

# Medical Progress

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## Gastrointestinal Manifestations of the Acquired Immunodeficiency Syndrome

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*In addition to abnormalities in systemic immune function, patients with the acquired immunodeficiency syndrome (AIDS) and the pre-AIDS syndromes have significant abnormalities in the distribution of T-cell subsets in the intestinal tract. Such immune deficits predispose such patients to opportunistic infections and tumors, many of which involve the gastrointestinal tract. For example, Candida albicans often causes stomatitis and esophagitis. Intestinal infections with parasites (Cryptosporidium, Isospora belli, Microsporidia) or bacteria (Mycobacterium avium-intracellulare) are associated with severe diarrhea and malabsorption, whereas viruses like cytomegalovirus and herpes simplex virus cause mucosal ulcerations. Clinically debilitating chronic diarrhea develops in many AIDS patients for which no clear cause can be identified. Enteric pathogens like Salmonella and Campylobacter can be associated with bacteremias. Kaposi's sarcoma and lymphoma involving the intestinal tract are now well-recognized complications of AIDS. Although AIDS is not associated with a pathognomonic liver lesion, opportunistic infections and Kaposi's sarcoma or lymphoma may involve the liver.*

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The acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a retrovirus that is lymphotropic for T cells.<sup>1,2</sup> This virus specifically attacks and depletes the T-helper-cell population.<sup>3</sup> Because of the central role of T-helper cells in the regulation of other components of the cellular immune system, infection with HIV indirectly impairs a broad array of immune reactions.<sup>4</sup> Documented immunologic abnormalities in AIDS have included lymphopenia,<sup>5</sup> a decrease in the ratio of T-helper to T-suppressor cells,<sup>6</sup> a decreased number of T-helper cells,<sup>7</sup> depressed T-cell blastogenesis to mitogens and antigens,<sup>8</sup> diminished cytotoxic cell responses,<sup>9</sup> impaired lymphokine production,<sup>10</sup> defects of monocyte chemotaxis and phagocytosis<sup>11</sup> and activation of B cells with resultant polyclonal gammopathy.<sup>12</sup> These abnormalities, alone and in combination, impair a host's immunocompetence and render the host susceptible to the development of severe opportunistic infections and rare malignant conditions.<sup>13</sup> In AIDS, almost every organ system including the gastrointestinal tract has been involved with unusual infections and malignant disorders. In this paper, we review the immunologic and clinical

manifestations of HIV-induced disease in the gastrointestinal tract.

### The Intestinal Immune System

Homosexual men have an increased incidence of sexually transmitted enteric infections,<sup>14</sup> and, in patients with AIDS, severe intestinal infections with unusual organisms such as *Cryptosporidium*, *Isospora belli* and *Mycobacterium avium-intracellulare* have been reported.<sup>15</sup> We recently examined changes in the distribution of T cells and other mononuclear cells in the intestinal tract of groups of homosexual men, including those with AIDS.<sup>16</sup> None of these men had chronic diarrhea at the time of evaluation, although many did have a history of diarrhea. Subjects were stratified into four groups: healthy homosexual men, homosexual men with the lymphadenopathy syndrome or those with AIDS and healthy heterosexual controls.

As summarized in Table 1, mononuclear cells were significantly increased in the small intestinal mucosa of persons with AIDS and the lymphadenopathy syndrome. In contrast, the same persons had a significant decrease in total T cells in

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## ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli  
 AIDS = acquired immunodeficiency syndrome  
 CMV = cytomegalovirus  
 HIV = human immunodeficiency virus  
 HSV = herpes simplex virus

the intestinal mucosa. This decrease most severely affected the T-cell subset identified by the Leu 3a monoclonal antibody that recognizes the CD4 antigen on T-helper/inducer cells (Figure 1). In addition, subjects with the lymphadenopathy syndrome and with AIDS had a significant decrease in the ratio of mucosal and circulating helper/suppressor T cells (Table 1, Figure 2). The proportion of mucosal T cells identified by Leu 2a, a monoclonal antibody that recognizes the CD8 antigen on cytotoxic/suppressor T cells, was significantly increased only in AIDS subjects (Table 1). In healthy homosexual men the ratio of mucosal helper/suppressor T cells was normal, but the circulating ratio was decreased (Table 1, Figure 2). These findings suggest that mucosal immune abnormalities may contribute to the development of intestinal and systemic opportunistic infections and perhaps to neoplastic disease in patients with HIV-induced disease. Although it was suggested that a decreased number of immunoglobulin A plasma cells in the intestinal mucosa of patients with AIDS may predispose them to infection,<sup>17</sup> a decreased number of IgA plasma cells was not found in the above group of homosexual men with AIDS (D. Kaiserlian, PhD; V. Rodgers, MD, and M. Kagnoff, MD, unpublished observations, July 1985).

**Candida albicans**

*Candida albicans* is a frequent opportunistic infection in immunocompromised hosts. Gastrointestinal infection in such persons can involve various mucosal surfaces.<sup>18</sup> *Candida* esophagitis, but not oral candidiasis, is an opportunistic infection that meets the surveillance criteria for AIDS.

Oral candidiasis often is a harbinger for the subsequent development of AIDS in persons at high risk, and such patients may have severe immune deficits.<sup>19</sup> Oral lesions occur as patchy pseudomembranes or ulcers that are painful and debilitating.<sup>20</sup> Recommended treatment includes administering clotrimazole troches, five times per day for seven to ten days, or nystatin suspension, 500,000 units four to six times a day.<sup>20</sup> Patients whose lesions are refractory to this therapy may be given ketoconazole, 200 to 400 mg daily for ten days.

