the solubility in the intratubular fluid is exceeded (see PRECAUTIONS). Acyclovir is dialyzable. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: CAUTION—RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED.

Dosage: ***MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS*****—**5 mg/kg infused at a constant rate over 1 hour, every 8 hours (15 mg/kg/day) for 7 days in adult patients with normal renal function. In children under 12 years of age, more accurate dosing can be attained by infusing 250 mg/M² at a constant rate over 1 hour, every 8 hours (750 mg/M²/day) for 7 days.

SEVERE INITIAL CLINICAL EPISODES OF HERPES GENITALIS**—**The same dose given above—administered for 5 days.

Therapy should be initiated as early as possible following onset of signs and symptoms.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT: Refer to DOSAGE AND ADMINISTRATION section for recommended doses, and adjust the dosing interval as indicated in the table below:

Creatinine Clearance (ml/min/1.73M²)	Dose (mg/kg)	Dosing Interval (hours)
>50	5	8
25-50	5	12
10-25	5	24
0-10	2.5	24

Hemodialysis: For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6 hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that a dose is administered after each dialysis.

Method of Preparation: Each 10 ml vial contains acyclovir sodium equivalent to 500 mg of acyclovir. The contents of the vial should be dissolved in 10 ml of sterile water for injection yielding a final concentration of 50 mg/ml of acyclovir (pH approximately 11). Shake the vial well to assure complete dissolution before measuring and transferring each individual dose.

Administration: The calculated dose should then be removed and added to any appropriate intravenous solution at a volume selected for administration during each 1 hour infusion. Infusion concentrations of approximately 7 mg/ml or lower are recommended. In clinical studies, the average 70 kg adult received approximately 60 ml of fluid per dose. Higher concentrations (e.g., 10 mg/ml) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not recommended.

Once in solution in the vial at a concentration of 50 mg/ml, the drug should be used within 12 hours. Once diluted for administration, each dose should be used within 24 hours. Refrigeration of reconstituted solutions may result in formation of a precipitate which will redissolve at room temperature.

HOW SUPPLIED: ZOVIRAX Sterile Powder is supplied in 10 ml sterile vials, each containing acyclovir sodium equivalent to 500 mg of acyclovir; carton of 25 (NDC 0081-0995-95). Store at 15°-30°C (59°-86°F).

Also available: ZOVIRAX Ointment, 5% in 15 g tubes. Each gram contains 50 mg acyclovir in a polyethylene glycol base.

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BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709 October 1982 647305

DARAPRIM®(PYRIMETHAMINE)

25 mg scored tablets

DESCRIPTION: Daraprim (Pyrimethamine) is chemically known as 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine. It is a tasteless and odorless substance.

ACTIONS: Daraprim is a folic acid antagonist and the rationale for its therapeutic action is based on the differential requirement between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against plasmodia and *Toxoplasma gondii*.

Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against malaria parasites of man. However, its blood schizonticidal activity may be slower than that of 4-aminoquinoline compounds. It does not destroy gametocytes, but arrests sporogony in the mosquito.

The action of Daraprim against *Toxoplasma gondii* is greatly enhanced when used in conjunction with sulfonamides. This was demonstrated by Eyles and Coleman in the treatment of experimental toxoplasmosis in the mouse. Jacobs *et al* demonstrated that combination of the two drugs effectively prevented the development of severe uveitis in most rabbits following the inoculation of the anterior chamber of the eye with toxoplasma.

INDICATIONS: Daraprim (Pyrimethamine) is indicated for the chemoprophylaxis of malaria due to susceptible strains of plasmodia. Fast-acting schizonticides (chloroquine, amodiaquin, quinacrine or quinine) are indicated and preferable for the treatment of acute attacks. However, conjoint use of Daraprim will initiate *transmission control* and *suppressive cure*.

Daraprim is also indicated for the treatment of toxoplasmosis. For this purpose the drug should be used conjointly with a sulfonamide since synergism exists with this combination.