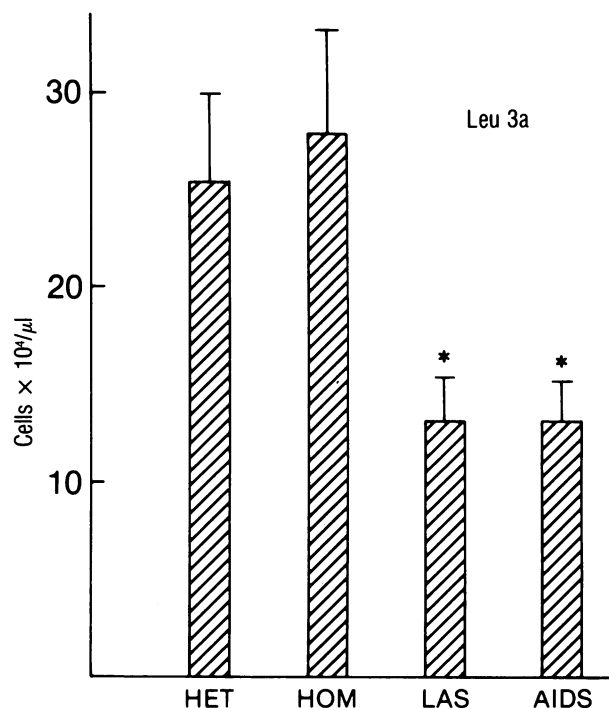
*Candida* esophagitis is seen frequently in patients with AIDS.<sup>21(pp101-103)</sup> Odynophagia, dysphagia and burning associated with swallowing are common symptoms. Patients occasionally present with upper gastrointestinal tract bleeding or esophageal perforation. Diagnosis using radiographic techniques can be difficult because of the superficial nature of the mucosal abnormality. Even with the use of double-contrast barium studies of the esophagus (Figure 3), a sensitivity of only 80% is achieved.<sup>22</sup> Typically, x-ray films show mucosal plaques that consist of raised areas of necrotic epithelial debris or actual colonies of the organisms. These plaques may be diffuse and produce linear or irregular filling defects with intervening segments of normal mucosa. Clinically unmistakable ulcerations may be seen with more dense disease. Unfor-

tunately, the radiographic appearance is not specific and can be mimicked by various other lesions including reflux esophagitis, herpes simplex esophagitis and cytomegalovirus esophagitis.

Endoscopic evaluation and biopsy are required to confirm a diagnosis of *Candida* esophagitis. Esophagoscopy typically shows linear ulcers and overlying exudate that usually is distributed throughout the esophagus.<sup>23</sup> Biopsy specimens showing acute and chronic inflammation with the presence of mycelia are diagnostic.<sup>23</sup>

One study of ketoconazole therapy in AIDS patients with *Candida* esophagitis showed poor resolution, even with as long as six months of therapy, although patients did note symptomatic improvement.<sup>24</sup> Oral lesions may resolve despite the persistence of esophageal lesions. Thus, neither resolution of symptoms nor oral lesions can be used to judge the efficacy of therapy. Short courses of amphotericin B at doses of 100 to 150 mg given intravenously for five to seven days are recommended for refractory cases. Topical therapy for *Candida* esophagitis is not adequate.

*Candida* enteritis is rare in patients with AIDS, with only one case reported.<sup>25</sup> That patient presented with watery diarrhea and oral and anal involvement with candidiasis. Small bowel radiographs revealed a dilated ileum with mildly thickened folds. Perforation and peritonitis subsequently developed. On autopsy extensive ulceration of the ileum due to *Candida* and multiple sites of perforation were noted. Disseminated candidiasis has been reported in patients with underlying malignant disorders and neutropenia and frequently



**Figure 1.**—Phenotypic analysis of intestinal mucosal lymphocyte populations using the Leu 3a monoclonal antibody in healthy heterosexual men (HET), healthy homosexual men (HOM), men with the lymphadenopathy syndrome (LAS) and those with the acquired immunodeficiency syndrome (AIDS). An asterisk indicates a significant difference from healthy heterosexual subjects ( $P < .05$ ). Values represent mean  $\pm$  standard error of the mean.

is associated with gastrointestinal ulceration.<sup>26</sup> In AIDS patients, however, disseminated candidiasis has been rare.

**Intestinal Parasites**

*Cryptosporidium*

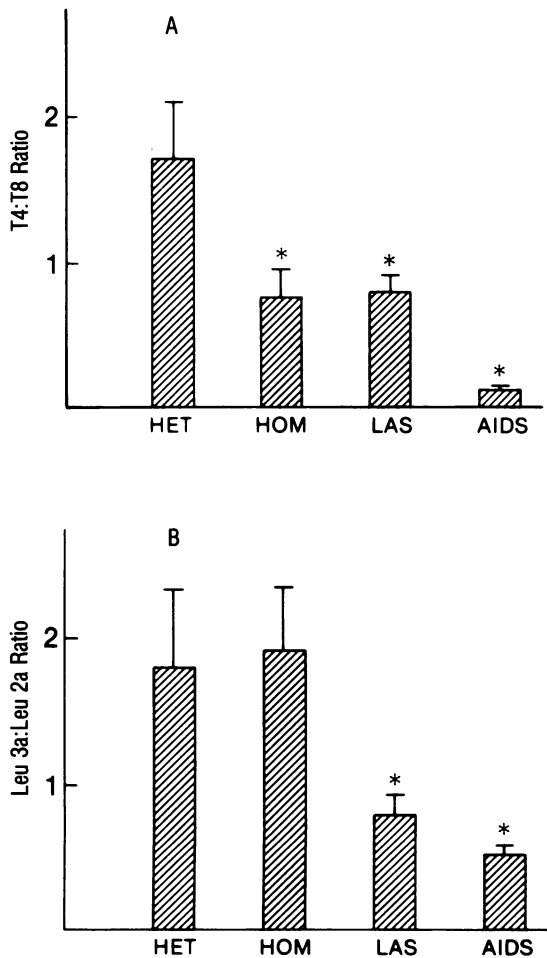
*Cryptosporidium muris*, a coccidial protozoan, was initially recognized in the gastric glands of mice.<sup>27</sup> Subsequently, the same organism has been reported to infect other animals including calves,<sup>28</sup> turkeys,<sup>29</sup> foals<sup>30</sup> and lambs.<sup>31</sup> *Cryptosporidium* in humans undergoes sexual and asexual stages of development within the mucosa of the small and large intestine. Subsequently, it produces oocysts that are excreted in the stool and that can infect another host.<sup>32</sup>

*Cryptosporidium* increasingly is being recognized as a pathogen in immunocompetent hosts, especially those with animal contact.<sup>33</sup> This organism is spread by the fecal-oral route. A survey of immunologically normal patients in hospital with gastroenteritis showed that 4.1% excreted *Cryptosporidium* oocysts in their feces.<sup>34</sup> Children had a higher infection rate (7%) than adults (1.6%). In an immunocompe-

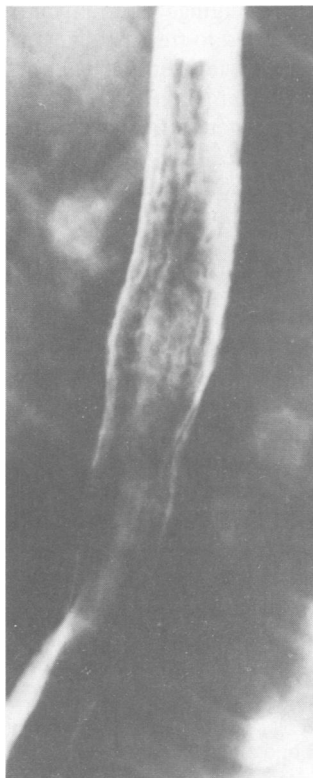
tent host, *Cryptosporidium* typically causes a self-limited flu-like illness, with diarrhea as its prominent symptom. Therapy is not required. In contrast, reports of infection with *Cryptosporidium* in patients with humoral and cellular immunodeficiencies and in those undergoing immunosuppressive therapy have documented a chronic and severe diarrheal illness.<sup>35,36</sup> Diarrhea may be accompanied by dehydration, electrolyte imbalance and malnutrition and may require parenteral nutritional and fluid support. Accompanying symptoms have included nausea, vomiting and abdominal pain. In those receiving immunosuppressive therapy, withdrawal of therapy often clears the infection.

*Cryptosporidium* in patients with AIDS can present as an incapacitating illness with chronic profuse diarrhea and weight loss.<sup>37</sup> The mechanism responsible for diarrhea is not clear, although active secretion in the small bowel has been suggested. Patients may have 6 to 25 liquid stools per day

TABLE 1.—Abnormalities in Mononuclear Cells in the Intestinal Mucosa of Groups of Homosexual Men	
Homosexual Men With the Lymphadenopathy Syndrome or AIDS	Increased mucosal mononuclear cells Decreased total mucosal T cells Decreased mucosal T helper/inducer cells Decreased helper/suppressor T-cell ratio in the intestinal mucosa and circulation
Homosexual Men With AIDS	Increased proportion of cytotoxic/suppressor T cells in the intestinal mucosa.
Healthy Homosexual Men	Helper/suppressor T-cell ratio normal in the intestinal mucosa but decreased in the circulation.
AIDS = acquired immunodeficiency syndrome	



**Figure 2.**—Helper (T4)-suppressor (T8) T-cell ratios in the intestinal mucosa and circulation of healthy heterosexual men (HET), healthy homosexual men (HOM), men with the lymphadenopathy syndrome (LAS) and those with the acquired immunodeficiency syndrome (AIDS). **A**, OKT 4:OKT 8 ratios in the circulation. **B**, Parallel Leu 3a:Leu 2a ratios in the intestinal mucosa. An asterisk indicates a significant difference from healthy heterosexual men ( $P < .05$ ). Values represent mean  $\pm$  standard error of the mean.



**Figure 3.**—A double-contrast barium roentgenogram of the esophagus in a patient with esophageal candidiasis shows diffuse mucosal irregularity and ulceration.

with total stool volumes of 1 to 17 liters. Fluid and electrolyte losses may be accompanied by malabsorption, leading also to severe nutritional and electrolyte abnormalities. Diarrhea can persist for months or until a patient's death due to other complications of AIDS. In some patients with AIDS, infection is asymptomatic, but the organism may be found on the screening of stool specimens.<sup>38</sup> *Cryptosporidium* in AIDS patients has infected mucosal surfaces in the small bowel, colon, gastric mucosa and biliary tract, and patients have been reported to have cholecystitis associated with this organism.<sup>39-41</sup>

The diagnosis of cryptosporidiosis is made by identifying the organism on stool examination using stool-concentration techniques and phase-contrast microscopy.<sup>42</sup> In addition, a modified Ziehl-Neelsen stain for acid-fast bacilli (AFB) will elicit the organism in stool as a 3- to 6-micron densely stained red spherule.<sup>43</sup> More recently, auramine, a fluorescent stain, has been used for detecting *Cryptosporidium* in stool specimens.<sup>44</sup> A small bowel biopsy specimen from a patient with cryptosporidiosis typically shows villous atrophy and crypt hypertrophy together with 2- to 5-micron round organisms that appear to be adherent to the mucosal membrane (Figure 4).<sup>45</sup> In tissue sections the organism is best shown by a modified Kinyoun stain.<sup>46</sup> Electron microscopy of the intestinal mucosa reveals the various life-cycle stages of *Cryptosporidium*, together with a specialized attachment organelle. Such studies suggest that the organism may be located beneath the apical membrane of intestinal epithelial cells.<sup>47</sup> Small bowel radiographs may show thickened and blunted mucosal folds in the proximal small intestine and occasionally a rigid contracted gastric antrum.<sup>48</sup> In some patients, combined stool examination and small bowel biopsy may be necessary for diagnosis.

In general, the results of using antibiotics in the treatment of cryptosporidiosis have been discouraging.<sup>49</sup> Spiramycin, an erythromycin-like drug initially used to treat patients infected with *Toxoplasma gondii*, has in a few reports had limited success when used at a dose of 1 gram three to four times per day for one week. In a study of ten patients, six had complete resolution of diarrhea and three of these had negative follow-up fecal examinations.<sup>50</sup> Another four patients in this study had symptomatic improvement, but the organism



**Figure 4.**—A biopsy specimen of small bowel mucosa shows cryptosporidia (arrows) at the epithelial cell surface (hematoxylin-eosin stain, original magnification  $\times 400$ ; photomicrograph courtesy of J.W.M. Gold, MD).

did not clear from the feces. A separate study reported that 3 of 13 patients were cured symptomatically and by results of a stool examination after three to four weeks of treatment with spiramycin.<sup>51</sup> In an additional three patients, there was symptomatic improvement but no clearing of the organism from the feces, and discontinuing the therapy in those patients resulted in relapse. The remaining seven patients did not have response to the medication.