WARNINGS: The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalarial dosage and approaches the toxic level. If signs of folic or folinic acid deficiency develop (see Adverse Reactions) reduce the dosage or discontinue the drugs according to the response of the patient. Folinic acid (leucovorin) may be administered in a dosage of 3 to 9 mg intramuscularly daily for 3 days, or as required to produce a return of depressed platelet or white blood cell counts to safe levels.

Patients should be warned to keep Daraprim out of the reach of children since accidental ingestion has led to fatality.

Use in Pregnancy: Pyrimethamine, like other folic acid antagonists, may, in large doses, produce teratogenic effects in laboratory animals. The large doses required to treat toxoplasmosis should be used only after a definitive diagnosis of acute toxoplasmosis has been made, and the possibility of teratogenic effects from the drug has been carefully weighed against the possible risks of permanent damage to the fetus from the infection.

Concurrent administration of folinic acid is recommended when pyrimethamine is used for treatment of toxoplasmosis during pregnancy.

PRECAUTIONS: The recommended dosage for malaria suppression should not be exceeded. In patients receiving high dosage, as for the treatment of toxoplasmosis, semi-weekly blood counts, including platelet counts, should be made. In patients with convulsive disorders a small "starting" dose (for toxoplasmosis) is recommended to avoid the potential nervous system toxicity of pyrimethamine.

DARAPRIM® (PYRIMETHAMINE)

ADVERSE REACTIONS: With large doses, anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with meals; it usually disappears promptly upon reduction of dosage. Also, large doses as used in toxoplasmosis may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia and atrophic glossitis. Acute intoxication may follow the ingestion of an excessive amount of pyrimethamine; this may involve central nervous system stimulation including convulsions. In such cases a parenteral barbiturate may be indicated followed by folinic acid (leucovorin).

DOSAGE AND ADMINISTRATION:

For Chemoprophylaxis of Malaria:

Adults and children over 10 years — 25 mg (1 tablet) once weekly
Children 4 through 10 years — 12.5 mg ($\frac{1}{2}$ tablet) once weekly
Infants and children under 1 years — 6.25 mg ($\frac{1}{4}$ tablet) once weekly

Regimens planned to include *suppressive cure* should be extended through any characteristic periods of early recrudescence and late relapse for at least 10 weeks in each case.

For Treatment of Acute Attacks: Daraprim is recommended in areas where only susceptible plasmodia exist. This drug is not recommended alone in the treatment of acute attacks of malaria in nonimmune persons. Fast-acting schizonticides (chloroquine, amodiaquin, quinacrine or quinine) are indicated for treatment of acute attacks. However, conjoint Daraprim dosage of 25 mg daily for two days will initiate *transmission control* and *suppressive cure*. Should circumstances arise wherein Daraprim must be used alone in semi-immune persons, the adult dosage for an acute attack is 50 mg daily for 2 days; children 4 through 10 years old may be given 25 mg daily for 2 days. In any event, clinical cure should be followed by the once-weekly regimen described above.

For Toxoplasmosis: The dosage of Daraprim (Pyrimethamine) in the treatment of toxoplasmosis must be carefully adjusted so as to provide maximum therapeutic effect and a minimum of side effects. At the high dosage required, there is a marked variation in the tolerance to the drug. Young patients may tolerate higher doses than older individuals.

The adult *starting* dose is 50 to 75 mg of the drug daily, together with 1 to 4 g daily of a sulfonamide drug of the sulfapyrimidine type, e.g., sulfadiazine, triple-sulfa. This dosage is ordinarily continued for 1 to 3 weeks, depending on the response of the patient and his tolerance of the therapy. The dosage may then be reduced to about one-half that previously given for each drug and continued for an additional 4 or 5 weeks.

The pediatric dosage of Daraprim is 1 mg/kg per day divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one-half and continued for approximately one month. The usual pediatric sulfonamide dosage is used in conjunction with Daraprim.

HOW SUPPLIED: Bottles of 100.

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RESEARCH TRIANGLE PARK, N.C. 27709

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