#### *Isospora belli*

*Isospora belli* is a rare intestinal parasite that is most common in the tropics and has been associated occasionally with intestinal infections among immunocompetent and immunocompromised hosts in the United States.<sup>52</sup> This organism has been identified in a small number of patients with AIDS who have chronic diarrhea and malabsorption, particularly in those from Haiti.<sup>53</sup> Transmission probably occurs by the fecal-oral route. In immunocompetent patients, infection typically presents as a transient illness characterized by diarrhea, weight loss, abdominal pain, anorexia, vomiting and fever.<sup>54</sup> Steatorrhea also may be present. Peripheral eosinophilia has been noted in about 50% of immunocompetent patients infected with *I belli*,<sup>55</sup> and Charcot-Leyden crystals variably have been found on stool examination.

*Isospora* infects epithelial cells of the small intestine (Figure 5). The organism undergoes asexual and sexual stages of replication, with subsequent production of the characteristic oval or flask-shaped double-walled oocyst.<sup>56</sup> Finding cysts in stool specimens is difficult, even during periods of severe diarrhea or steatorrhea, although identification can be enhanced by using flotation techniques to concentrate the



**Figure 5.**—An electron micrograph shows an *Isospora belli* organism within an intestinal epithelial cell (arrow) (uranyl acetate and lead citrate stain, original magnification  $\times 7,000$ ).

cysts.<sup>57</sup>(pp1002-1003) AFB stains also may be helpful for identifying cysts in stool specimens.<sup>58</sup> The diagnosis is more typically made by examining the duodenal contents or a biopsy specimen of small intestinal mucosa.<sup>59</sup> Giemsa staining has been the most useful technique for showing the various stages of *I belli* within the epithelial cells of the small intestinal mucosa. The mucosal architecture usually is altered with villous clubbing or flattening and lymphocytic infiltration of the lamina propria. Radiographic examination of the small bowel may elicit no abnormalities or may show distended small bowel loops and edema of the mucosa.

Infection is self-limited in immunocompetent persons and may last from six weeks to six months. In immunocompromised patients, however, including those with AIDS, symptoms may be prolonged.<sup>60</sup> Various antibiotics such as pyrimethamine and sulfadiazine,<sup>59</sup> trimethoprim-sulfamethoxazole and co-trimoxazole<sup>61</sup> have been tried with some success.

### Microsporidia

Microsporidia belong to a phylum of protozoan parasites that includes pathogens for mammals,<sup>62</sup> fish<sup>63</sup> and arthropods.<sup>63</sup> In AIDS patients, the microsporidia found in the intestinal mucosa have differed morphologically from those reported previously in other organs.<sup>64</sup> Microsporidia have typically been found in patients with AIDS who have diarrhea that, after careful examination for enteric pathogens, has been termed idiopathic.<sup>65</sup> These organisms frequently are missed, even on careful examination of intestinal tissue by light microscopy, because of their small size, intracellular location and poor staining with the usual tissue stains. Small intestinal biopsy specimens may show an increase in mucosal macrophages or plasma cells, but not villous atrophy. Electron microscopy is currently the most useful technique for identifying microsporidia in the intestinal mucosa.<sup>66</sup> The organism typically is seen in the apical area of a villus, and approximately 10% of the epithelial cells are invaded. In some persons, an increase in secretory granules within epithelial cells has been recognized. Microsporidia spores are 1 to 2 microns in diameter and have not been identified in the feces of patients. Even though microsporidia are associated with diarrhea, it has not been proved thus far to be the cause of the diarrhea. There is no known effective treatment of infection with this organism.

### Bacteria

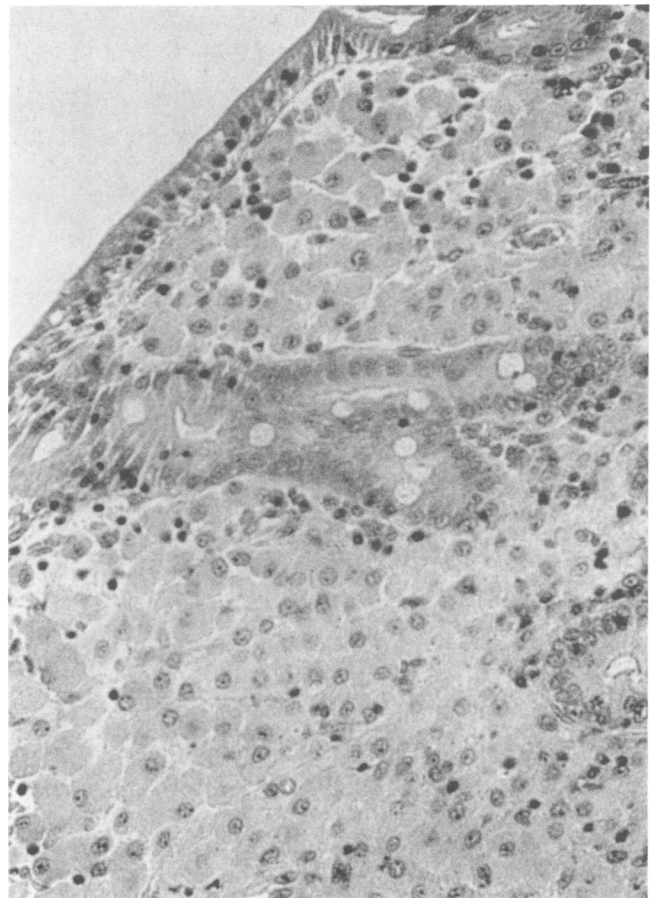
#### *Mycobacterium avium-intracellulare*

*Mycobacterium avium-intracellulare* is an atypical mycobacterium that is an important pathogen in patients with AIDS.<sup>67</sup> *M avium-intracellulare* is common in the environment. Before the description of AIDS, it was recognized occasionally to cause disseminated infection in patients with proved or suspected immunocompromised states.<sup>68</sup> It was more typically recognized as a pulmonary pathogen in persons with intrinsic lung disease.<sup>69</sup>

In patients with AIDS, *M avium-intracellulare* often is widespread with involvement of the lymph nodes, spleen, liver, bone marrow, intestinal tract, adrenal glands and brain.<sup>70</sup> It typically is spread hematogenously and blood cultures may be positive.<sup>71</sup> Identification, however, may require the use of specialized culture media, such as the Dupont isolator.<sup>72</sup> Typically, once blood cultures are positive, subsequent blood cultures remain positive, suggesting a sustained

bacteremia.<sup>73</sup> Diagnosis also can be confirmed by examining bone marrow, liver or lymph node biopsy specimens. Tissue sections may show granulomas, which microscopically consist of a collection of large, round macrophages with pale, somewhat foamy cytoplasm.<sup>74</sup> On Ziehl-Neelsen staining, typical acid-fast bacilli can be seen within the macrophages. A lymph node biopsy specimen often shows lymphocyte depletion together with macrophages containing abundant AFB. Of note, granuloma formation may not be present in AIDS patients due to abnormal macrophage and T-cell function. Acid-fast bacilli should be sought in all tissues in suspected cases.

Gastrointestinal involvement, typically in the small bowel, can result in diarrhea and malabsorption.<sup>75</sup> Upper gastrointestinal tract endoscopy may show small superficial ulcerations of the duodenal mucosa.<sup>76</sup> On biopsy specimens, periodic acid-Schiff-positive, diastase-resistant macrophages may be present throughout the intestinal mucosa, reminiscent of the appearance of Whipple's disease (Figure 6).<sup>76</sup> Acid-fast bacilli can be found in macrophages and free in the lamina propria. By electron microscopy, intact rod-shaped bacilli are seen within the cytoplasm of the macrophages. In contrast, in Whipple's disease, a disease also reported to have T-cell or macrophage abnormalities or both,<sup>77,78</sup> the bacilli within intestinal mucosal macrophages typically show partial dissolution.<sup>79</sup>



**Figure 6.**—A small bowel biopsy specimen shows multiple foamy macrophages in the lamina propria of a patient with *Mycobacterium avium-intracellulare* (hematoxylin-eosin stain, original magnification  $\times 400$ ).

Treatment of infection with *M avium-intracellulare* has been difficult. The use of combinations of multiple antituberculous drugs has had disappointing results.<sup>80</sup> Ansamycin and clofazimine have shown some in vitro activity against many isolates of *M avium-intracellulare*, but in vivo experience with these drugs has been limited.

## Viruses

### Cytomegalovirus

Mounting evidence, including identifying cytomegalovirus (CMV) in specimens from the uterine cervix,<sup>81</sup> urine and semen,<sup>82,83</sup> has suggested sexual transmission of this virus. In one study, significant CMV antibody titers were found in 94% of homosexual men compared with 54% of heterosexual men attending a venereal disease clinic.<sup>84</sup>

Before AIDS was recognized, disseminated CMV infection usually was limited to immunosuppressed patients, especially those who had undergone renal,<sup>85</sup> cardiac<sup>86</sup> or bone marrow transplants.<sup>87</sup> Gastrointestinal involvement was rare and was mainly limited to isolated segments of the intestine, with single or multiple mucosal ulcerations. Complications included bleeding or perforation.<sup>88,89</sup> In some cases, CMV appeared to be a secondary invader of ulcerating lesions of the gastric mucosa.<sup>90</sup>

In patients with AIDS, CMV has been identified at autopsy in the small intestine, colon, liver and pancreas.<sup>91</sup> CMV has been reported in association with either discrete colonic lesions<sup>92</sup> or, more commonly, with patchy diffuse lesions suggestive of inflammatory bowel disease.<sup>93</sup> Most patients have a protracted course of diarrhea, although some may present with severe hemorrhagic colitis or colonic perforation and peritonitis.<sup>94</sup> Esophageal, gastric or duodenal involvement characterized by discrete ulcers or generalized edema and inflammation also may be seen.

Radiographic findings vary depending on the site of infection. On upper gastrointestinal tract barium studies, CMV involvement of the stomach and duodenum may be recognized by edema, nodularity, ulceration and poor distensibility of the mucosa.<sup>95</sup> Small bowel involvement has typically been confined to the duodenum, proximal jejunum and terminal ileum. Colonic involvement may appear on plain films as irregular, thickened, air-filled colon as occasionally seen in patients with acute ulcerative colitis. A barium enema study may show diffuse inflammatory changes with mucosal granularity, superficial erosions, luminal narrowing and absent haustral markings.<sup>96</sup> Some patients may have involvement limited to the terminal ileum or cecum.

Endoscopic findings in AIDS patients with gastrointestinal CMV infection vary substantially. In some, discrete ulcers suggestive of early pseudomembranous colitis are seen.<sup>92</sup> Others have more diffuse inflammatory changes characterized by edema, erythema and mucosal erosion.<sup>93</sup> An endoscopic biopsy of these lesions typically shows mucosal ulceration and an inflammatory infiltrate. Intranuclear inclusion bodies are seen in epithelial and endothelial cells (Figure 7). CMV may induce a vasculitis that affects the submucosal capillaries and arterioles resulting in thrombosis and ischemic damage with subsequent perforation and peritonitis.<sup>97</sup>

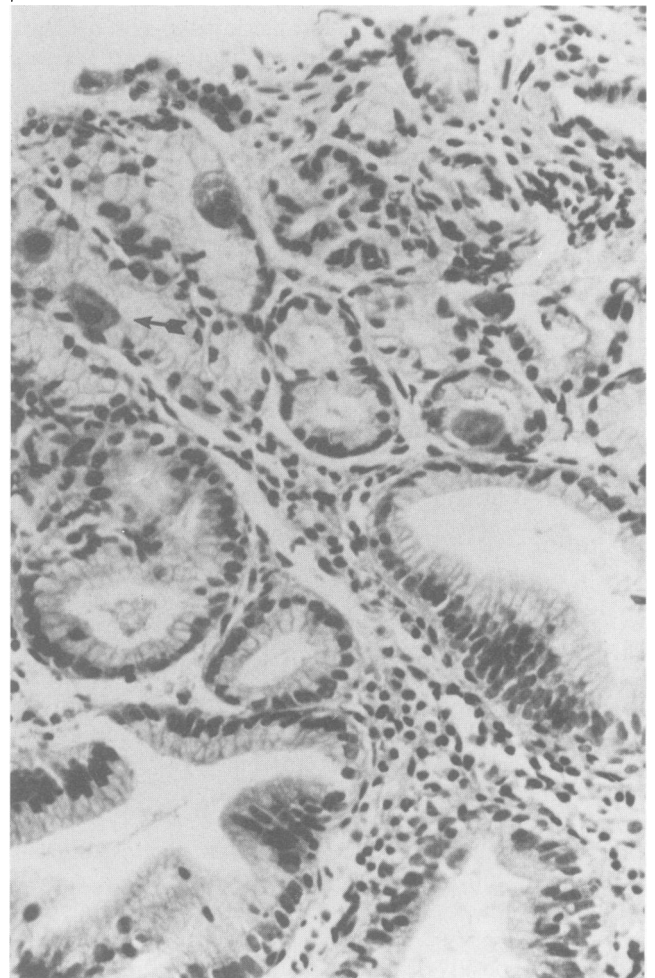
Treatment results have been disappointing. CMV, like herpes simplex, is a DNA virus. Nonetheless, treatment of CMV infection with acyclovir has not been effective.<sup>98</sup> How-

ever, 9-(1,3-dihydroxy-2-propoxymethyl)guanine, a drug that is structurally similar to acyclovir, has shown efficacy in patients with CMV colitis and retinochoroiditis.<sup>99</sup>

### Herpes Simplex Virus

Chronic ulcerating lesions due to herpes simplex virus (HSV) are unusual. Such lesions typically are found in patients receiving immunosuppressive therapy or high-dose corticosteroids,<sup>100,101</sup> those with advanced lymphoproliferative disease<sup>102</sup> or in patients with primary immunodeficiency syndromes.<sup>103</sup>

Herpes simplex proctitis in homosexual men may be associated with perianal involvement.<sup>104</sup> Spread outside the perianal area suggests a compromised immune system and, when chronic, is diagnostic of AIDS.<sup>105</sup> HSV proctitis has clinical features that distinguish it from other infectious causes of acute proctitis.<sup>106</sup> It tends to be limited to the distal 10 cm of the rectal mucosa, and associated inguinal lymphadenopathy may be found. Symptoms of HSV proctitis characteristically include hematochezia, tenesmus and constipation. The anorectal pain, however, typically is more severe than with other forms of proctitis. Other symptoms in men with HSV proctitis include hesitancy of urination, perianal paresthesias, posterior thigh pain and impotence. Involvement of the sacral



**Figure 7.**—A specimen of colonic biopsy from a patient with cytomegalovirus colitis shows an intranuclear inclusion (arrow) (hematoxylin-eosin stain, original magnification  $\times 400$ ).

autonomic nerve roots is thought to be the cause of many of these symptoms. In the terminal stages of disease, the virus may spread to the spinal cord.

Biopsy specimens of lesions may show inclusion bodies characteristic of herpes simplex virus. Viral cultures are also helpful in establishing the diagnosis, but serologic evidence of HSV infection often is unreliable. These patients usually respond to therapy with antiviral drugs such as acyclovir, but relapse is common.<sup>107</sup>

### Kaposi's Sarcoma

Kaposi's sarcoma is a multifocal tumor of the reticuloendothelial system that involves the skin and subsequently the viscera.<sup>108</sup> Classic Kaposi's sarcoma seen in an elderly ethnic population is an indolent disease, typically affecting the extremities, with a mean survival of 8 to 13 years after diagnosis.<sup>109</sup> Visceral involvement is clinically noted in 10% of those with cutaneous disease, although results of autopsy studies suggest visceral involvement in as many as two thirds of affected persons.<sup>110</sup>

A more aggressive lymphadenopathic form of Kaposi's sarcoma has been recognized in young men in equatorial Africa and more recently in young homosexual men with AIDS.<sup>111,112</sup> Approximately 50% of AIDS patients who have cutaneous involvement with Kaposi's sarcoma also have visceral involvement assessed by radiographic and endoscopic studies.<sup>113</sup>

Oropharyngeal involvement is common and this area should be carefully examined in patients at risk for Kaposi's sarcoma.<sup>114</sup> The hard and soft palates are the most commonly affected sites, although lesions of the oral mucosa and gingiva also occur.<sup>115</sup> Oral involvement does not appear to correlate with the presence of Kaposi's sarcoma in other gastrointestinal organs.<sup>116</sup> In patients with AIDS, visceral involvement of the stomach, colon, small bowel, liver and spleen with Kaposi's sarcoma has been found.<sup>117</sup> Typically the lesions are asymptomatic clinically and found at autopsy.<sup>118</sup> Documentation of visceral involvement indicates a worse prognosis in patients with either classic Kaposi's sarcoma or AIDS.<sup>116</sup>

Radiographic evaluation of patients with cutaneous disease often is useful in showing gastrointestinal involvement.<sup>119</sup> Esophageal radiographs have shown polypoid lesions in the midesophagus.<sup>120</sup> The stomach and proximal small bowel are involved more commonly than the distal small bowel or colon.<sup>121</sup> Multiple submucosal defects are typically seen randomly distributed in the stomach, but are more numerous in the antrum. These appear as smoothly contoured polyps ranging from a few millimeters to several centimeters in size. In rare cases lesions have central collections of barium, consistent with the classically described bull's-eye lesion. Other lesions have thickened and irregular mucosal folds. Lesions in the distal small bowel appear nodular, at times with diffuse thickening. Colonic lesions usually appear as distinct nodular submucosal defects. They also may have a skip pattern suggestive of Crohn's disease or present as narrowed nodular rigid lesions typical of adenocarcinoma.

Evaluation of visceral involvement in Kaposi's sarcoma by computed tomography (CT) may show retroperitoneal lymphadenopathy. In patients who also have documented peripheral lymph node involvement, this suggests infiltration with tumor.<sup>122</sup> Adenopathy may vary from large matted col-

lections of lymph nodes with obscuration of surrounding vascular structures, to more discrete and isolated lymphadenopathy. Two cases have been reported of patients with thickening of the posterior rectal wall on computed tomography that was proved histologically to be infiltration with Kaposi's sarcoma.<sup>122</sup>

Endoscopy is more sensitive for detecting gastrointestinal tract involvement of Kaposi's sarcoma than radiography due to its ability to show small flat lesions that may be missed by x-ray film. The usual lesion identified at endoscopy is a discrete, round, nodular lesion that is reddish, purplish or bluish and protrudes into the lumen. Some of these lesions have central umbilication whereas others have superficial ulcerations. Results of endoscopic biopsy usually are normal because of the submucosal nature of the lesions. A histologic diagnosis is based on the presence of bundles of spindle-shaped cells that produce a vascular structure with cleftlike spaces containing erythrocytes or hemosiderin. The surrounding tissue may show infiltration by erythrocytes, lymphocytes and histiocytes. The tumor originates in the submucosa, but may spread through the muscularis to the serosa. Mesenteric lymph node involvement has been noted at operations and at autopsy.

Most Kaposi's sarcoma lesions are clinically asymptomatic. More advanced lesions may result in gastrointestinal tract bleeding and occasionally have been associated with intestinal obstruction, diarrhea and protein-losing enteropathy.<sup>123</sup> One patient was reported to have a periappendiceal abscess due to an obstructing Kaposi's sarcoma tumor in the lumen of the appendix.<sup>119</sup>

Treatment of Kaposi's sarcoma with chemotherapeutic agents has been complicated by the immunosuppression caused by these drugs in already immunocompromised hosts. Patients, however, have shown some tumor regression with both a single agent and combination chemotherapy,<sup>124</sup> and interferon therapy has been useful in reducing tumor size in some patients.<sup>125</sup>

### Lymphoma

An increased incidence of B-cell lymphoma has been recognized in patients with AIDS, particularly those with a preceding lymphadenopathy syndrome.<sup>126</sup> These tumors are associated with unusual prodromal manifestations. They often present at an advanced stage and frequently with primary brain or extranodal involvement.<sup>127</sup> Most commonly, these lymphomas involve the central nervous system, although disseminated visceral involvement has been identified in a small number of patients.

In patients who do not have AIDS, 1% to 2% of all primary gastrointestinal malignant disorders occur in the small intestine, and less than 30% of these are lymphomatous in nature.<sup>128-130</sup> The tumors are usually localized in the ileum and often present as a single lesion.

A small number of patients with AIDS have had lymphomas primarily involving the gastrointestinal tract.<sup>131</sup> All patients with primary small bowel lymphoma have preceding generalized lymphadenopathy, but the clinical presentation has varied. For example, one patient presented with a right lower quadrant abdominal mass with a presumptive diagnosis of appendicitis. At laparotomy he had a midileal perforation with peritonitis. On histologic examination there was a

large-cell lymphoma with associated ulceration and peritonitis. A second patient presented with rectal pain, drainage and rectal abscess. Colonoscopy showed involvement of the hepatic flexure and rectum with an ulcerated mass that did not reveal tumor on biopsy. A subsequent laparotomy for small bowel obstruction showed several tumor nodules in the small bowel mesentery. On histologic examination there was a large-cell lymphoma involving the mesenteric lymph nodes and adipose tissue. A third patient presented with abdominal pain, weight loss and constipation. A small bowel series showed a mass in the jejunum. Laparotomy and subsequent resection showed a circumferential, transmural large-cell lymphoma. At least one case of primary large-cell lymphoma of the liver has been reported.<sup>132</sup> Several other cases have been reported of patients with oral lesions.<sup>126</sup>

Due to the rarity of such tumors, the diagnosis usually is not made until late in the clinical course. Treatment of these patients with chemotherapy is complicated because of their underlying immune deficiency and the risk of opportunistic infection. These tumors may be palliated by resective therapy, however.

### Idiopathic Diarrhea

Diarrhea, alone or accompanied by generalized lymphadenopathy, fever and weight loss, may precede a diagnosis of AIDS by months and can remain a chronic debilitating problem throughout the course of disease.<sup>133</sup> Often in these patients and in patients with AIDS there is no clear cause for the diarrhea despite aggressive measures to identify a pathogen. Before being classified as idiopathic, evaluation of the diarrhea in such persons should include screening of a stool specimen for enteric pathogens, examination of specimens of small bowel biopsy and aspirates, endoscopic evaluation of the colonic mucosa and barium contrast studies.

Among 72 AIDS patients referred for diarrhea in one study, no identifiable cause could be found in 20 by stool screening for pathogens.<sup>134</sup> All 20 patients had positive D-xylose tests and evidence of fat malabsorption. In 5 of the 20, histologic examination of a duodenal biopsy specimen showed a dense histiocytic infiltration containing AFB-positive organisms that suggested intestinal involvement with *M avium-intracellulare*. Chronic nonspecific inflammation characterized by plasma cell and lymphocytic infiltrates with normal villous architecture was found in 13 of the 20. Two patients had normal-appearing intestinal mucosa. Another study has documented significant weight loss and a decrease in hemoglobin, iron-binding capacity, albumin levels and mid-arm circumference in patients with AIDS who have chronic diarrhea compared with homosexual controls.<sup>17</sup> D-Xylose absorption was abnormal in all, and fat malabsorption was noted in 8 of 11 patients with AIDS. Jejunal biopsy specimens from several of the AIDS patients with diarrhea revealed partial villous atrophy, crypt hyperplasia and an increase in intraepithelial lymphocytes. Rectal biopsy specimens showed focal epithelial cell degeneration, viral inclusions and mast cells located near the base of the rectal crypts.

The cause of diarrhea in many patients with AIDS has defied diagnostic techniques. One may speculate that unidentified viral infections are responsible. In one study, electron microscopy of postmortem intestinal mucosal specimens showed small spherical viruslike particles within epithelial

cells of two of six patients with AIDS.<sup>135</sup> In one patient, they were localized to the ileal mucosa and in the other to the rectal mucosa. The significance of those findings, however, or of HIV infection in the gut with respect to diarrhea is unclear at present.

### Enteric Bacteremias

#### *Salmonella*

*Salmonella* can be sexually transmitted in homosexual men.<sup>136</sup> In patients with AIDS, *Salmonella* bacteremias can be recurrent despite prolonged antibiotic therapy,<sup>137-140</sup> perhaps reflecting an abnormality in macrophage function. Most cases have involved *Salmonella typhimurium*, and cases often have occurred in patients from Zaire or Haiti, possibly reflecting a higher exposure and carrier rate in those populations. Antibiotics such as ampicillin and chloramphenicol have been used for treatment. Long-term suppressive therapy with oral administration of antibiotics has been suggested, although there is some concern over inducing antibiotic resistance with such prolonged therapy.

#### *Campylobacter*

*Campylobacter* species, particularly *Campylobacter jejuni*, are well recognized as a cause of enterocolitis.<sup>141</sup> These organisms are transmitted by the ingestion of contaminated food, milk and water or by close contact with infected humans or other animals.<sup>142-144</sup> In addition, three groups of *Campylobacter*-like organisms can be distinguished by their growth pattern, temperature sensitivity and biochemical profile.<sup>145</sup>

Previous studies failed to show an increased incidence of infection with *C jejuni* in homosexual men.<sup>146,147</sup> A recent study of homosexual men attending a venereal disease clinic, however, found *C jejuni* in 10/158 (6.3%) of those persons with intestinal symptoms and in 2/75 (2.7%) of those without intestinal symptoms.<sup>148</sup> Other *Campylobacter*-like organisms were identified in 26/158 (16%) of symptomatic homosexual men and in 6/75 (8%) of asymptomatic homosexual men, but in none of 150 asymptomatic heterosexuals.<sup>148</sup> Infection was more frequent in patients with a history of oral-anal contact.

Presenting symptoms in *Campylobacter* infection may include diarrhea, abdominal cramps, tenesmus and hematochezia. Endoscopic evaluation of the rectal mucosa is characterized by focal and diffuse friability and ulceration. A stool specimen typically shows fecal leukocytes. Isolation and identification of these organisms requires specialized culture media.

A recent study described the cases of two patients with bacteremia caused by *Campylobacter*-like organisms.<sup>149</sup> Typically the patients presented with prolonged fever, and one was found to have a compromised immune system. Neither of these patients had gastrointestinal tract symptoms. Although cultures of stool specimens were not done, the organisms were identified using special blood culture media. Treatment with antibiotics, including rifampin and tetracycline, led to clearing of the bacteremia.

### Liver Disease

There is no pathognomonic lesion of the liver in cases of AIDS. Patients with AIDS, however, have one or more risk factors for the development of liver disease. These include a past history of hepatitis or intravenous drug abuse, dissemi-



nated infection, neoplastic disease and treatment with hepatotoxic medications. Hepatomegaly, elevation of serum aminotransferase levels and mild increases in alkaline phosphatase levels are commonly noted in patients with AIDS.<sup>150</sup> A normal bilirubin and elevated alkaline phosphatase values may be seen in those with opportunistic infections or tumors involving the hepatic parenchyma. On histologic examination of hepatic tissue at autopsy, congestion, fatty change, inflammatory processes or tumor is typically found.<sup>150</sup>

Opportunistic infections often involve the liver in patients with AIDS. Hepatic involvement is reported in 5% to 44% of patients with CMV infection. CMV on a liver biopsy specimen is characterized typically by intranuclear and intracytoplasmic inclusions in Kupffer's cells, endothelial cells and hepatocytes, particularly in the sinusoidal areas.<sup>150,151</sup> In one series of patients with disseminated infection with *M avium-intracellulare*, 57% had hepatic involvement.<sup>150</sup> Involvement may be diffuse and characterized by poorly formed granuloma containing foamy histiocytic cells and a lack of other inflammatory cells.<sup>150</sup> Often there is no granuloma, however, and the organism is recognized only on AFB stain or culture. Several AIDS patients have had hepatic involvement with disseminated *Cryptococcus neoformans*. The organism was found in the sinusoids and accompanied by minimal inflammatory response.<sup>150</sup>

Viral hepatitis is common in homosexual men, although the prevalence of seropositivity for hepatitis B in homosexual men with AIDS does not appear to be higher than among other groups of homosexual men.<sup>152</sup> At autopsy of AIDS patients with hepatitis B, there has been a relative paucity of evidence of chronic active hepatitis, as assessed by histology.<sup>151</sup> This may reflect an impaired immune system and an inflammatory response.

Histologic studies in children with AIDS and hepatitis have shown lobular and portal lymphocytic infiltrates, hepatocellular and bile duct damage, sinusoidal cell hyperplasia and endothelialitis suggestive of chronic active hepatitis.<sup>153</sup> T cells of the T8 suppressor/cytotoxic subset predominated in the lymphocytic infiltration. By electron microscopy, vesicular rosettes and tubuloreticular structures were found. The children lacked hepatitis B surface antigen and antibody, yet all were positive for Epstein-Barr virus antibody, leading to the suggestion that such lesions may be caused by Epstein-Barr virus or HIV.

Kaposi's sarcoma involves the liver in 14% of cases.<sup>151</sup> Typically these patients also have involvement of the skin and other abdominal organs. Spindle cell proliferation is frequently seen in the capsule of the liver and appears to extend into the liver parenchyma in a multifocal fashion with a predilection for the portal tracts.<sup>150</sup> Elevated alkaline phosphatase levels have been noted in every case. Finally, primary hepatic involvement with lymphoma has been reported in at least one patient with AIDS.<sup>154</sup>

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## GASTROINTESTINAL MANIFESTATIONS OF AIDS

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